HOMOGENEOUS HYDROGENATION OF ELECTRON-DEFICIENT ALKENES BY USING IRIDIUM-COMPLEXES

Dissertation
zur Erlangung des akademischen Grades
eines Doktors der Naturwissenschaften
an der Universität Konstanz

vorgelegt von

Volodymyr Semeniuchenko

Konstanz 2009

Tag der mündlichen Prüfung: 19.05.2009
Erstgutachter: Prof. Dr. Ulrich Groth
Zweitgutachter: Prof. Dr. Helmut Fischer
Prüfungsvorsitzender: Prof. Dr. Thomas Exner

For my wonderful family

The present work has been completed from October 2005 to February 2009 in the workgroup of Prof. Ulrich M. Groth, Department of Chemistry of the University of Konstanz, within the partnership between the University of Konstanz and the National Taras Shevchenko University Kiev.

Special thanks to:
Prof. Dr. Ulrich Groth for giving me the opportunity to work in his group, for discussions concerning my work and for his entire support;
Prof. Dr. Volodymyr Khilya for the interesting topic, for discussions concerning my work and for his entire support;
Prof. Dr. Thomas Exner for quantum-chemical computations, theirs interpretation and discussions;
Prof. Dr. Helmut Fischer, for writing the second evaluation;
Michael Burgert, Victor Iaroshenko, Dr. Thomas Huhn, Anton Kotljarov, Dr. Markus Ringwald, Dr. Olga Tšubrik, Dr. Christian Kesenheimer, Aleksei Bredihhin, Kateryna Gura, Angelika Früh, Steffen Lang and all the members of workgroup Groth for interesting discussions and useful comments regarding the topic of the work and to Milena Quentin for all the help she gave me;
Anke Friemel, Ulrich Haunz, Prof. Dr. Heiko Möller and Andreas Berkefeld for measurements and discussions of NMR-spectra;
Michael Burgert, Rheinhold Weber, Dmitry Galetsky and Sascha Keller for measurements and discussions of mass-spectra;
Thomas Haas for a possibility to perform column chormatography at low temperature;
Qiong Tong and Yan Wang for Chinese translations, Stelmakh Svetlana and Christian Kesenheimer for Japanese translations;
All my friends in Konstanz with whom I had a wonderful time here;
Last but not least I wish to thank and to express my deep gratitude to my family and my parents for supporting and encouraging me during this time.

The research would not have been possible without the scholarships on part of the Herbert-Quandt Stiftung der Altana AG (now Nycomed) and the Deutsche Akademische Austauschdienst (DAAD). The scholarships are kindly acknowledged.

This dissertation has been published in part, and presented at the following conferences:

PUBLICATIONS

Volodymyr Semeniuchenko, Volodymyr Khilya, Ulrich Groth. Nucleophilic Homogeneous Hydrogenation by Iridium Complexes, Synlett, 2009, 2, 271-275

CONFERENCE PRESENTATIONS

Volodymyr Semeniuchenko, Volodymyr Khilya, Ulrich Groth. Nucleophilic homogeneous hydrogenation by Ir-complexes, *10th Frühjarssymposium, 27th-29th March 2008, Rostock (Germany).*

Volodymyr Semeniuchenko, Volodymyr Khilya, Ulrich Groth. Nucleophilic homogeneous hydrogenation by Ir-complexes, *International Synposium on Homogeneous Catalysis ISHC-XVI, 6th-11th July 2008, Florence (Italy).*

Volodymyr Semeniuchenko, Volodymyr Khilya, Ulrich Groth. High-efficient Synthesis of (Phosphanodihydrooxazole) (1,5-cyclooctadiene) Iridium Complexes, *11th Frühjarssymposium, 11th-14th March 2009, Essen (Germany).*

TABLE OF CONTENTS

ABBREVIATIONS

Ac	**Acetyl (actinium is not mentioned in the dissertation)**
ATR	**Attenuated Total Reflectance**
B3LYP	**Becke 3-Parameter (Exchange), Lee, Yang and Parr (correlation; density functional theory)**
BARF	**Tetrakis(3,5-bis(trifluoromethyl)phenyl) borate**
9-BBN	**9-Borabicyclo[3.3.1]nonane**
BEMP	**2-*tert*-Butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,3,2-diazaphosphorin**
BINAP	**2,2`-Bis(diphenylphosphino)-1,1`-binaphtyl**
borsm	**Based on recovery of starting material**
BTED	**Bis[t-butylthio]ethane-diborane**
iBu	***iso*-Butyl**
nBu	***n*-Butyl**
sBu	***sec*-Butyl**
tBu	***tert*-Butyl**
C^N	**Chelating ligand, having coordinations sites at carbon (carbene) and on nitogen atoms**
C^P	**Chelating ligand, having coordinations sites at carbon (carbene) and on phosphorus atoms**
CD	**Circular Dichroism**
COD	**1,5-Cyclooctadiene**
COE	**Cyclooctene**
COSY	**COrrelation SpectroscopY**
COX	**Cyclooxygenase**
CP	**Cross-Polarization**
CPTOSS	**Cross-Polarization TOtal Side-band Suppresion**
CTH	**Catalytic Transfer Hydrogenation**
Cy	**Cyclohexyl**
de	**Diastereomeric excess**
DFT	**Density Functional Theory**

DIPEA	**Diisopropylethylamine, Hünig's base**
DMF	**Dimethylformamide**
DMSO	**Dimethylsulfoxide**
DPPB	**1.4-Bis(diphenylphosphinyl)butane**
DPPP	**1.4-Bis(diphenylphosphinyl)propane**
ee	**Enantiomeric excess**
ESI	**ElectroSpray Ionisation**
ESP	**Electro-Static Potential**
Et	**Ethyl**
EWG	**Electron Withdrawing Group**
FT-ICR	**Fourier Transfrom - Ion-Cyclotrone Resonance**
GC/MS	**Gas-Chromatogphy with Mass Selective detector**
GLC	**Gas-Liquid Chromatography**
GLYMO	**Glycidoxypropyltrimethoxysilane (trimethoxy(3-(oxiran-2-ylmethoxy)propyl)silane)**
HMBC	**Heteronuclear Multiple Bond Correlation**
HMDS	**Hexamethyldisilazane**
HOMO	**Highest Occupied Molecular Orbital**
HRMS	**High-Resolved Mass-Spectrometry**
HSQC	**Heteronuclear Single Quantum Coherence**
HTC	**High Throughput Computation**
HTE	**High Throughput Experimentation**
HTS	**High Throughput Screening**
IL	**Interleukin**
IMe	**1,3-dimethylimidazol-2-ene**
IR	**Infrared**
LAH	**Lithium tetrahydridoaluminate, $LiAlH_4$**
LHMDS	**Lithium hyxamethyldisilazide**
LOX	**Lypooxygenase**
LSR	**Lantanoid Shift Reagent**
LUMO	**Lowest Unoccupied Molecular Orbital**
MAS	**Magic Angle Spinning**
Me	**Methyl**

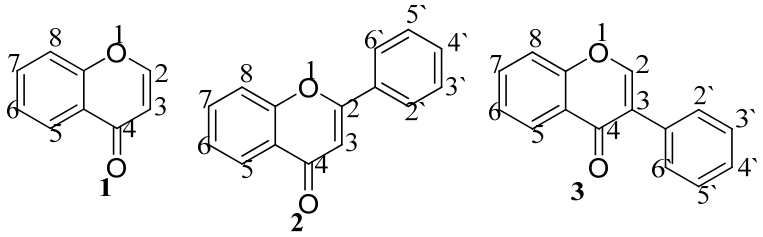
MeO	**Methoxy**
MOM	**Methoxymethyl**
MS	**Mass-Spectrometry**
MW	**Microwave**
N/A	**Not available**
Na_2EDTA	**Dinatrium salt of ethylendiamine tetraacetic acid**
NADH	**Nicotinamide Adenine Dinucleotide carrying two electrons and bonded with H^+**
NADPH	**Nicotinamide adenine dinucleotide phosphate carrying two electrons and bonded with H^+**
NBD	**Nor-bornadiene**
NBO	**Natural Bond Orbital**
NHC	**N-Hetecocyclic Carbene**
NMR	**Nuclear Magnetic Resonance**
NOESY	**Nuclear Overhauser Effect SpectroscopY**
NPA	**Natural Population Analysis**
P^N	**Chelating ligand, having coordinations sites at phosphorus and on nitogen atoms**
P^P	**Chelating ligand, having coordination sites at both phosphorus atoms**
PCC	**Pyridinium chlorochromate**
PM3	**Parameterized Model number 3 (semi-empirical method, based on Neglect of Differential Diatomic Overlap)**
Ph	**Phenyl**
Phox	**Phosphinooxazoline**
iPr	***iso*-Propyl**
Py	**Pyridine**
Rf	**Retention factor**
ROESY	**Rotational nuclear Overhauser Effect SpectroscopY**
r.t.	**Room temperature**
Tf	**Triflyl**
TFA	**Trifluoroacetic acid**
THF	**Tetrahydrofuran**
TLC	**Thin-Layer Chromatography**

TMEDA	**Tetramethylethylenediamine**
TMS	**Trimethylsilyl**
TOF	**Time Of Flight**
o-Tol	***ortho*-Tolyl, 2-methylphenyl**
Ts	**Tosyl, *p*-methylbenzosulphonyl**
US	**Ultrasound**
WCA	**Weakly Coordinating Anion**
2,6-Xyl	**2,6-Xylyl, 2,6-dimethylphenyl**

1 INTRODUCTION

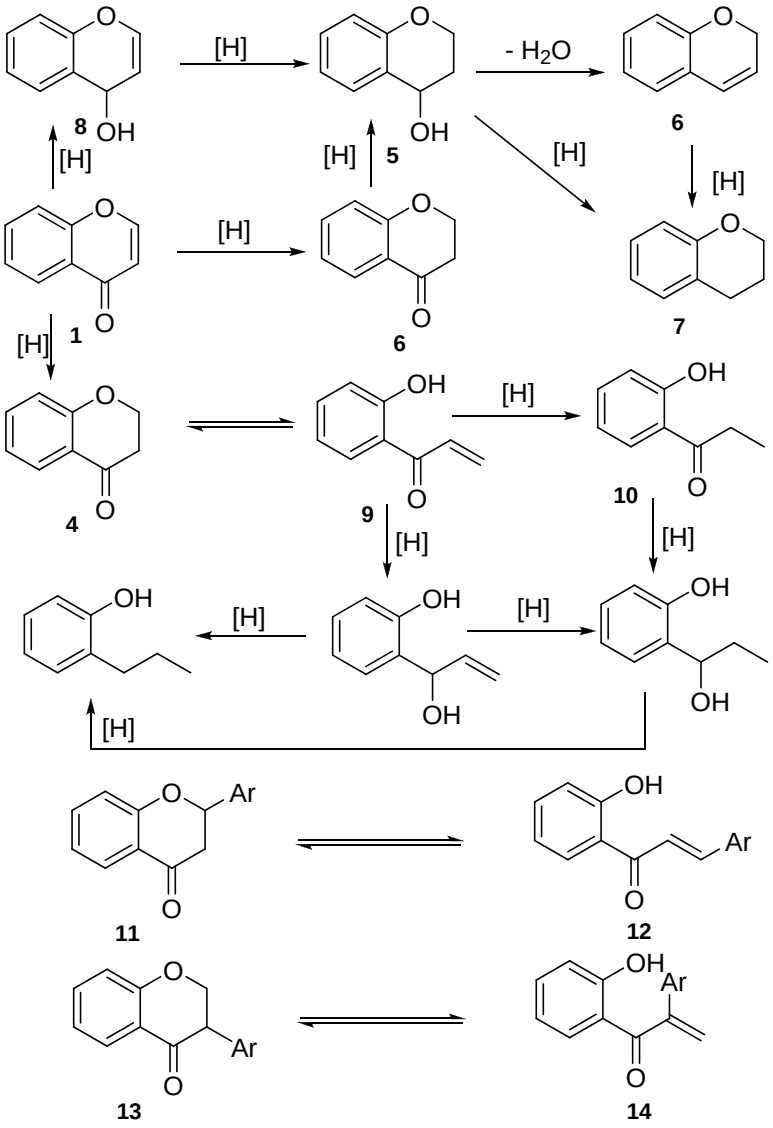
1.1 Synthesis of chroman-4-ons by reduction of chromones

The flavonoids are widely spread in plants and are known as biologically active compounds (the most recent rewievs and books[1]). Chromones **1** (4H-chromen-4-ones, 1-benzopyran-4-ones) and coumarins (2H-chromen-2-ones, 1-benzopyran-2-ones) with their derivatives belong to the class of flavonoids. Natural chromones **1** are represented in most cases by flavones **2** (2-arylbenzopyran-4-ones) and isoflavones **3** (3-arylbenzopyran-4-ones). The numeration in such systems is given in scheme 1. Natural flavonoids are mono- or polyhydroxylated, methoxylated or glycosylated in annelated and/or side aryl-ring.



Scheme 1

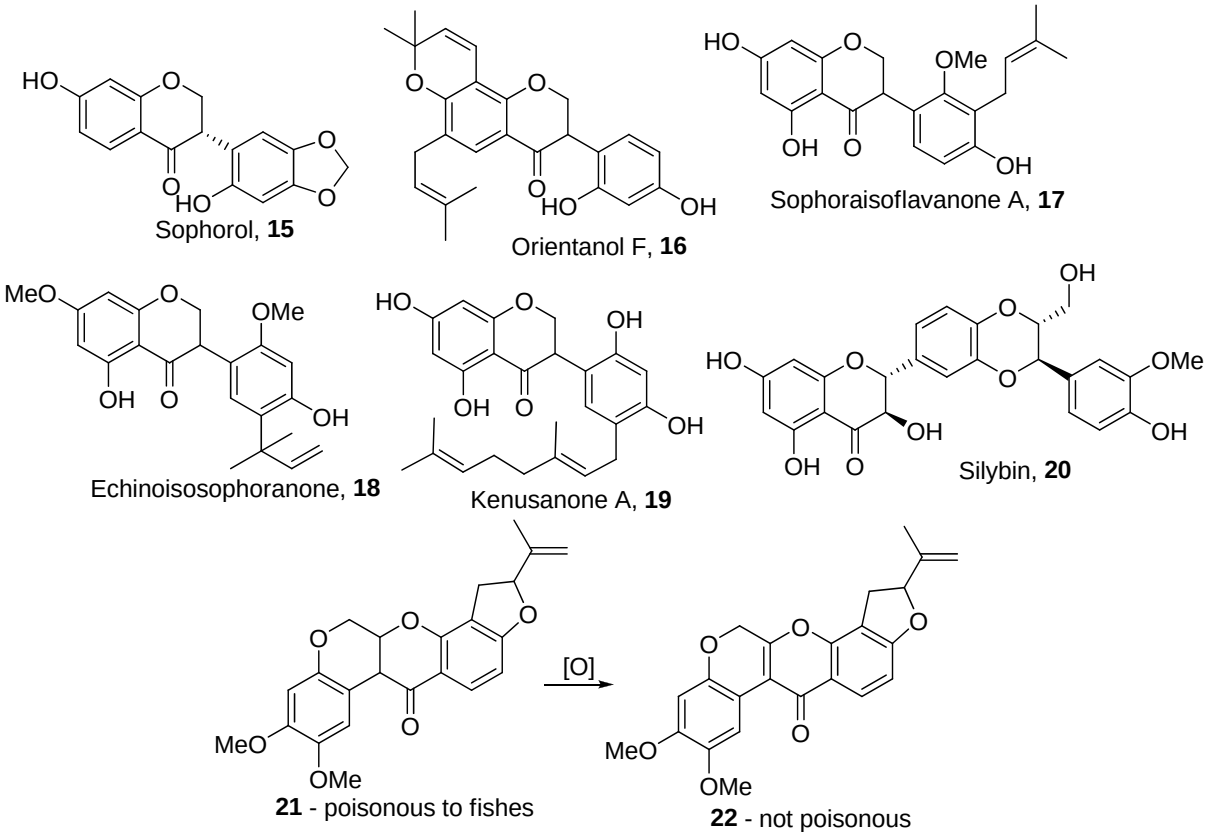
If you want to reduce the chromone **1**, it is possible to obtain several compounds (see scheme 2): chromanones **4**, chromanols **5**, chromenes **6**, chromans **7**. The preparation of chromenols **8** is also reported[2]. The chromanones could be opened by alkali or spontaneously to alkenes **9**, the latter could be reduced to arylpropanones **10**. The conversion **4→9** is especially easy for flavanones **11**, since a stabilized chalcone **12** is formed. Of course, chalcone **12** is notably more stable than **14**, but a similar transformation **13→14** is reported to exist[3-5]. The ketones **9** and **10** could be further reduced to alcohols and alkanes.



Scheme 2

Chroman-4-ones have a wide spectrum of biological activity, hence the synthesis of such compounds has both a theoretical and practical significance. Many isoflavanones and related compounds show estrogenic activity, hence are active against human breast cancer[6]. Sophorol **15** is a phytoalexine, active against fungi[7]. Orientanol F **16** can suppress methicillin-resistant *Staphylococcus aureus*[8]. Sophoraisoflavanone A **17** inhibits cyclooxygenase-1 (COX-1), echinoisosophoranone **18** and kenusanone A **19** inhibit 5-lipoxygenase (5-LOX)[9]. G. Bojase et al.[10] report about antimicrobial isoflavanones. Natural homoisoflavanones are phytoalexins[11]. The silybin **20** has a hepatoprotective[12] and anti-cancer (skin[13] and prostate[14]) activity, which is associated with its antioxidative properties[15]. It is also proven to be effective in the treatment of type II diabetes[16]. The flavonol, derived from silybin (2,3-dehydroxilybin) also has an antioxidative activity[17]. Rotenon **21** is poisonous for fishes, while compound **22** is

not[18]. The chromone and the chromanone ring can serve as a steroid-isosteric group which is proven in articles[19, 20].



Scheme 3

There are several methods for chromones' reduction. These methods, their benefits and disadvantages are described in this review. The search was carried out with SciFinder Scholar 2007 by the American Chemical Society. Only the reduction of chromones is reviewed, e.g. the addition of organometallics to chromone can give 2-substituted chromanone, but it is not a reduction, hence is not reviewed.

One rewiev is available where the reduction of isoflavones is described[5]. It refers only to the reduction by DIBAL, Selectride and NaHTe, but the authors give information about their own experience in this field. Another review[21] dedicated to biflavonoids includes the reactions of reduction relevant to biflavonoids synthesis.

Some books have information about chromones reduction[22, 23]. It is noted therin that commonly there is no sense to reduce the chromone in order to obtain the chromanone since chromanones are readily accessible from the other precursors. The reduction of chromone makes sense if this chromone is cheap and readily accessible or if there is no other way to obtain a purposeful chromanone. On the other hand, the flavanones and isoflavanones have one or several chiral centers and enantioselective reduction which is studied quite well[24, 25],

could be a method of chiral chromanones' preparation. The examples of enantioselective reduction of chromones are reviewed in the corresponding sections.

1.1.1 Hydrogenation of chromones

1.1.1.1 With palladium on charcoal

This method is the most common one for the chromones. It gives various yields and goes with various chemical selectivity. If the other is not stated, 10% Pd/C was used. Table 2 represents the information about chromones' hydrogenation on Pd/C that gives chromanones.

In 1973 Szabo et al. published the articles[26] about the selective hydrogenation of the isoflavone. They assert that its hydrogenation goes almost quantitative in dioxane to give the corresponding chromanone, while hydrogenation in ethanol gives the isoflavonol (3-phenylchroman-4-ol, mixture of diastereomers). If the hydrogenation of 3-phenylchromone in ethanol is interrupted after 1 equivalent of hydrogen is consumed, the mixture of isoflavanone and isoflavanol with the educt is obtained. The selectivity of chromanone's formation was dependent on the supplier of Pd/C. The authors also designed a method of selective chromanone synthesis by reduction of chromone in aqueous ethanol. The selectivity was pH-dependent.

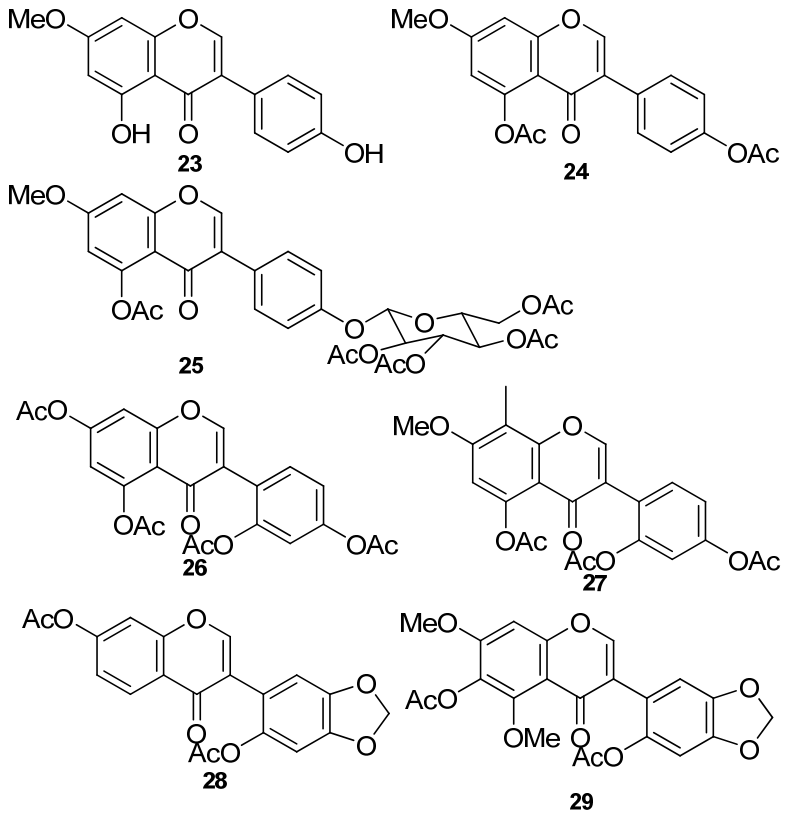
Chinese researcher[27] have optimized the hydrogenation of 5,7-dihydroxyflavon. They have used ethanol as a solvent, Pd/C as a catalyst, and the hydrogenation was performed under pressure of 3 bar of hydrogen. They have varied the amount of the catalyst, the temperature and reaction time. The amount of the substrate was fixed to 5 g in each experiment. The results are shown in table 1. In case of too low catalyst amount, too little reaction time or low temperature, the whole educt failed to convert to the 5,7-dihydroxyisoflavanone, otherwise an overreduction and formation of flavonol took place. Another interesting fact is that the three-component mixture of solvents was used for the products' separation by silica gel chromatography: MeOH/EtOAc/petrol ether 2/10/100. A little later the same authors[28] have slightly improved the method and had the yield of 5,7-dihydroxyflavanone 84.44% (0.2 cat./substrate ratio, 60º C, 2 h, EtOH).

Table 1. Optimization of hydrogenation of 5,7-dihydroxyflavon[27]

Fixed parameter	Varied parameter	Yield of 5,7-dihydroxyflavanon, %
Temperature = 53º C, time = 2 h, $p(H_2)$ = 3 bar	Catalyst amount: 0.5 g	50.45
	Catalyst amount: 1.0 g	83.26

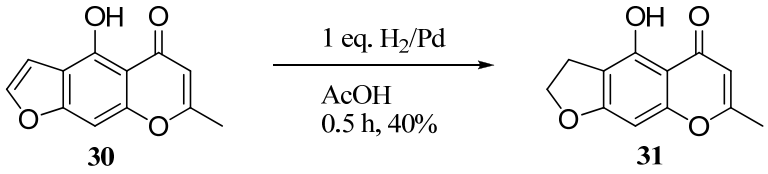
	Catalyst amount: 1.5 g	71.87
	Catalyst amount: 2.0 g	66.63
	Catalyst amount: 2.5 g	60.51
	Catalyst amount: 3.0 g	46.12
Catalyst amount = 1.0 g, time = 2 h, $p(H_2)$ = 3 bar	Temperature: 25º C	23.45
	Temperature: 32º C	38.34
	Temperature: 39º C	43.87
	Temperature: 46º C	66.63
	Temperature: 53º C	83.26
	Temperature: 60º C	52.62
Catalyst amount = 1.0 g, temperature = 53º C, $p(H_2)$ = 3 bar	Time: 1 h	31.45
	Time: 2 h	83.26
	Time: 3 h	73.51
	Time: 4 h	60.62
	Time: 5 h	51.65
	Time: 6 h	43.87
	Time: 7 h	33.21

Farkas et al.[29] have successfully hydrogenated **23**, **24** and prunitrin pentaacetate **25** in AcOH by allowing to absorb only one equivalent of hydrogen by reaction mixture. The same strategy was applied in further publications of this group: **26**, **27**[30]**; 28, 29**[31] were reduced.



Scheme 4

A successful application of "titration with hydrogen" is illustrated in patent[32], where isoflavones were hydrogenated either to isoflavan-4-ones or to isoflavans, by allowing to absorb 1 or 3 equivalents of hydrogen. The same technique was applied in order to reduce **30** into **31**[33].

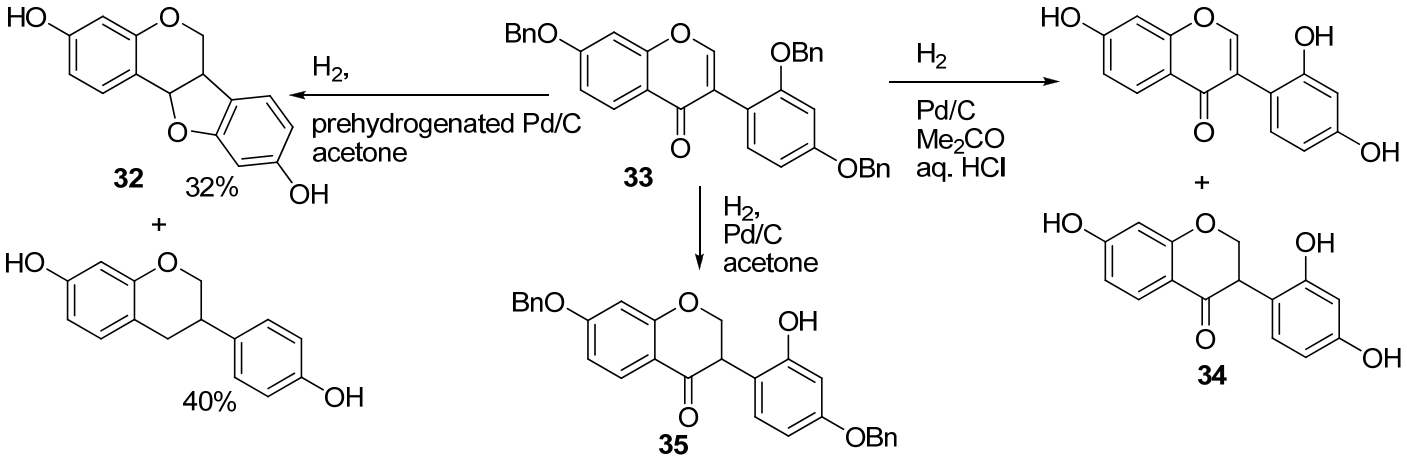


Scheme 5

In order to hydrogenate very insoluble 5,7-dihydroxy-2`,4`-dimethoxyisoflavone K. G. Neill[34] has acetylated it, then hydrogenated (in AcOH, 43%) and desacetylated.

F. Visser and G. Lane[35] tried to synthesize 3,9-dihydroxypterocarpan **32** through the hydrogenation of 2`,4`,7-tribenzyloxyisoflavone **33**. They have studied the selectivity of such a hydrogenation. The mixture of a fully deprotected isoflavone and isoflavanone was obtained by hydrogenation in acetone with aqueous HCl. Compound **34** was separated by preparative TLC. Partially deprotected isoflavones and **35** were proven to exist in the reacting mixture after the hydrogenation in acetone with low catalyst/substrate ratio (160 g/mol). However, **35** was not isolated due to coeluting with the other compounds. On the other hand, 7,2`-

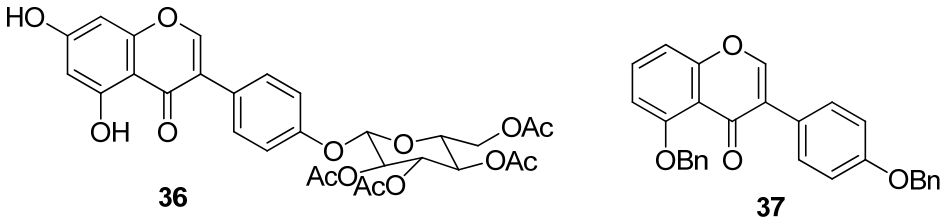
dibenzyloxy-4`,5`-methylenedioxyisoflavone was selectively debenzylated over Pd/C in EtOAc (67% yield of 7,2`-dihydroxy-4`,5`-methylenedioxyisoflavone)[36]. In patent[37] the debenzylation of chromones under 1 bar of hydrogen on 5% or 10% Pd/C in MeOH, EtOH or EtOAc is described, while actually chromone was reduced with Raney-Nickel.



Scheme 6

M. D. Woodward[38] made a debenzylation of 7,2′,4′-tribenzyloxyisoflavone by hydrogenation over 5% Pd/C under 3 bar of hydrogen. 7,2′,4′-trihydroxyisoflavone was not hydrogenated in such conditions. In order to obtain 7,2′,4′-trihydroxyisoflavanon he had to acetylate it and reduce the 7,2′,4′-triacetoxyisoflavone. It is interesting that hydrogenation of 7-(benzyloxy)-2-(4-(furan-3-yl)-3-methoxyphenyl)-3,5-dimethoxychromone at 40º C under 1 bar of hydrogen over 10% Pd/C in EtOH/EtOAc 1/1 yielded 7-hydroxy-3,5-dimethoxy-2-(3-methoxy-4-(tetrahydrofuran-3-yl)phenyl)chromone, i.e. furane-ring was reduced, but chromone was not affected[39].

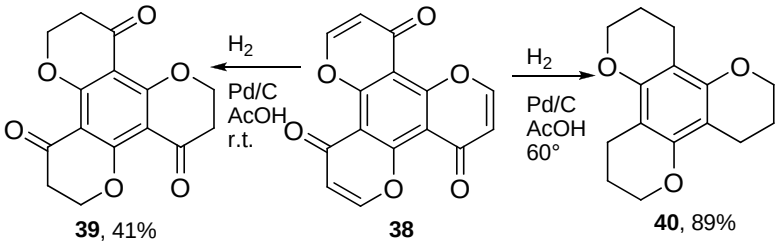
In order to design the new inhibitors of interleukin-5 the derivatives of sophoricoside were studied[40]. Actually, the hydrogenation of partially acetylated sophoricoside **36** and of **37** is described. The latter compound could be debenzylated in MeOH over Pd/C under 1.3 bar of hydrogen, while under 2 bar it is reduced to chromanone. The other O-benzylated chromones were also deprotected by such a method, but not reduced to chromanones. Parmar et al.[41] also describe the hydrogenation of chromones with simultaneous debenzylation.



Scheme 7

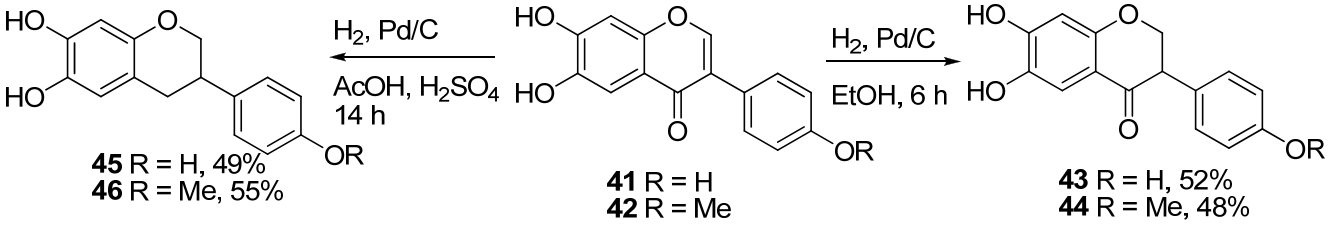
Patent[42] describes the hydrogenation of chromone-2-carboxylic acid and chiral resolution of the esters of this acid using the lipase.

C. Schmiz and F. Eiden[43] have reduced **38** to trichromanone **39** or to trichroman **40** by this method. The yield of chromanone was not very good (41%), that of chromane was better (89%). J. H. Kwak et al.[44] report about similar hydrogenation of ethyl 7-hydroxychromon-2-carboxylate in EtOH/AcOH 25/1 over Pd/C directly to the corresponding chromane.



Scheme 8

Y. Vasquez-Martinez et al.[45] report about the hydrogenation of isoflavones **41** and **42.** Hydrogenation in ethanol over 10% Pd/C gave isoflavanones **43-44**, while the use of 0.1% AcOH in EtOH as a solvent leads to the formation of chromans **45-46**.



Scheme 9

Table 2. Summary table of chromones' hydrogenation on palladium on charcoal. If otherwise is not stated, 10% Pd/C was used. If otherwise not stated, the product is the corresponding 4-chromanone.

Substrate	p(H_2), bar	solvent	yield, %	time	additional information	ref.
2-R-chromon-7-yl sulfamate (R=phenyl, cyclohexyl, 1-adamanthyl)	1	EtOAc	61, 20, 49, resp.	3 h	unselective hydrogenation, chromanols are isolated	[19]
isoflavone	N/A	dioxane, ethanol with Britton-Robinson buffer	100, 90, resp.	N/A	cannot be hydrogenated in benzene	[26]
5,7-dihydroxyflavon	3	EtOH	83.26	2 h	53º C, optimization	[27]

					study	
5,7-dihydroxyflavon	3	EtOH	84.44	2 h	60º C, 0.2 cat./substrate ratio, optimisation study	[28]
23, 24, 25	N/A	AcOH	40, 80, 80, resp.	N/A		[29]
26, **27**	N/A	AcOH	39, 38, resp.	N/A		[30]
2`,5,7-triacetyloxy-4`-methoxyisoflavone	N/A	AcOH	N/A	N/A	crude product was further deacetylated. Overall yield (2 stage) – 45%	[30]
26, 27	N/A	AcOH	N/A	N/A	synthetical procedure – from article[30]	[31]
7-n-hexadecyloxyisoflavone, 7-ethoxy-5-methylisoflavone, 7-(1-cyclohex-2-enyloxyl)isoflavone	N/A	Acetone	82	N/A	patent, reaction given as an example	[32]
5,7-diacetoxy-2`,4`-dimethoxyisoflavone	N/A	AcOH	43	N/A	concentration of Pd on C is unknown	[34]
36, **37**	2	Methanol	94.5, 68.7, resp.	15, 2 h resp.	**37** – hydrogenated with debenzylation	[40]
7-benzyloxy-8-methoxychromone	N/A	EtOAc/MeOH 1/1	78	32 h	with debenzylation	[41]
2-carboxychormone	2	Ac_2O/AcOH	41-69	N/A	60º C, patent, reaction is given as an example	[42]
38	N/A	AcOH	41	16 h		[43]
7,2′,4′-triacetoxyisoflavone	N/A	EtOAc	39	16 h	5% Pd/C used	[38]
41, 42	1	EtOH	52, 48m resp.	6 h		[45]
5-hydroxy-7-methoxy-6,8-dimethylchromone, 5-acetoxy-7-methoxy-6,8-dimethylchromone	N/A	MeOH, EtOH	50, 46 resp	N/A	5% Pd/C used	[46]
7,4`-diacetoxyisoflavone	N/A	EtOAc	80	72 h	5% Pd/C used, patent, reaction given as an example	[47]
prunetin diacetate (5,4`-diacetoxy-7-methoxyisoflavone)	3.3	AcOH	63	8 h		[48]
4`-benzyloxy-2`,5-dimethoxy-7-methoxymethoxyisoflavone	N/A	EtOH	86	N/A	with debenzylation	[49]
7-methoxychromone **53**, 7-hydroxy-2-methylchromone	N/A	AcOH	100	3 h, 9 h	Synthetic procedure published in[50]	[51]
5,7-dihydroxychromone	N/A	DMF	77	N/A	DMF was prehydrogenated	[52]
8-methoxy-2,5-dimethylchromone	N/A	MeOH	14	N/A		[53]
5,7-dihydroxy-6-methoxychromone, 5,7-dimethoxy-3-(4-methoxybenzyl)-chromone	N/A	acetone, EtOAc, resp.	N/A	N/A	no synthetic procedure available	[54]
7-benzyloxy-5-hydroxy-8-methoxychromone, 7-benzyloxy-5-methoxychromone	N/A	EtOAc/MeOH, DMF/MeOH, resp.	N/A	N/A	with debenzylation, no synthetic procedure available	
3-(3,4-dimethoxybenzyl)-7-methoxy-4-chromone	1.72	EtOAc	98	4 h		[55]
2'-methoxy-7-pivaloyloxyisoflavone, 7,4'-dipivaloyloxyisoflavone, 4'-methoxy-7-pivaloyloxyisoflavone	2	acetone	60, 70, 85, resp.	9 h	5% Pd/C	[56]
3-benzylchromone, 3-(3,4-dimethoxybenzyl)-5,7-	1	THF	73, 79 resp.	N/A	hydrogenation until 1.2 equvalents of	[57]

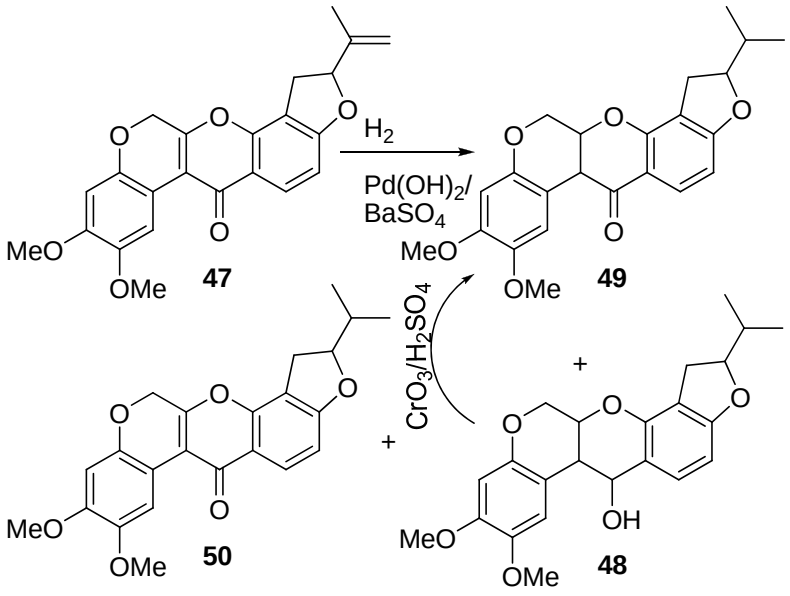
dimethoxychromone					hydrogen are consumed	
2-butylchromone-6-carboxylic acid methyl ester	4	N/A	N/A	7 h	5% Pd/C, patent, reaction is given as an example	[58]
6,7-dihydroxy-3-(4-methoxyphenol)chromone	1	EtOH	N/A	N/A	with NEt_3, patent, reaction is given as an example	[59]
5,7-dihydroxy-3-(4-hydroxybenzyl)chromone	1	MeOH	N/A	N/A	with overreduction to chroman	[60]
2-hydroxymethylchromone	1	MeOH	42	N/A	5% Pd/C used, hydrogenation until computed amount of hydrogen is consumed	[61]
5,7-dihydroxy-2,3-dimethylchromone	N/A	N/A	N/A	N/A	no information about this reaction is provided	[62]
7-benzyloxychromone	N/A	EtOAc	46	4 h	with debenzylation, with overreduction	[63]
2-carboxychromone, 6-bromo-2-carboxychromone	1	EtOH	40, 55 resp.	N/A	hydrogenation until computed amount of hydrogen is consumed	[64]
5,6,7,4`-tetramethoxyisoflavone (dimethylmuningin)	N/A	EtOH	77	35 min	concentration of Pd on C is unknown	[65]
5,7-dimethoxy-3-(4-methoxybenzyl)chromone	N/A	N/A	98	N/A	no synthetic procedure available	[66]
5,7-dibenzoyloxychromone	N/A	EtOAc	100	N/A		[67]
5,7,4′-trimethoxyisoflavone	N/A	MeOH	80	N/A	Pd/C prepared from 0.5 g of charcoal and 20 ml of 1% solution of $PdCl_2$	[68]
9-methoxy-7-(2-methoxyphenyl)-8H-[1,3]dioxolo[4,5-g]chromen-8-one	N/A	EtOH	85	42 min	5% Pd/C used	[69]
5,5',7,7'-tetramethoxy-2,2'-diphenyl-4H,4'H-3,3'-bichromene-4,4'-dione	N/A	AcOH	N/A	4 h or 12 h	80º C, products are 5,5',7,7'-tetramethoxy-2,2'-diphenyl-2H,4'H-3,3'-bichromene-4,4'(3H)-dione and 5,5',7,7'-tetramethoxy-2,2'-diphenyl-3,3'-bichroman-4,4'-dione, procedure very unselective, in the other solvents no hydrogenation observed	[70]
5,5',7,7'-tetramethoxy-2,2'-diphenyl-2H,4'H-3,3'-bichromene-4,4'(3H)-dione	N/A	AcOH	N/A	N/A	Product is 5,5',7,7'-tetramethoxy-2,2'-diphenyl-3,3'-bichroman-4,4'-dione	[70]

In summary, the hydrogenation of chromones over Pd/C is a good method of chroman-4-ones synthesis, a good starting point if a new chromone should be reduced. Although an overreduction to chromanol (in acid even to chroman because of acid-induced elimination,

hence chromene appearance) is possible, almost always a "titration with hydrogen" is possible, i.e. quenching of reaction after 1 equivalent of hydrogen is absorbed. On the other hand, a solvent screening should be performed in order to achieve the desired "hydrogen titration", otherwise a simultaneous hydrogenation of chromone and chroman-4-one is possible. A problem with this method is a strong dependence of the hydrogenation possibility on substrate and on hydrogen pressure. And, of course, the hydrogenation of chromone is impossible without debenzylation and without hydrogenation of side alkene-groups, though the opposite is possible.

1.1.1.2 With palladium on the other support or elemental palladium

O. Dann and G. Volz have published several articles about the hydrogenation of chromones over $Pd(OH)_2/BaSO_4$. The method described in article[71] presumes the two-stage procedure: at first the chromone is reduced to chromanol, then the latter is oxidized by PCC. In article[72] this two-stage procedure is not mentioned, but no method at all is described there. They have tested several methods of dehydrorotenons' hydrogenation in order to obtain the purposeful rotenons[18]. The best procedure was the hydrogenation of **47** to the corresponding chromanol **48** over PdO or over $Pd(OH)_2/BaSO_4$ under 250 bar of H_2, then oxidation by Jones reagent. But they have found that hydrogenation over $Pd(OH)_2/BaSO_4$ under low H_2 pressure gives directly **49**, unfortunately contaminated with **48** and with **50**. LAH have reduced **47** to the chromanol without affecting the side isopropenyl-group (see section 1.1.3).



Scheme 10

Later the same authors report about hydrogenation of khellin **90** (see section 1.1.3) on $Pd(OH)_2/BaSO_4$[73]. The product is the corresponding chromanol, which was oxidized to the chroman-4-one.

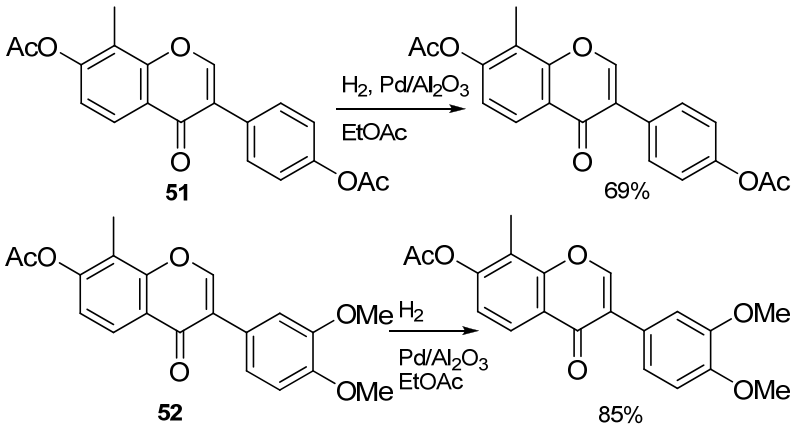
E. Müller and W. Wiesemann[74] inform about 2-methylchromone hydrogenation over $Pd/CaCO_3$ in benzene. The 2-methylchroman-4-one was characterized through its *p*-nitrophenylhydrazone. They have also tested the hydrogenation of methylchromonelithium (product of reaction of 2-methylchromone with buthyllithium, the formula is not assigned).

T.A. Geissman and A. Armen[75] have hydrogenated 2-methylchromone in benzene over $Pd/CaCO_3$ with a yield of 56% in 22 hours (purified through formation of hydrazide with Girard reagent T.).

V. Szabo and E. Antal[26] report about the use of $Pd/BaSO_4$ and Pd/Al_2O_3, although the selectivity in hydrogenation was achieved only by using of Pd/C.

Patent[76] describes the hydrogenation of 6-epoxyethyl-3-(1H-tetrazol-5-yl)-chromone to 6-hydroxyethyl-3-(1H-tetrazol-5-yl)-chromone with palladium black or 5% Pt on activated carbon at r.t. or 100ºC. The chromone ring was not reduced.

Patent[77] describes the hydrogenation of two isoflavones **51** and **52** in EtOAc over 10% Pd/Al_2O_3. The rate of hydrogenation of **51** was too low, and overall 105 weight-% of the catalyst was added in 64 h in order to achieve a full conversion of **51**. On the other hand, **52** was hydrogenated in 4 h using 45 weight-% of the catalyst.



Scheme 11

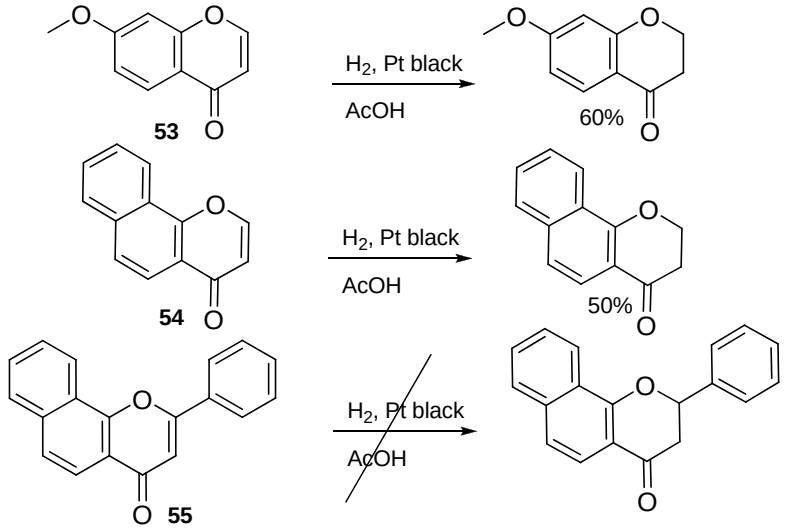
Japanese researchers[78] have tested several metal catalysts in hydrogenation of 2-methyl- and 3-methylchromone in ethanol. Pd black was not effective for chroman-2-ones synthesis (yields 12 and 11%, resp.), the main products were chromanols and chromans. The article is not synthetical, and the products (after 50% conversion of the starting chromone) were only analyzed by GLC.

In summary, elemental palladium or palladium on the support, other than activated carbon, are not very well studied concerning the chromones' reduction. Such catalysts are usually not as active as Pd/C, and a high load of catalyst or a high pressure of hydrogen should be used. On the other hand, this can and does result in overreduction.

1.1.1.3 With platinum

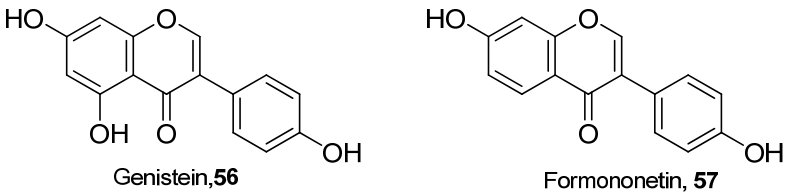
Platinum is used for heterogeneous hydrogenation much more rarely than palladium. Hence there are less examples of chromones' hydrogenation, catalyzed by platinum. In this reaction platinum could be involved as platinum black, Adams catalyst (PtO_2) or platinum on charcoal. Table 3 presents the information about chromones' hydrogenation on platinum that gives chromanone.

P. Pfeiffer and J. Grimmer[79] report about a reduction of 3-methoxychromone, 7-methoxychromone **53** and **54** on platinum black in AcOH. However, **55** could not be hydrogenated under such conditions.



Scheme 12

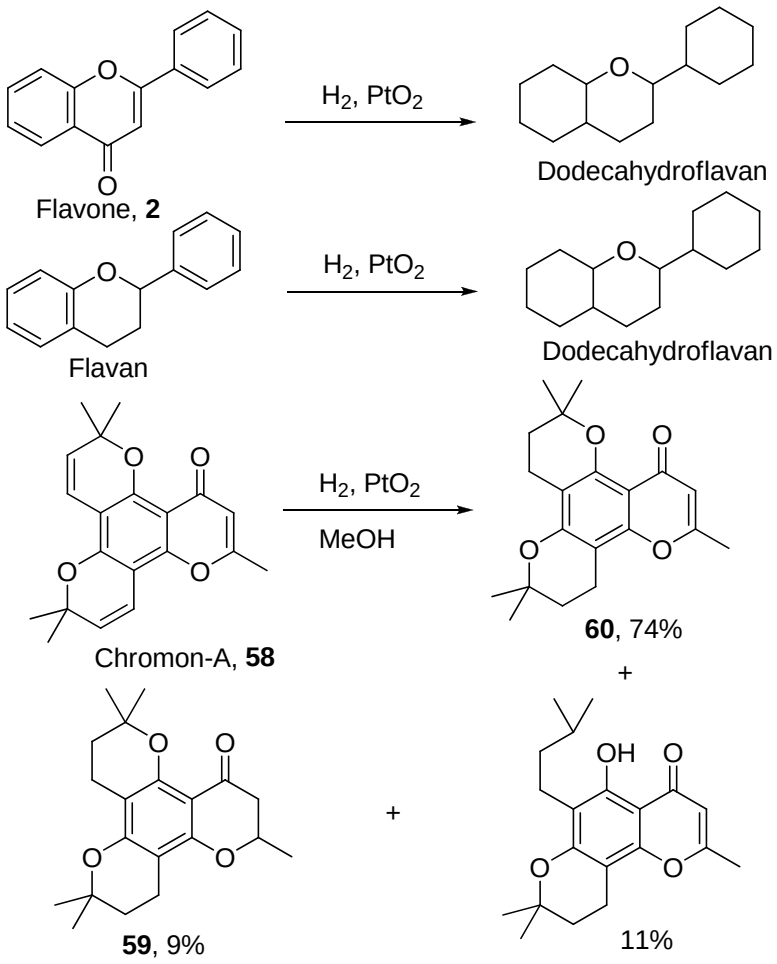
R. B. Bradbury and D. E. White[80] have studied the hydrogenation of derivatives of genistein **56** and formononetin **57** over PtO_2. Some isoflavones were hydrogenated with bad yields, while 5,7,4`-trimethoxyisoflavone was hydrogenated within 5 min with a yield of 70%. An attempt was made to hydrogenate genistein, but it resulted in an inseparable mixture of compounds.



Scheme 13

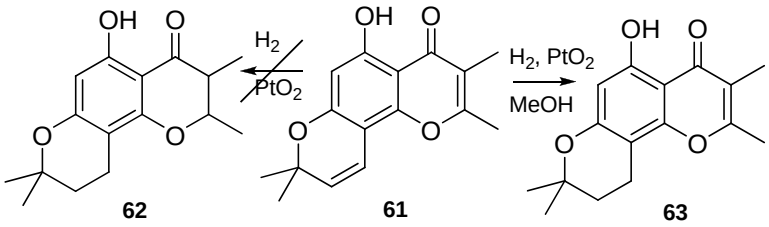
Methylated formononetin (7,4′-dimethoxyisoflavone) was proven to be not reducible by Na/Hg and by hydrogen in EtOH on PtO_2[81]. However, it was hydrogenated in AcOH on PtO_2.

Hydrogenation over PtO_2 often goes with overreduction. M. Suzuki et al.[82],[83] report about a phenyl-ring reduction (with double-bond and carbonyl groups) of flavones. Flavan and flavone were hydrogenated by S. Mitsui[84] in AcOH over PtO_2 under 1 bar of hydrogen to dodecahydroflavan. On the other hand, Albert Mondon et al.[85] have reduced Chromon A **58** on PtO_2 (Adams), and chromanone **59** is only the side-compound, while the yield of **60** is 73%.



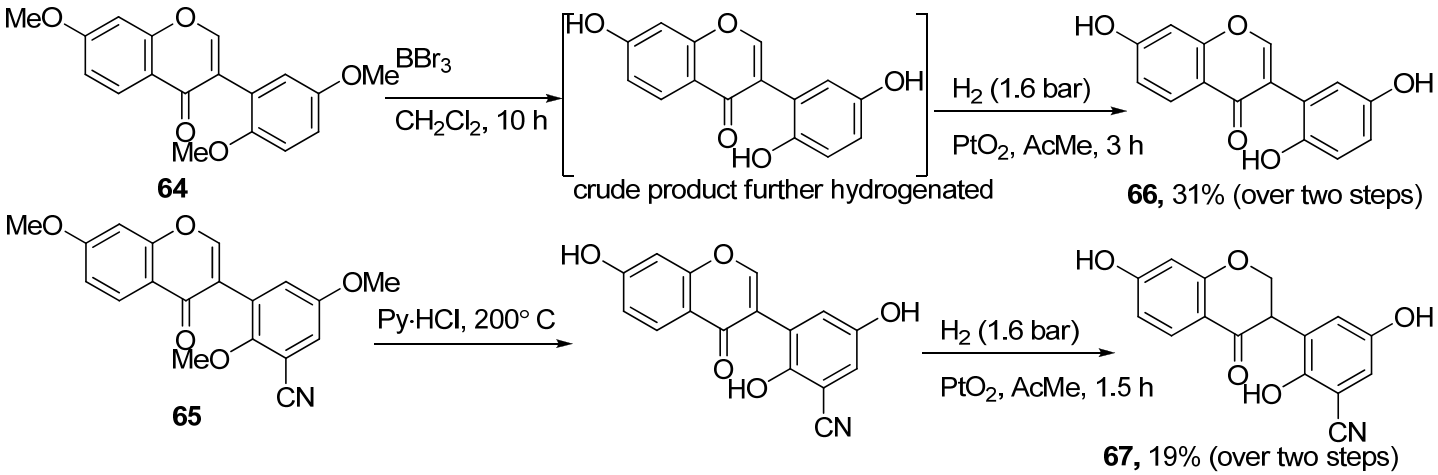
Scheme 14

K.S. Rehder and J. Kepler[62] could not hydrogenate **61** to **62** over PtO_2, only **63** was obtained. Unfortunately, they do not provide an information about the solvent for the former hydrogenation.



Scheme 15

Patent[86] describes the hydrogenation of isoflavone **64** and **65** to give the corresponding isoflavanone **66** and **67**. The methylated compounds were first demethylated and then without purification or after column chromatography hydrogenated over PtO_2.



Scheme 16

Table 3. Summary table of chromones' hydrogenation on platinum. If otherwise not stated, the product is the corresponding 4-chromanone.

Substrate	p(H_2), bar	solvent	yield, %	time	additional information	ref.
3-methylchromone	N/A	EtOH	66	27.2 h	Pt black used. With overreduction, only 50% conversion of educt, not synthetical article, reaction mixture was analyzed by GLC	[78]
7-methoxychromone **53** , **54**	N/A	AcOH	60, 50, resp.	N/A	Pt black used	[79]
7-acetoxy-4`-methoxy-2-methyl-, 7,4`-diacetoxy-2-methyl-, 2-methyl-7,4`-dimethoxy-, 7,4`-dimethoxy-, 5,7,4`-trimethoxyisoflavone	1	AcOH	27, 33, 27, 70	0.5 h, night, 5 min	PtO_2 used	[80]
7,4′-dimethoxyisoflavone	N/A	AcOH	70	12 min	PtO_2 used	[81]
Chromon-A **58**	N/A	MeOH	9	N/A	PtO_2 used, chromanon is side-compound of hydrogenation	[85]

64	1.6	AcMe	31	3 h	first demethylated, then hydrogenated, yield of **66** or **67** over two steps, PtO_2 used, patent, reactions are given as examples	[86]
2,5-dihydroxy-3-(7-hydroxychromone-3-yl)benzonitrile (derivative of **65**)	1.6	AcMe	19	1.5 h		[86]
luteolin (5,7,3`,4`-tetrahydroxyflavone)	2-2.5	EtOH	31	5 h	PtO_2 used, the crude product was acetylated, and tetraacetate isolated	[87]
7,8-dimethoxychromone	N/A	AcOH	100	N/A	Pt black used	[88]
6-methoxy-2-methylchromone	3.44	EtOH/ HCl	6	N/A	PtO_2 used	[89]
3-dimethylaminomethyl-7-methoxychromone hydrochloride	3.44	EtOH	1.5	N/A	PtO_2 used	[90]
7-acetyloxychromone	N/A	AcOH	74	N/A	Pt black used	[91]
N,N-diethyl-chromone-2-carboxamide	N/A	EtOH	58	N/A	PtO_2 used	[92]
7-carboxymethyl-5-chloro-3-phenylchromone	N/A	MeOH	40	N/A	PtO_2 used, patent, reaction is given as an example	[93]
6-fluoro-N-((S)-1-phenylethyl)-chromone-2-carboxamide	7	EtOH	84	N/A	Pt/C with $MeSO_3H$ was used, de 60%, patent, reaction is given as an example	[94]
6-fluorochromone-2-carboxylic acid	7	EtOH	89	N/A	Pt/C was used, patent, reaction is given as an example	[95]
N-(1-phenylethyl)-chromone-2-carboxamide	5.5	AcOH	77	N/A	Pt/C used, 50 °, patent, reaction is given as an example	[96]
isoflavone, 7-hydroxy-, 7-methoxy-, 6-hydroxy-, 6-methoxy-, 7-hydroxy-4′-methoxy-, 7-acetoxy-3′,4′-methylenedioxy-, 7-methoxy-3′,4′-methylenedioxy-, 5,7-dimethoxyisoflavone	1	AcOH	50, 60, 20, 60, 30, 40, 60, 20, 75, resp.	7-55 min	PtO_2 used, isoflavanone was isolated through formation of semicarbazone with further hydrolisis	[97]
7,2`,4`-trimethoxyisoflavone	1	AcOH	35	56 min	PtO_2 used	[98]

In summary, the hydrogenation of chromones over Platinum-derived catalysts is very solvent-dependent. The best conditions are the use of acetic acid as a solvent, and "titration with hydrogen", until one equivalent is absorbed. In alcoholic solvents this hydrogenation often fails to complete, sometimes also fails to start. The latter peculiarity could allow the side-chains hydrogenation of the appropriate substrates.

1.1.1.4 With Raney-Nickel

Table 4 presents the information about chromones' hydrogenation on Raney-Nickel that gives chromanones. Here, hydrogenation means that hydrogen as a gas was involved in the reaction, although a reduction is also possible in case of Raney-Nickel (reaction without gaseous hydrogen or some other sources of hydrogen, other that Ni_{Ra}).

7-Hydroxychromone and 6-ethyl-7-hydroxychromone were hydrogenated on Raney-Nickel with high yields (79 and 88%, resp.)[99]. 7-hydroxychromanone obtained was further hydrogenated on Raney-Nickel to give 7-hydroxychroman.

The hydrogenation of chromones on Raney-Nickel is not used often because the result of such a reduction is not well predictable. S. Mitsui et al. [84] report about the reduction of flavone and flavan to 2-(3-phenylpropyl)phenol with 95% yield (in presence of traces of NaOH). V. Ramanathan and K. Venkataraman[100] made reductive detosylation of 5-hydroxy-7-tosyloxyflavone and 5-hydroxy-3-methoxy-7-tosyloxyflavone by hydrogen on Raney-Nickel (without chromone-ring reduction). J.E. Gowan et al.[101] also made reductive detosylation of 5-tosyloxyflavone, but have isolated only a mixture of α- and β-4-hydroxyflavans. C. I. Jarowski et al.[102] report that the hydrogenation of ethyl 5-hydroxychromon-2-carboxylate on Raney-Nickel needed more than the required amount of hydrogen, although the starting compound was recovered alone with chromanone. M. Tsukayama et al.[103, 104] report about the reduction of triple bond (without hydrogenation of chromone ring) of 8-(3-methyl-3-hydroxybutynyl)-5,7,4'-tribenzyloxyisoflavone with hydrogen over Raney-Nickel.

Table 4. Summary table of chromones' hydrogenation on Raney-Nickel. If otherwise not stated, the product is the corresponding 4-chromanone.

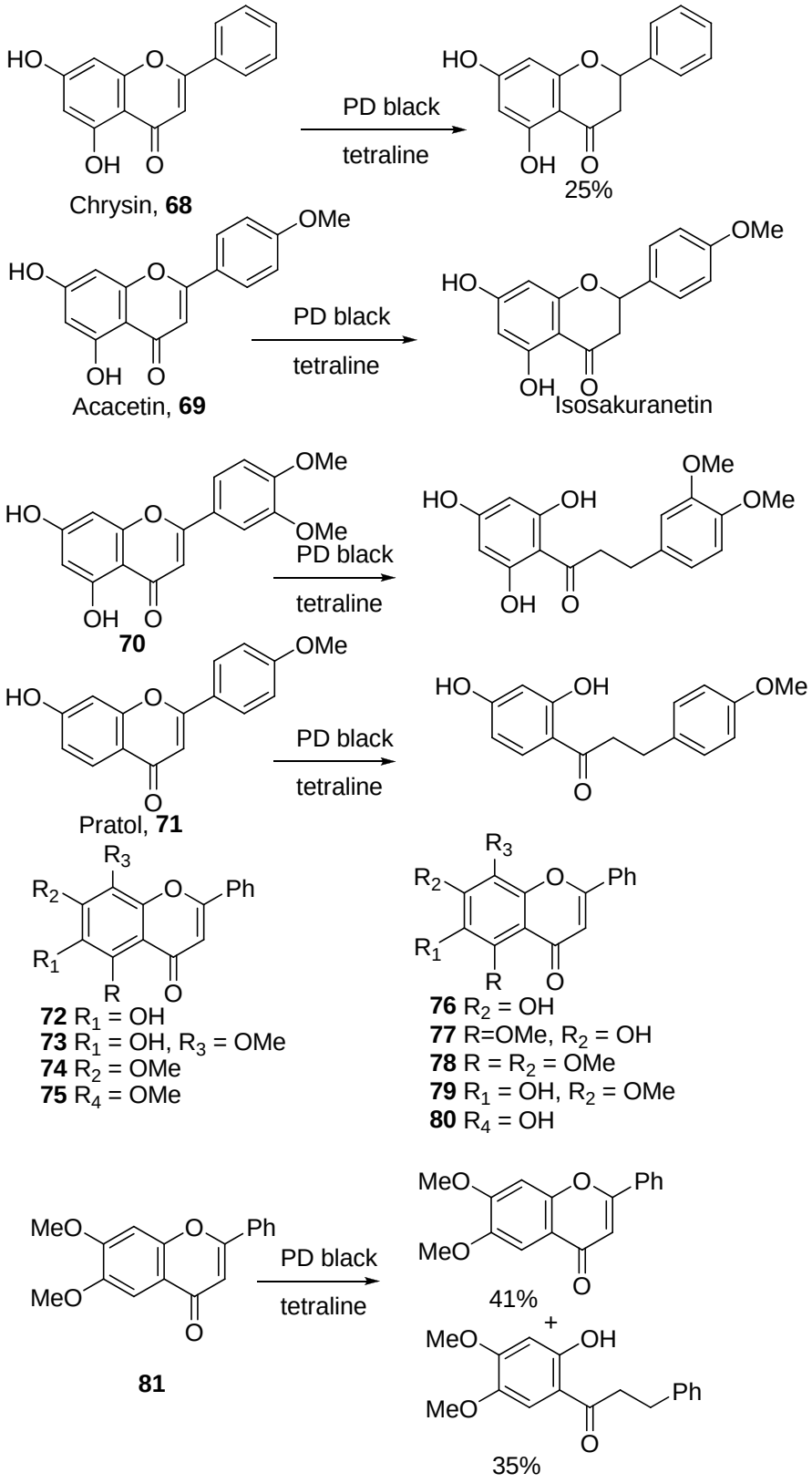
Substrate	$p(H_2)$, bar	solvent	yield, %	time	additional information	ref.
2-methylchromone, 3-methylchromone	N/A	EtOH	94, 90, resp.	0.1 h	With overreduction, only 50% conversion of educt, not synthetical article, reaction mixture was analyzed by GLC	78
6-ethyl-7-hydroxychromone	N/A	EtOH	88	3,5 h	45º	99
7-hydroxychromone	N/A	EtOH/ MeOH	79	3 h		99, 105
5-hydroxychromon-2-carboxylic acid ethyl ester	2	EtOH	44	10 min	80º, part of starting compound recovered	102
2'-benzyloxy-6-(3-hydroxy-3-methylbutynyl)-7-methoxy-4',5'-methylenedioxyisoflavone	N/A	MeOH	77	N/A	20ºC, with hydrogenation of triple C≡C bond	104
ethyl 7-(5-(4-acetyl-3-hydroxy-2-propylphenoxy)pentyloxy)-4-oxo-8-propylchromone-2-carboxylate, 2-carboethoxy-7-[5-(2-n-propylphenoxy)pentoxy]-8-n-propylchromone	1.13	EtOH, THF/ EtOH	51, 89 resp.	7 h, 30 min	patent, reactions are given as examples	106
2-ethylchromone	100-200	EtOH	30	16 min	120-130ºC	107

1.1.2 Transfer hydrogenation of chromones on palladium

This type of hydrogenation does not involve hydrogen in form of a gas, but uses the other reducing compounds. The reaction is an abstraction of hydrogen from the reducer onto catalyst with subsequent hydrogenation of the oxidizer (substrate). There is an interesting review[108] dedicated to such a method of hydrogenation. Among the reducing reagents isopropanol, dioxane, cyclohexene, formic acid, ammonium formate, triethylamine and complexes of formic acid with triethylamine are the best known ones.

Table 5 presents the information about chromones' catalytic transfer hydrogenation (CTH) that gives chromanones-4. If not stated otherwise, 10% Pd/C was used as a catalyst.

J. Massicot et al.[109] have found that chrysin **68** and acacetin **69** could be hydrogenated by tetraline, catalyzed by Pd black, to give the corresponding isoflavanones. The CTH of the structurally similar **70** and **72** yielded the corresponding dihydrochalcones. In their further publication[110] the regularities of product formation were found. The flavones **72-75** were reduced to the corresponding flavanones, while the compounds **76-80** – gave the dihydrochalcones. Compound **81** was reduced to the mixture of flavanone and dihydrochalcone.



Scheme 17

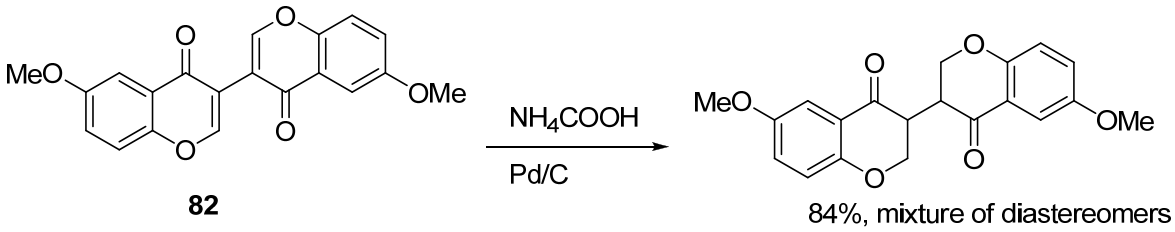
3-Imidazolylchromone was reduced by natrium hypophosphite over 10% Pd/C[111] with yield of 53%.

The authors of the article[112] have investigated CTH of isoflavone. They report that cyclohexene and isopropanol are ineffective in this reaction. The use of such systems as sodium formate – fomic acid, ammonium formate and triethylamine – formic acid was studied. Although isoflavone could be reduced by all three systems, the highest yield was 62%.

K. Wähälä and T.A. Hase[113] report that the yields are not very high because of flavan-4-ol formation. The latter is not too stable and undergoes further transformations. In the series of flavones' reductions they have synthesized flavanones with yields of 52-60% and also have isolated flavan-4-ols with yields of 13-21%.

Korean researcher[114] have reduced the isoflavone using ammonium formate and Pd/C in EtOH within 2 h with a yield of 94%. The prolongued reaction time (12 h) leads to isoflavonol formation[115]. The same authors report that CTH of flavone in MeOH by ammonium formate over Pd/C during a day is very unselective and gives eight compounds[116].

In order to establish a structure of biologically active flavonoid from *Aloe barbadensis* R. Hong et al.[117] have reduced compound **82**. They have found out that **82** was sparingly reactive under the standard catalytic hydrogenation. If it had been stored in a refrigerator, it could be hydrogenated by CTH. Hydrogenation of **82** stored at room temperature did not occur.



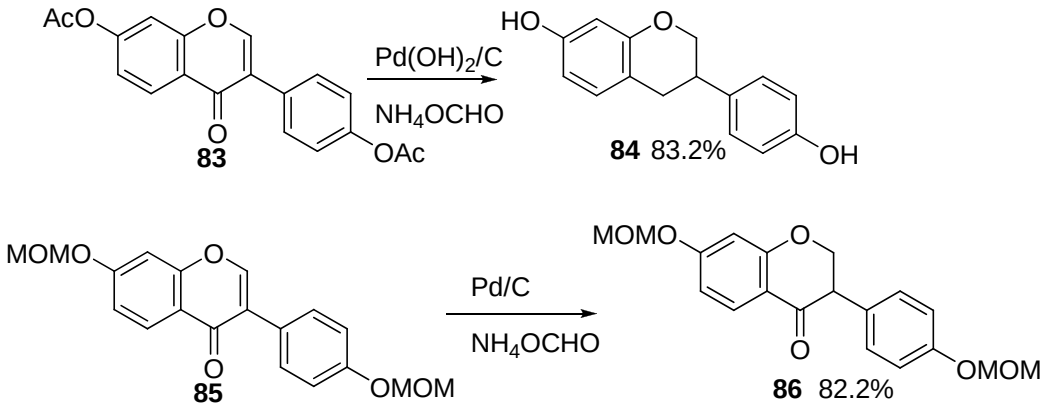
Scheme 18

S. K. Sabui et al.[118] have prepared a series of 9 lipophilic chromones (without OH-groups) in order to perform hydrogenation in CTH-conditions. They report about very high yields (93-95%), and only one compound (2,3,7-trimethylchromone) was hydrogenated with a 70% yield and 15%-recovery of the starting compound. In case of 7-methylflavone no chromanone is obtained, but 1-(2-hydroxy-4-methylphenyl)-3-phenylpropan-1-one is synthesized. In the other article[119] they inform about CTH of ethyl 7-methyl-6-methoxychromone-2-carboxylate to the corresponding chromanone with a 75% yield, while hydrogenation on Pd/C leads to chromanol which was oxidized to chromanone with Jones' reagent (70% yield).

H.G. Krishnamurty et al.[120] report about debenzylation of phenyl-benzyloxy ethers using CTH. The 7-benzyloxyisoflavone was deprotected and hydrogenated to 7-hydroxyisoflavanone, while 5-hydroxy-7-benzyloxyflavone was only deprotected. Similar transformation of 2`,4`-dibenzyloxy-7-methoxyisoflavone (hydrogenation with debenzylation) is reported by American scientists[121].

The similar CTH of side-chain of 2-stirylchormones is known. The chromone ring was not affected, only the 2-stiryl substituent[122].

An interesting reaction was found in patent[123]. 7,4`-diacetoxyisoflavone **83** was converted to rac-equol **84** in AcOH by ammonium formate, using $Pd(OH)_2/C$. In this reaction, ammonium formate played a role as a reducing reagent and also performed deacetylation since acetamide was detected. The similar 7,4`-bis(methoxymethoxy)isoflavone **85** was hydrogenated to the corresponding isoflavanone **86** by ammonium formate on Pd/C[124].



Scheme 19

Table 5. Summary table of chromones' catalytic thransfer hydrogenation. If otherwise not stated, the product is the corresponding 4-chromanone, and a catalyst - 10% Pd/C.

Substrate	reducing reagent	solvent	yield, %	time	additional information	ref.
7-benzyloxychromone	NaCOOH	MeOH/ AcOH	61	5 h	reflux, with debenzylation	63
68, 69	tetraline	tetraline	25, N/A, resp.	N/A	210º C, Pd black used, not reacted chrysin partially recovered	109
72, 73, 74, 75, 81	tetraline	tetraline	20, 16, 24, 4, 41, resp.	N/A	210º C, Pd black used, not reacted substrate partially recovered, **81** yilded dihydrochalcone with yield of 35%	110
3-(imidazol-1-yl)chromone	NaH_2PO_2	aqueous EtOH	53	16 h	reflux	111
7-hydroxy-, 7-methoxy-, 5,7-dihydroxy-, 5,7,2`,4`-tetramethoxy-, 5,7,2`,5`-tetramethoxyisoflavone	HCOOH	MeOH	40-62	3 h	reflux	112
	NH_4OCHO	MeOH	52-60	3-4 h	reflux	112
	NEt_3-HCOOH	no solvent	50-54	3 h	100º	112
7-hydroxy-, 7,41-dihydroxy-, 7-	NH_4OCHO	MeOH	52-60	2 h	reflux, isoflavanols isolated	113

hydroxy-4`-methoxy-, 7,4`-dihydroxy-3`-methoxy-, 5,7,4`-trihydroxyisoflavone					with yield 13-21%	
isoflavone	NH_4OCHO	EtOH	94	2 h		[114]
3,3`-bis(6-methoxychromone) **82**	NH_4OCHO	THF/MeOH 4/1	85	6 h	although reaction was carried out at r.t., the substrate must be precooled	[117]
7-metyl-, 2,7-dimethyl-, 3-methyl-, 7-methyl-3-methoxy-, 2-methyl-3-methoxychromone, 6-chloro-3-(1,3-dioxolan-2-yl)-chromone	NH_4OCHO	MeOH	93-95	2-7 h	reflux	[118]
7-methylchromone-2-carboxylic acid ethyl ester	NH_4OCHO	MeOH	95	5 h	reflux, transesterification took place, methyl ester of chromanone-2-carboxilyc acid isolated	[118]
2,3,7-trimethylchromone	NH_4OCHO	MeOH	70	10 h	reflux, 15% of starting compound recovered	[118]
7-methyl-2-phenylchromone	NH_4OCHO	MeOH	95	2 h	1-(2-hydroxy-4-methylphenyl)-3-phenylpropan-1-one is synthesised	[118]
7-methyl-6-methoxychromone-2-carboxylic acid ethyl ester	NH_4OCHO	EtOH	75	6 h	reflux	[119]
7-benzyloxyisoflavone	HCOOH/ NaCOOH	MeOH	54	2 h	with debenzylation	[120]
2`,4`-dibenzyloxy-7-methoxyisoflavone	NH_4OCHO	AcMe/ MeOH 10/1	78	8 h	mixing of reagents at 0º C, then stirring at r.t.	[121]
7,4`-bis(methoxymethoxy)-isoflavone **85**	NH_4OCHO	MeOH	82.2	5 h	substrate load – 336.5 g, patent, reaction is given as an example	[124]
7,4`-dihydroxyisoflavone (daidzein)	NH_4OCHO	MeOH	71	2 h	reflux, reproducing from[112], patent	[125]
5,7,4`-trihydroxy-isoflavone (genistein)	NH_4OCHO	MeOH	59	N/A		[126]
isoflavone, 7,4`-dihydroxyisoflavone (daidzein)	NH_4OCHO	N/A	N/A	N/A	no synthetic procedure available	[127]
7,4`-dihydroxyisoflavone (daidzein)	NH_4OCHO	MeOH	N/A	2 h	65º	[128]

In summary, CTH is a good alternative to catalytic hydrogenation. Its disadvantages are the strong dependence from the catalyst and hydrogenation of unsaturated side groups or debenzyation. Since an excess of the reducing reagent must be used, selective debezylation/side group reduction usually is not possible. On the other hand, sometimes the stepwise reduction process allows to quench the reaction after the certain bond is reduced before the overreduction is started.

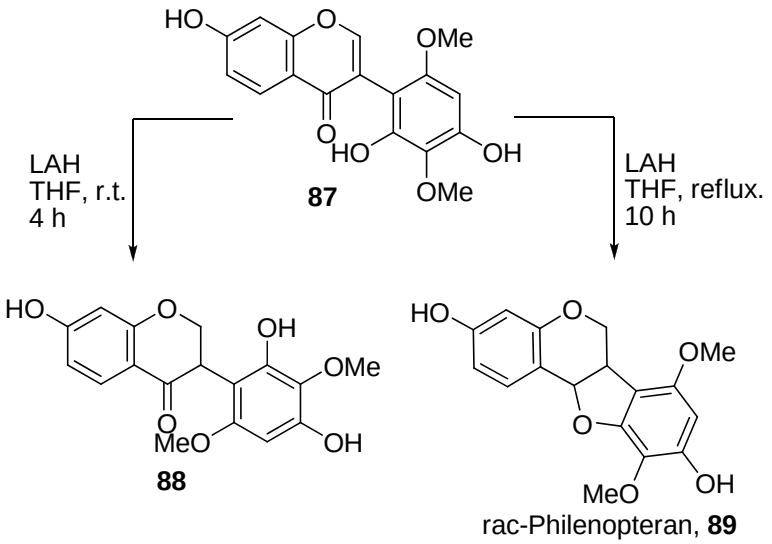
1.1.3 Reduction of chromones with complex hydrides

Table 6 presents the information about chromones' reduction with complex hydrides that gives chromanone.

The typical product of chromones' reduction by complex hydrides of aluminium and boron are chromanols, although further reduction is also possible (see[111, 129-132]). G. P. Thakar et al.[2] have studied the reduction of chromones and coumarins by BH_3 and $NaBH_4$ in presence or absence of Lewis acids. Although many products could be obtained by varying the solvent, reducing reagent and by adding Lewis acids, chromanones were not isolated.

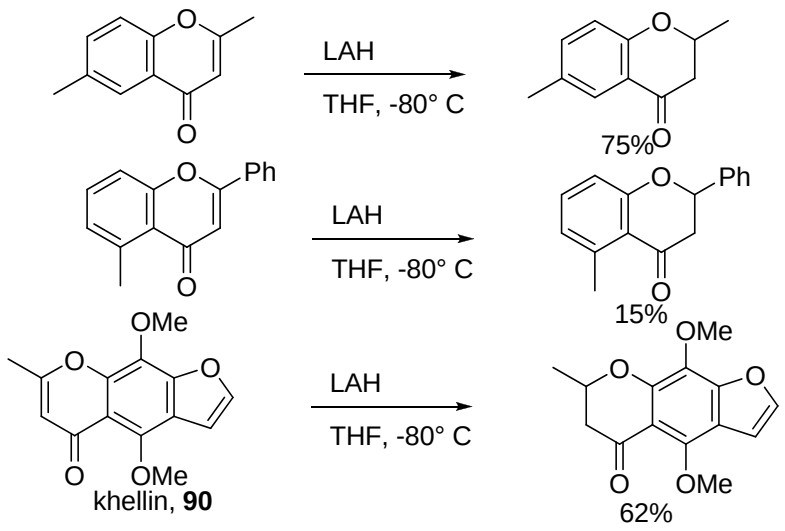
The flavanone could also be obtained from flavanol, e.g. by oxidation with Jones' reagent[18, 71-73, 133].

Several articles[31, 73, 131] and one patent[58] report about chromanones' synthesis from chromones with LAH. E. Toth et al.[131] made selective deuteration of 2`-methoxymethoxyisoflavone with $LiAlD_4$. It is interesting that the carbonyl group of 2`-methoxymethoxyisoflavanone was further reduced by $NaBH_4$. L. Farkas et al.[31] have reduced **87** to **88** by LAH in mild conditions, while refluxing in THF during 10 h leads (after acidification) to rac-philenopteran **89**. Obviously the latter product should be produced from isoflavanol.



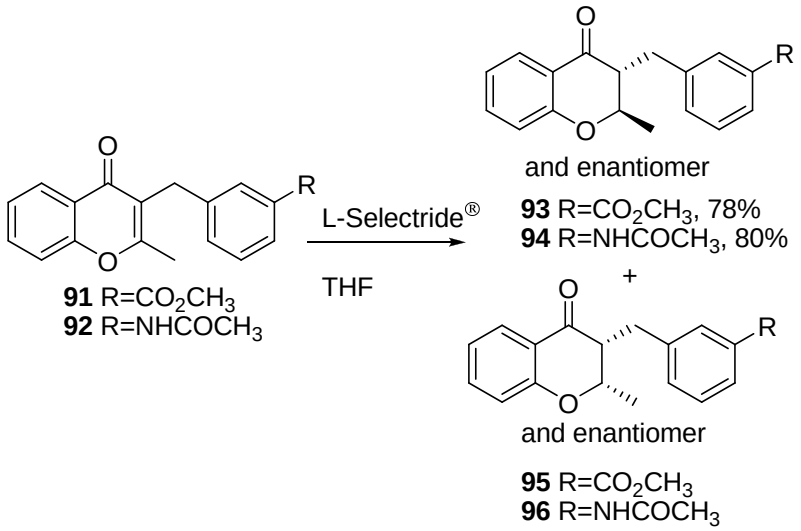
Scheme 20

O. Dann and G. Volz[73] report about selective reduction of 2,6-dimethylchromone, 5-methylflavone and khellin **90** by LAH.



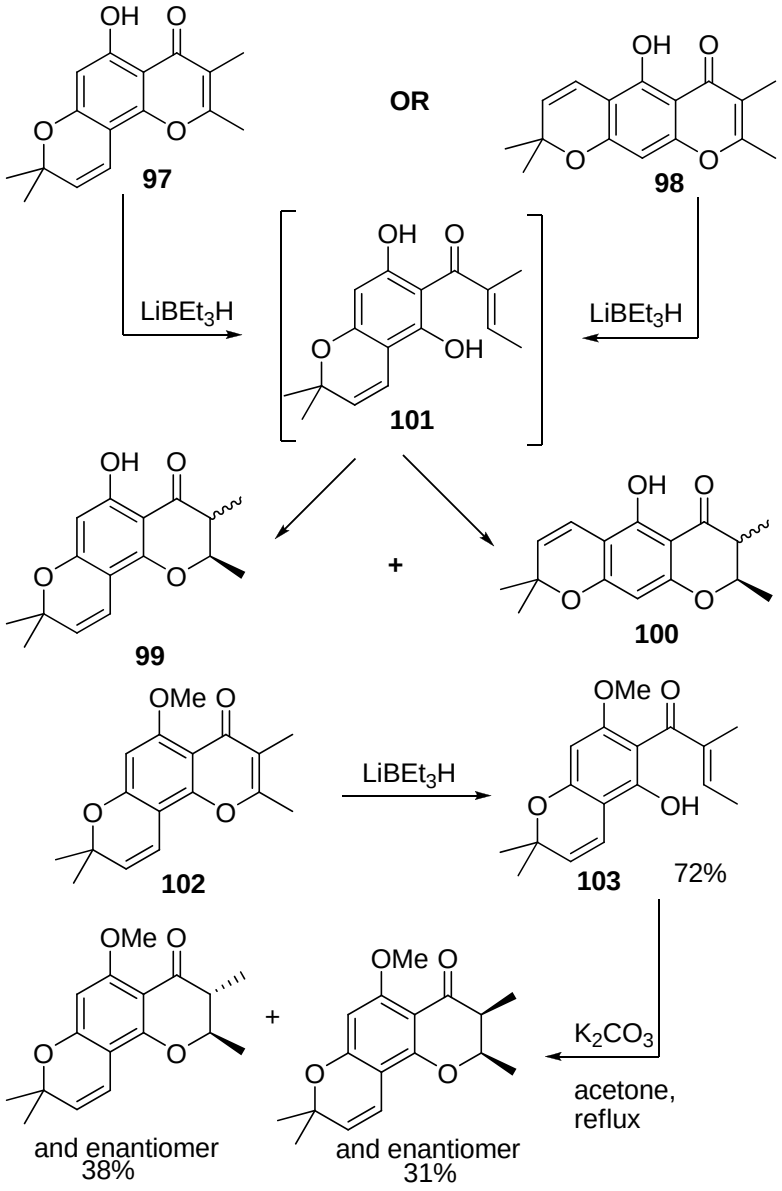
Scheme 21

R.J. Chambers and A. Marfat[134] have performed a reduction of **91** and **92** with L-Selectride® (Li[B(*s*-Bu)$_3$H]). If the reduction was carried out at -78ºC, only trans-products **93** and **94** were obtained, while reduction at 0º C or epimerization with NaOMe in methanol gave the mixture of diastereomers **93**+**95** or **94**+**96**, respectively. Several isoflavones were reduced with L- and K-Selectride by A.K. Salakka et al.[5]



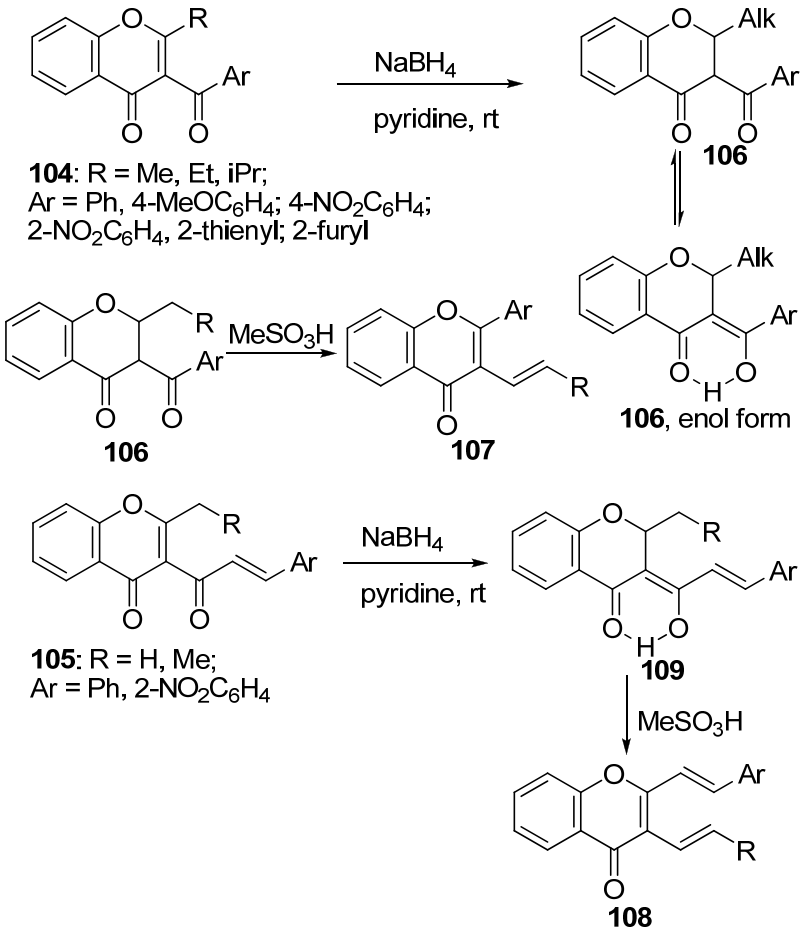
Scheme 22

K.S. Rehder and J. Kepler[62] have reduced **97** and **98** by Li[BEt$_3$H]. Each compound yields four chromanones (cis- and trans-**99** and **100**), probably because of chalcone **101** formation as intermediate. **102** was reduced by this method to chalcone **103**, the latter was cyclized by K_2CO_3 to give the mixture of diastereomeric chroman-4-ones.



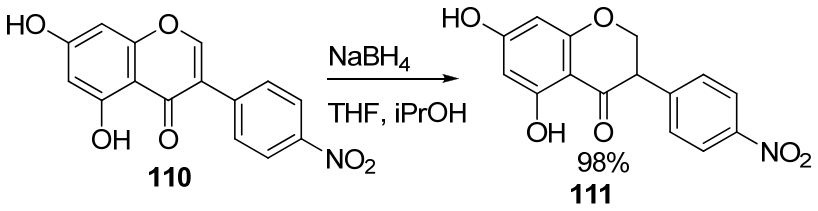
Scheme 23

Sometimes it is also possible to reduce chromone by natrium borohydride to chromanone[135, 136]. D.S. Clarke, C. D. Gabbutt et al.[137] report about a series of reductions of 3-aroyl-2-alkylchromones **104** and of 3-cinnamoyl-2-alkylchromones **105** by $NaBH_4$ in pyridine. The aim compounds **106** are rearranged by $MeSO_3H$, *via* retro-Michael ring cleavage to chromones **107**. Interesting 2,3-dialkenylchromones **108** were obtained after similar rearrangement of **109**. Earlier this method has succefully been applied for xantones[136].



Scheme 24

5,7-dihydroxy-4`-nitroisoflavone **110** was reduced with excellent yield (98% of **111**) by applying 1.1 eq of $NaBH_4$[138], hence no overreduction took place.



Scheme 25

G. Mouysset et al.[61] have performed the reduction of methyl 6,7-dialkylchromone-2-carboxylates to the corresponding 6,7-dialkyl-2-oxymethylchromones, thus $NaBH_4$ did not reduce the chromone ring but only affected the ester side-group. The same was made by M. Payard and J. Couquelet[139] with methyl chromone-2-carboxylate.

J.M. Khurana and S. Chauhan[140] report that flavone, 2-methylchromone and 7-methoxyisoflavone could not be reduced by $NaBH_4$ in methanol. They have reduced these chromones by nickel boride (see section 1.1.6).

Some articles report about the selective keton-group reduction with complex hydrides. In such a reaction 2,3-double bond is not reduced. It was made by LAH[141], by $NaBH_4$ with $CeCl_3$[142] and by 9-BBN with (-)-α,α-diphenylpyrrolidinemethanol[143].

Table 6. Summary table of chromones' reduction with complex hydrides. If otherwise not stated, the product is the corresponding 4-chromanone.

Substrate	reducing reagent	solvent	yield, %	time	additional information	ref.
isoflavone, 7-methoxyisoflavone, 7, 4`-dimethoxyisoflavone	L- or K-Selectrid®	THF	96, 84, 82, resp.	N/A	- 72 °	5
2`,4`,7-trihydroxy-3`,6`-dimethoxy-isoflavone **87**	LAH	THF	N/A	4 h	r.t.	31
5,7-dihydroxy-3-(5-methoxy-2,2-dimethyl-2*H*-1-benzopyran-6-yl)-4*H*-1-benzopyran-4-one	$NaBH_4$	THF/EtOH 1/1	2.5	3 days	DIBAL was much more effective for similar substrate, see[49]	49
6,7-dichloro-2-methylchromone, 6,7-dichloro-2-trifluoromethylchromone	LAH	THF	84, 86	1 h, 3 h	-78º, patent, reaction is given as an example	58
97, **98**	$LiBEt_3H$	N/A	N/A	N/A	no synthetic procedure is reported, reduction is very unselective	62
102	$LiBEt_3H$	THF	72 (chal-cone)	15 min	chalcone synthesised, chromanone is obtained after chalcone's cyclization by K_2CO_3	62
2,6-dimethylchromon, 6-methylflavone and khellin **90**	LAH	THF	75, 15, 62, resp.	6 h	-80º	73
2`-methoxymethoxyisoflavone	LAH, $LiAlD_4$	THF	60	N/A	-55-60º	131
3-(6-methoxy-2-methylchromone-3-yl methyl)-benzoic acid methyl ester, N-[3-(6-methoxy-2-methylchromone-3-yl methyl)-phenyl]acetamide	L-Selectrid®	THF	79, 80 resp.	30 min	-78º, yielded only trans-product, at 0º - sum of cis- and trans-products	134
4-methoxy-5H-furo[3,2-g]chromen-5-one	$NaBH_4$	EtOH	76	1 h		135
2,3,4,9-tetrahydro-1H-xanthene-1,9-dione, 2,3,4,9-tetrahydro-3-methyl-1H-xanthene-1,9-dione, 2,3,4,9-3,3-dimethyl-tetrahydro-1H-xanthene-1,9-dione	$NaBH_4$	pyridine	100,85, 78 resp.	3 h	obtained structures are in enol-form	136
2-methyl-3-(4-nitro-benzoyl)chromone	$NaBH_4$	pyridine	80	2 h		137
104, 105	$NaBH_4$	pyridine	52-85	2 h	exact yields are not reported	137
5,7-dihydroxy-4`-nitroisoflavone **110**	$NaBH_4$	THF/2-propanol	98	1 h	0º C	138
7,2`,4`-tris(methoxymethoxy)isoflavone	L-Selectrid®	THF	74 (borsm)		-55º C	144
7-hydroxy-3-benzoylflavone	$NaBH_4$	N/A	55	N/A	no synthetic procedure available	145

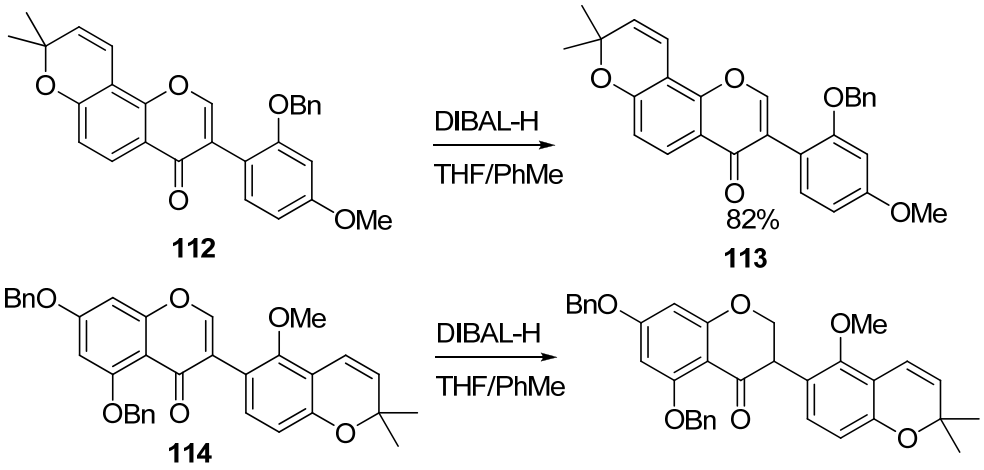
In summary, the use of complex hydrides, unless they are not sterically hindered (as Selectrides), is not reasonable for chromanones' synthesis. Although there are some

exceptions it usually leads to chromanols. On the other hand, the chromones which bear an EWG in the 3rd position can be smoothly reduced by $NaBH_4$.

1.1.4 Reduction of chromones with diisobutylaluminium hydride

The reduction with metallohydrides is closely coupled with the reduction with complex hydrides. It does not involve salt-like complex hydrides but the neutral metallohydrides. Concerning the chromones only the use of DIBAL-H is reported. Table 7 presents the information relevant for this section.

DIBAL-H was used in the synthesis of rotenoids[146],[147] and isoflavanones[130], [148]. S. Antus et al.[148] report about the reduction of a series of chromones with high (87-90%) or moderate (57%) yields. With such a method benzyloxychromone could be reduced without deprotection[148]. **112** was converted to **113** without side-chain reduction and without debenzylation[3]. **114** was also cleanly reduced to the corresponding isolfavanone by DIBAL-H[49].



Scheme 26

K. Salakka, T.H. Jokela and K. Wähälä[5] have performed the reduction of many isoflavones by DIBAL-H. The comparison with L- and K-selectrides shows that selectrides are ineffective in most cases (see table 7). The selectrides were more effective only in case of isoflavone.

Table 7. Summary table of chromones' reduction with DIBALH. If otherwise not stated, the product is the corresponding 4-chromanone.

substrate	solvent	yield, %	time	Additional information	ref.
112	THF/PhMe	82	1 h	-65° C. Product: **113**	[3]
2`,3`,8-tribenzyloxy-4`,5`,7-trimethoxyisoflavone, 2`,3`-dibenzyloxy-4`,5`,7-trimethoxyisoflavone, 2`,8-dibenzyloxy-3`,4`,7-trimethoxyisoflavone,	THF/PhMe	66, 52, 61, 58, 57, resp.	5 h	-60° C	[4], [149]

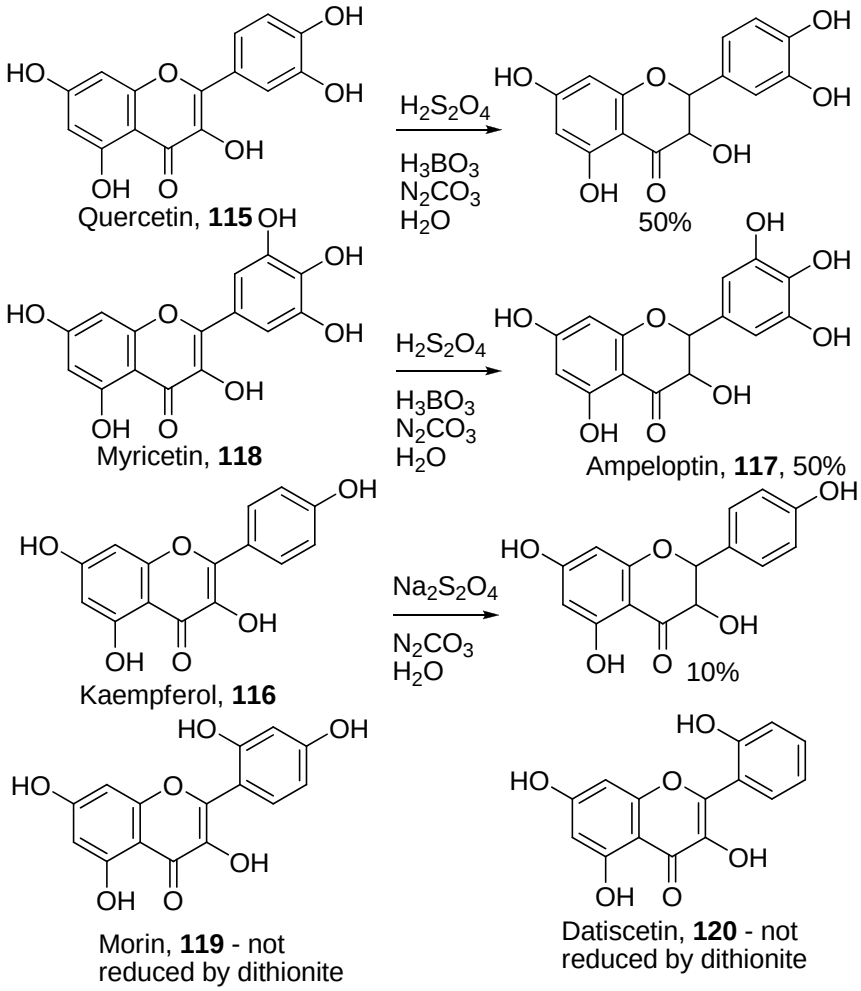
2`,3`,4`,8-tetrabenzyloxy-6`,7-dimethoxyisoflavone, 2`,3`,4`-tribenzyloxy-6`,7-dimethoxyisoflavone					
isoflavone	THF/PhMe	72	N/A	-72º C (yield of 96% in case of selectride)	[5]
7-hydroxyisoflavone, 7,4`-dihydroxyisoflavone, 5,7,4`-trihydroxyisoflavone	THF/PhMe	68, 70, 50, resp.	N/A	-72º C (selectride – ineffective)	[5]
7-hydroxy-4`-methoxyisoflavone, 5,7-dihydroxy-4`-methoxyisoflavone	THF/PhMe	60, 57, resp.	N/A	-72º C	[5]
114	PhMe/THF 2/1	81	30 min	-70º C	[49, 150]
7,4`-dibenzyloxy-2`,3`-dimethoxyisoflavone	PhMe/THF 1/1	80	1 h	-65º C	[130]
7,4`-bis(methoxymethoxy)isoflavone, 7,2`,4`-tris(methoxymethoxy)isoflavone, 2`-(2-methoxyethoxy)methoxy-7,4`-bis(methoxymethoxy)isoflavone	PhMe/THF 1/1	93, 87, 81, resp.	3.5	-60º C, during 2.5 h warming to -45º C, quench with $NaKH_4C_4O_6$, warming to -10º C, then 1 h stirring	[144]
7,2`,4`-tris(methoxymethoxy)isoflavone	PhMe/THF 1/1	75	2.5	quench by methanol	[144]
2-isopropyl-8,9-dimethoxy-1,2-dihydrochromeno[3,4-b]furo[2,3-h]chromen-6(12H)-one (dehydroisorotenone)	PhMe/THF	32	1 h	-78º, epimerisation of crude compound is made	[146]
5,6-dihydro-12H-benzo[a]xanthen-12-one	N/A	54 (cis) + 20 (trans)	N/A	no synthetic procedure is provided	[147]
7-methoxyisoflavone	PhMe/THF 2/1	90	1 h	-65º C (yield of 57% in [5], 84% with selectride[5])	[148]
7,4`-dimethoxyisoflavone	PhMe/THF 2/1	87	1 h	-65º C (yield of 54% in [5], 82% with selectride[5])	[148]
7,4`-dimethoxy-, 5,6,7-trimethoxy-, 8-methyl-5,7-dimethoxy-, 7-methoxy-2-methyl-isoflavone, 7-benzyloxychromone	PhMe/THF 2/1	87, 89, 75, 21+42, 57, resp.	1 h	-65º C	[148]

DIBAL is very effective and selective for reduction of chromones even if the latter have phenolic OH-groups.

1.1.5 Reduction of flavonols with sodium dithionite

In his pioneer work, John C. Pew[151] has reported about the reduction of quercetin **115** by sodium dithionite ($Na_2S_2O_4$) in aqueous Na_2CO_3 (45% yield, 15 min heating). The same strategy was applied for the reduction of kaempferol **116**[152] and for the preparation of ampeloptin **117** from myricetin **118**[153] (yield 10%). Japanese scientists[154] improved his synthesis by applying dithionous acid in borate buffer, thus reducing quercetin **115** and myricetin **117**. This modification gave the corresponding chroman-3-ol-4-ones with yields of 50%. The procedure of Pew[151] was reproduced several times[155, 156]. It is not applicable for morin **119**, datiscetin **120** and some other flavonols[156].

S. Ramanujan and T.R. Seshadri[48] reported that sodium metabisulphite ($Na_2S_2O_5$) is inappropriate for the reduction of prunetin.



Scheme 27

1.1.6 Other methods for the reduction of chromones

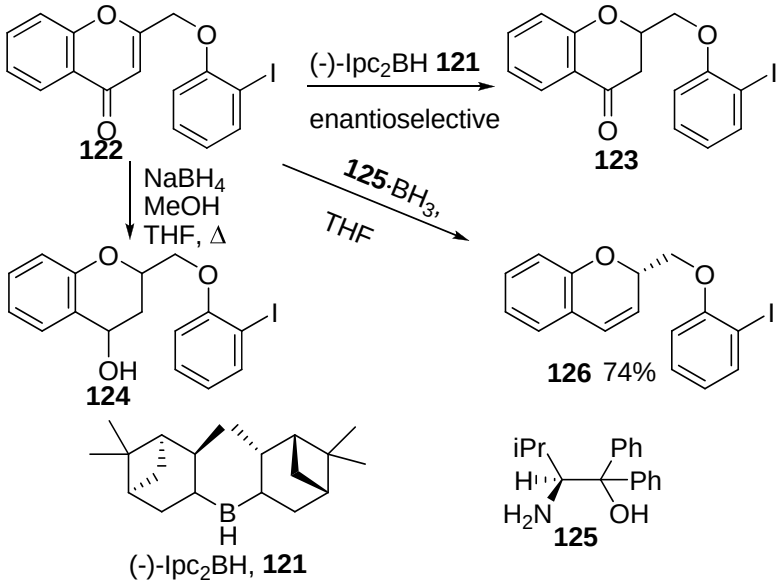
In this section the methods are rewieved which are represented only by a few articles. Table 8 represents the information about chromones' reduction by the other methods.

Japanese scientists[78] have tested Raney-Co, Raney-Ni, Ru black, Rh black, Pd black, Os black, Ir black and Pt black in hydrogenation of 2-methyl- and of 3-methylchromone. After the conversion of chromone had achieved 50%, the reaction was quenched and analysed by GLC. The products were not isolated. No catalyst was selective for chroman-4-ones formation, and an overreduction usually took place.

A.C. Jain et al.[157] report about isoflavones' reduction by NaHTe. The latter reagent was prepared *in situ* from elemental tellurium and $NaBH_4$.

Bulky secondary boranes, namely disiamylborane, catecholborane and dicyclohexylborane, were tested in the reduction of chromone[132]. The latter was reduced with poor yields (12-33%), while the application of 9-BBN resulted in formation of 2H-chromene.

S. A. Ahmad-Junan[158] has used (-)-Ipc_2BH **121** for reduction of 2-((2-iodophenoxy)methyl)chromone **122**. The reduction goes enantioselectively, but unfortunately the ee was not measured, only the rotation angle of the product **123** was observed. The best optical yield was obtained if the (-)-Ipc_2BH was formed from $BH_3 \cdot Me_2S$ and (+)-α-pinene in THF, then the substrate **122** was added. The chemical yield of this reaction is not given. As expected, the use of $NaBH_4$ leads to the chromanol **124** but the use of chiral aminoethanol **125** – borane complex leads to chromene **126** probably through the formation of **124**.



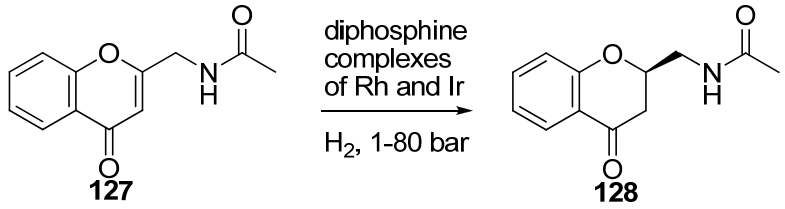
Scheme 28

Nickel boride was applied by J.M. Khurana and P. Sharma[159]. It was prepared *in situ* from $NiCl_2 \cdot 6H_2O$ and $NaBH_4$. Chromones and flavones were reduced to give the corresponding chroman-4-ones in aqueous methanol (chromones with yields of 74-68%, flavones – 34-32%). The use of dry methanol and anhydrous $NiCl_2$ to prepare nickel boride switches this reaction to give the corresponding chromanols[140, 160]. The nickel boride is a non-stoichiometric compound, the fresh nickel boride has a formula $(Ni_2B)H_3$, but it looses hydrogen on aging[161]. Since an excess of $NaBH_4$ relative to $NiCl_2$ was used, the nickel boride promoted reduction by $NaBH_4$ should also not be excluded.

R. Mozingo and H. Adkins[107] have reduced 2-ethylchromone and flavone by hydrogen on copper chromite. The yields of chromanones were bad, although different conditions of hydrogenation were tested.

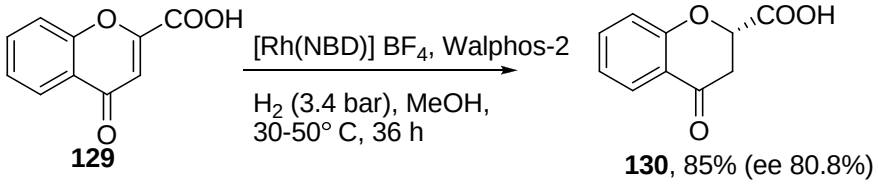
J. R. Hwu et al.[162] propose the use of calcium in liquid ammonia as reducing reagent for chromone, coumarin and the other compounds. In their experiments chromone was reduced by Ca/NH_3 to 4-chromanone (75% yield, 24% of starting material recovered), while reduction with Li/NH_3 or Na/NH_3 gave 1-(2-hydroxyphenyl)propan-1-one (89 and 95%, resp.).

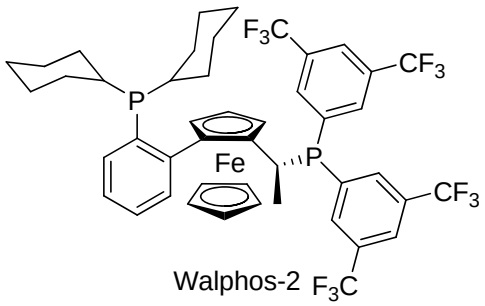
Patent[163] describes enantioselective hydrogenation of 2-acetylaminomethylchromone **127** in presence of diphosphine complexes of rhodium and iridium, yielding **128** as product. Nowadays this method of hydrogenation is very popular, it was applicated to many classes of organic compounds[24]. The authors have used BINAP, Chiraphos, DIOP, Skewphos (BDPP), BPPM, Norphos, BPPFOH, PFctBu as chiral ligands for Rh or Ir. Pressure of hydrogen was 1-80 bar.



Scheme 29

Another example of homogeneous hydrogenation is reported in patent[164]. Chromone-2-carboxylic acid **129** was hydrogenated in presence of 1 mol-% of Rh and Ru-complexes with various chiral ligands. (S)-Chroman-4-on-2-carboxylic acid **130** was prepared with ee 80.8% by using the *in-situ* prepared complex from $[Rh(NBD)_2]BF_4$ and Walphos-2 ligand. The carboxylic acid of R-configuration was prepared with ee 77.6% by using the enantiomer of the ligand (Walphos-1). 7-Iodochromonone-2-carboxylic acid was reduced similarly.





Scheme 30

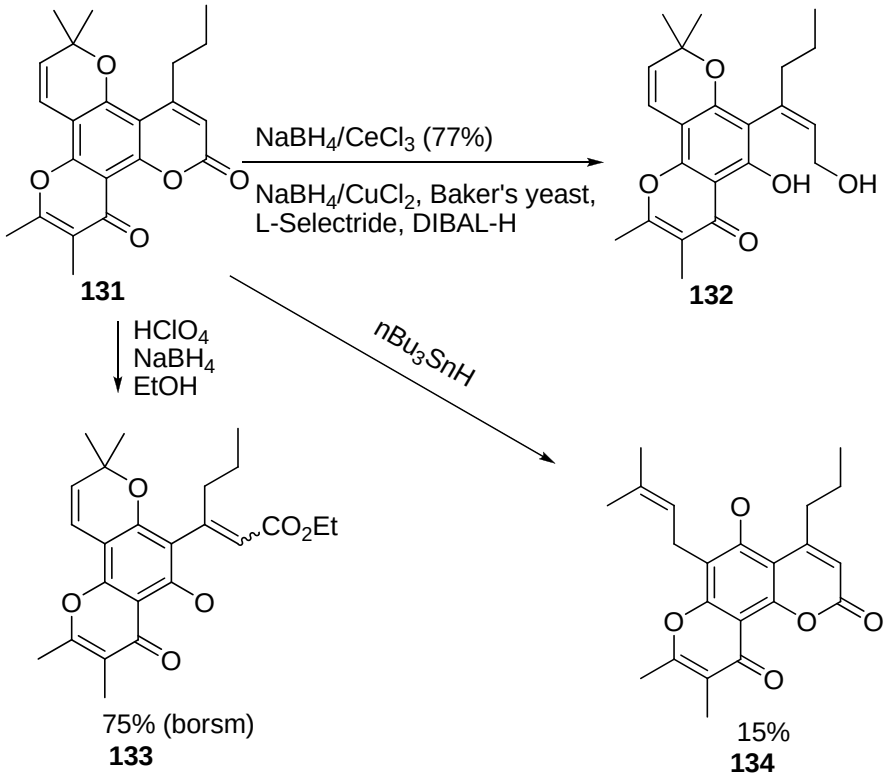
A.-H. Chen. et al.[165] report about the photochemical dimerization of flavone. A side-reaction of such a process is the reduction of flavone. Unfortunately, neither the yields of 2,2`-biflavonoids, nor those of flavanone are excellent. Organic amine (triethylamine or 2-(N,N-dimethylamino)ethanol) was used as electron donor. There is an article dealing with the mechanism of photoreduction of chromones and chromanones in presence of phenols or amines[166]. However, it is not a synthetical article.

P. Boutoute and G. Mousset[167] report about the electrochemical reduction of 2-acetylchromone to 2-acetylchroman-4-one in DMF in presence of 2 equivalents of AcOH with a 55% yield. It is interesting that 2-bezoylchromone was electrochemically reduced to 2-(hydroxy(phenyl)methyl)-chromone, i.e. the carbonyl of the side group was reduced.

A.-H. Chen. et al.[165] describe the electrochemical reduction of flavone. This reaction goes with flavone dimerization (2,2`-biflavone formation), and the yield of flavanone depends on the nature of the electrode, supporting electrolyte and temperature. Cu(-)/C(+)-electrode with 0.1M H_2SO_4 are the best conditions for flavanone yield (62.1%). Unfortunately, nothing is reported about the process temperature dependence for this electrode.

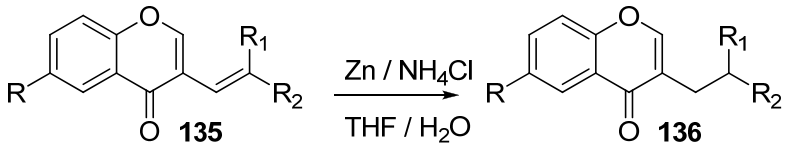
Some 2′-hydroxyisoflavones are shown to be reduced by NADPH in presence of 2′-hydroxydaidzein oxidoreductase, isolated from elicitor-challenged soybean cell cultures[168]. 7,2`-Dihydroxy-4`,5`-methylenedioxyisoflavone was reduced to (S)-sophorol **15** by NADPH/NADPH:7,2`-dihydroxy-4`,5`-methylenedioxyisoflavone oxidoreductase from pea[36]. This enzyme is specific for this isoflavone; 7-hydroxy-5,8-dimethoxyisoflavone, 5,4`-dihydroxy-6,7-dimethoxyisoflavone, biochanin A, kaempferol and quercetin were not reduced. 7,2`-Dihydroxy-4`-methoxyisoflavone and again 7,2`-Dihydroxy-4`,5`-methylenedioxyisoflavone were shown to be reduced by NADPH:isoflavone oxidoreductase from chickpea[169]. In plants these 2`-hydroxyisoflavanones are further reduced to highly toxic pterocarpanes.

Article[170] reports about the chromonocoumarin **131** which was very inactive toward hydrogenation. No reducing reagent ($NaBH_4/CeCl_3$, $NaBH_4/CuCl_2$, Baker's yeast, L-Selectride, DIBAL-H) could reduce the chromone ring but coumarin was reduced by these reagents and gave the corresponding diol **132**. N-$BuSn_3H$, SmI_2/HMPA, 9-BBN and $[(PPh_3)CuH]_6$ were also ineffective. The action of $HClO_4/NaBH_4$ gave transesterified product **133**, and reduction by nBu_3SnH gave the product **134**. The purposeful chromanone was synthesized from the other precursors.



Scheme 31

The Zn/NH_4Cl[171] system was found to reduce the exocyclic C=C-bonds of compounds **135**, yielding **136** without chromanones as side-products.



$R_1 = R_2 = CO_2Et$, R = H, 70%
$R_1 = R_2 = COCH_3$, R = H (46%) or Me (40%)
$R_1 = COPh$, $R_2 = CO_2Et$, R = H, 40%

Scheme 32

Table 8. Summary table of chromones' reduction by the other methods. If otherwise not stated, the product is the corresponding 4-chromanone.

Substrate	reducing reagent	solvent	yield, %	time	additional information	ref.
2-methyl-, 3-methylchromone	H_2 / Raney Co	EtOH	18, 22	6, 30 h	With overreduction, only 50% conversion of educt, not synthetical article, reaction mixture was analyzed by GLC	[78]
2-methyl-, 3-methylchromone	H_2 / Ru black	EtOH	44, 42	50, 26.5 h		[78]
2-methyl-, 3-methylchromone	H_2 / Rh black	EtOH	20, 18	1, 1.8 h		[78]
2-methyl-, 3-methylchromone	H_2 / Os black	EtOH	10, 48	30, 8.8 h		[78]
2-methyl-, 3-methylchromone	H_2 / Ir black	EtOH	46, 86	54, 12.8 h		[78]
2-ethylchromone	H_2 / CuCrO	EtOH	29, 15	92, 5 min resp.	100-200 bar H_2, 140-150ºC, 110-113ºC	[107]

flavone	H_2 / CuCrO	EtOH	13	19 min	140-149ºC	[107]
flavone	electricity / H_2SO_4 or TsOH	MeOH	2.0-62.1	N/A	electrochemical reduction, yield depends on electrodes type, electrolyte and temperature	[128]
chromone	disiamylbornae, catecholborane, dicyclohexylborane	THF	33, 12, 31, resp.	N/A		[132]
7,4`-dimethoxy-, 7,8,4`-trimethoxy-, 6,7,3`,4`-tetramethoxyisoflavone	NaHTe	EtOH/CH_2Cl_2	61, 69, 70, resp.	30 min	refluxing	[157]
122	(-)-Ipc_2BH **121**	THF	N/A	2 h	enantioselective, 60 hours for **121** formation, then 2 h reduction	[158]
chromone, 6-methylchromone, 7-methoxychromone	$NiCl_2 \cdot 6H_2O$ + $NaBH_4$	MeOH/H_2O	74, 68, 68, resp.	4 h		[159]
flavone, 6-methylflavone	$NiCl_2 \cdot 6H_2O$ + $NaBH_4$	MeOH/H_2O	32, 34, resp.	10 h		[159]
chromone	Ca/NH3	THF/NH_3 1/4	75	2 h	-33ºC, starting chromone recovered with 24% yield	[162]
127	H_2/Ir or Rh/chiral phosphine	CH_2Cl_2, THF, MeOH, iPrOH, PhMe/MeOH 5/1	N/A	15 h	H_2 pressure: 1-80 bar, ee 0-91%, patent, reactions are given as examples	[163]
chromone-2-carboxylic acid **129**, 7-iodochromone-2-carboxylic acid	H_2 / $[Rh(NBD)_2]BF_4$ / Walphos	MeOH	85	36 h	EE 80.8% (for S-**130**) or 77.6% (for R-**130**), Rh and Ru-complexes with many other chiral ligands were tested, patent, reactions are given as examples	[164]
flavone	light / amine	PhH, MeCN, CH_2Cl_2	8.9-16.9	14 h	photochemical reduction, chromanon is a by-product	[165]
2-acetylchromone	electricity / AcOH	DMF	55	N/A	electrochemical reduction	[167]
7,2`-dihydroxy-4`,5`-methylenedioxyisoflavone	NADPH/ NADPH:7,2`-dihydroxy-4`,5`-methylenedioxyisoflavone oxidoreductase	H_2O	66	15 min	enanthiopecific enzymatic reduction, product is (S)-sophorol **15**	[36]
7,2′,4′-trihydroxyisoflavone, 7,2′-dihydroxy-4′-methoxyisoflavone, 5,7,2′,4′-tetrahydroxyisoflavone	NADPH/2′-hydroxydaidzein oxidoreductase	H_2O	60	10 min	enanthioselective enzymatic reduction	[168]
7,2`-dihydroxy-4`-methoxyisoflavone, 7,2`-Dihydroxy-4`,5`-methylenedioxyisoflavone	NADPH:isoflavone oxidoreductase	H_2O	N/A	15 min	enzymatic reduction, isoflavanones were only detected, not separated	[169]

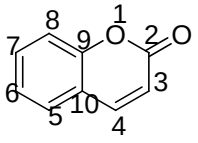
1.1.7 Conclusion

The reduction of chromones represents an important synthetical method of chroman-4-ones synthesis. Many methods of selective or unselective reduction of such compounds are reported. One of the best methods is the reduction by DIBAL-H. A good starting point for hydrogenation of an unknown chromone can be a "titration with hydrogen" over Pd/C in some aprotic solvent or in AcOH. The chromones, which bear an EWG in the 3rd position can be smoothly reduced by $NaBH_4$.

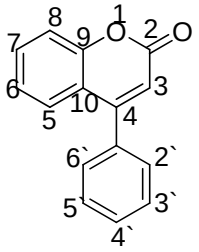
The flavanones and isoflavanones are the most important chroman-4-ones. They have a chiral centrum and are very sensitive to racemization. Enantioselective homogeneous hydrogenation/reduction which is quite well developped for various substrates[24, 25] is represented here by three publications only.

1.2 Synthesis of chroman-2-ons by reduction of coumarins

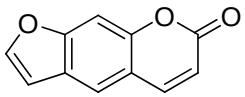
As well as chromones, the coumarins **137**, with their derivatives also belong to the class of flavonoids. The 4-arylcoumarins **138** have a trivial name: neoflavones. The numeration for such systems is given in scheme 33. Natural flavonoids are usually mono- or polyhydroxylated, alkoxylated or glucosylated in annelated and/or side aryl-ring. Often an alkoxylation is hidden under the annelation of a new cycle, e. g. in psoralen **139**.



137, coumarin



138, 4-phenylcoumarin
or neoflavone

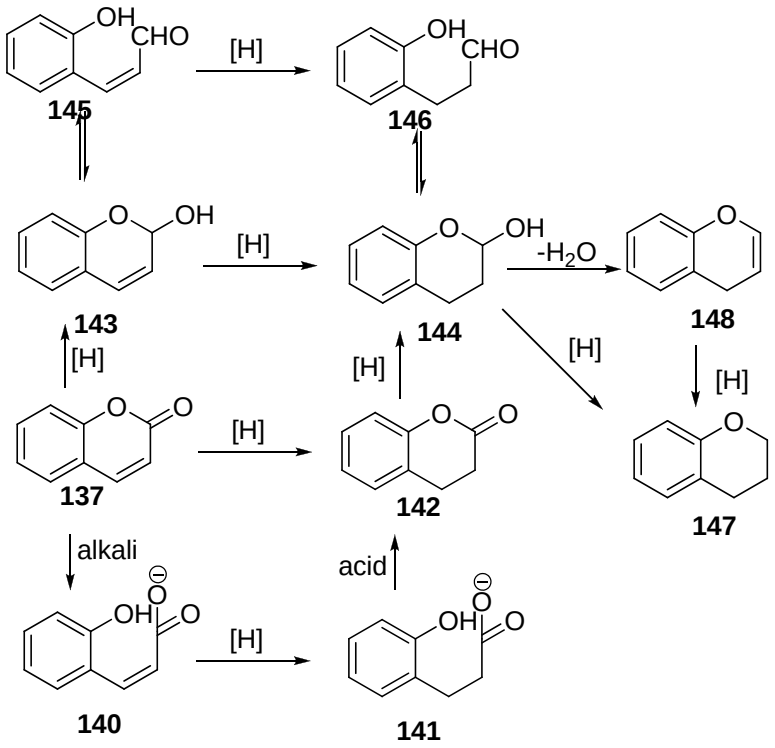


139, psoralen

Scheme 33

If a coumarin is subjected to hydrogenation/reduction, several possible products can be generated and many more products can be isolated because of the lactonic character of the coumarin cycle. Actually, the coumarin **137** can be opened by alkali to the salt of *o*-oxy-cinnamic acid (coumaric acid, **140**). The latter can be reduced, and the salt of the carboxylic acid **141** can be cyclized by acid to chroman-2-one **142** (another name is 3,4-dihydrocoumarin). The coumarin can also be directly reduced to chroman-2-one **142**. Coumarin can be reduced into the carboxylic group and **143** can be obtained. The reduction of

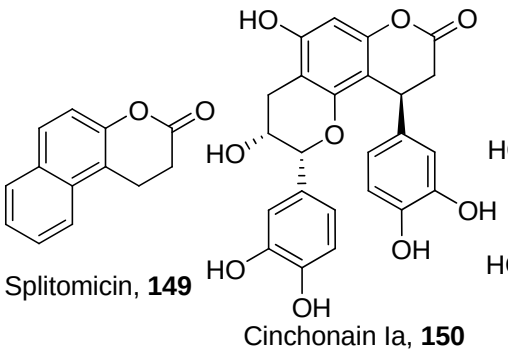
chromanone gives **144**. **144** and **143** represent semi-acetals which are known to posess cycle-chain tautomerism (structures **145** and **146**). **144** Can be either reduced to chroman **147** or dehydrated to chromene **148**. The latter can also be reduced to chroman. Very often the products are isolated with the opened chroman cycle (e.g. *o*-hydroxyphenylpropanol).



Scheme 34

Among the chroman-2-ones a number of biologically acive compounds is found. Splitomicin **149** and its mimetics are proven to be histone deacetylase inhibitors[172] and sirtuin inhibitors[173], thus having an antiproliferative activity and being potential anticancer drugs. Cinchonains Ia **150** and Id **151** function as free-radical scavengers[174]. Both glabraosides A **152** and B **153** have a scavenging activity against DPPH[175]. The glabraoside A **152** has additionally hepatoprotective activity in vitro, while its epimer glabraoside B **153** cannot prevent the death of liver cells[176]. The free-radical scavenger neoflavanone **154** has antioxidative, immunoregulating and antitumoral properties[177]. Acetylated coumarins and 3,4-dihydrocoumarins are proven to be the substrates of protein transacetylase[178]. Some compounds bearing a chroman-2-one system have an oestrogenic activity[179]. Chroman-2-one has a weak anti-helmintic effect[180]. It is also used as flavouring substance[181]. Several methyl coumarin- and methyl 3,4-dihydrocoumarin-3-carboxylates are patented as useful compunds for the treatment of type 2 diabetes[182]. Some neoflavanones are patented for the use in protein trafficking[183] and have anti-malarial activity[184]. 6-(4-(Trifluoromethyl)phenyl)chroman-2-one is patented as a compound, useful against proliferative diseases and disorders[185].

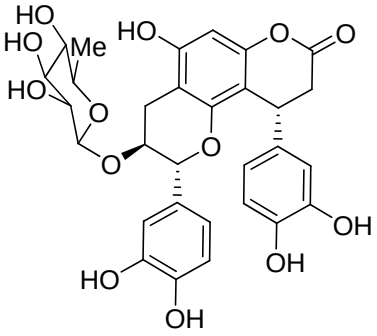
Spiro[pyranoxanthene-isobenzofuran]diones, bearing chroman-2-one cycle, are patented for fluorescent labelling of biological materials[186]. Tannins from Picrorhiza kurroa Seeds containig the chroman-2-one cycle have a weak COX-inhibiting effect[187]. The gnetumontanin C **155** inhibits the production of TNF-α by murine peritoneal macrophages, thus having a moderate anti-inflammatory activity[188]. The chroman-2-one ring is recognized by various β-lactamases thus being a lead for construction of the inhibitors of such enzymes[189]. The chroman-2-one **156**, as well as coumarins **157** and **158**, can inhibit LOX, thus having anti-inflammatory activity in-vivo[190]. A number of chroman-2-ones are useful synthetic intermediates[191-196].



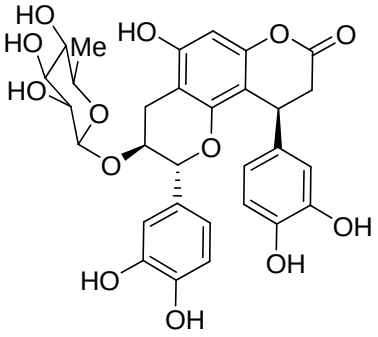
Splitomicin, **149**

Cinchonain Ia, **150**

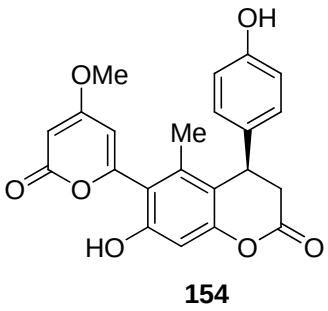
Cinchonain Id, **151**



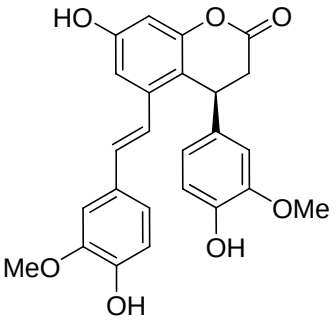
Glabraoside A, **152**



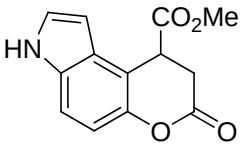
Glabraoside B, **153**



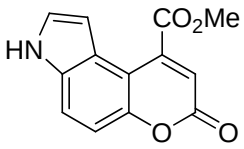
154



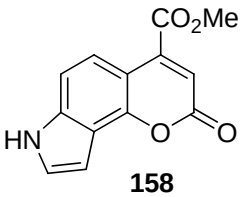
Gnetumontanin C, **155**



156



157



158

Scheme 35

There are many methods of the chroman-2-ones synthesis and the reduction of coumarins is one of them. The methods of reduction, their benefits and disadvantages are described in this review. The search was carried out with SciFinder Scholar 2007 by the American Chemical Society. Only the reduction of coumarins is reviewed, e.g. the palladium-

catalyzed coupling of arylboronic acids with coumarin gives 4-substituted chroman-2-one, but this is not a reduction, hence is not reviewed.

The essential information about coumarins' reduction is described in the tables (for widely used methods). Also many exceptions and interesting transformations are described in the text. If they do not represent the above-mentioned reaction of coumarin's reduction, leading to chroman-2-one, these transfromations are not included in the tables.

The book[197] is dedicated to coumarins. Some information about coumarins' hydrogenation is available there.

1.2.1 Hydrogenation of coumarins

1.2.1.1 With palladium on charcoal

This method is the mostly used one for coumarins. If the other one is not stated, 10% Pd/C was used. Table 9 represents the information about coumarins' hydrogenation on Pd/C that gives chroman-2-ones.

Coumarins are not very active towards the catalytic hydrogenation, and often it is possible to hydrogenate some side-chains, leaving the coumarin-ring intact[197-199].

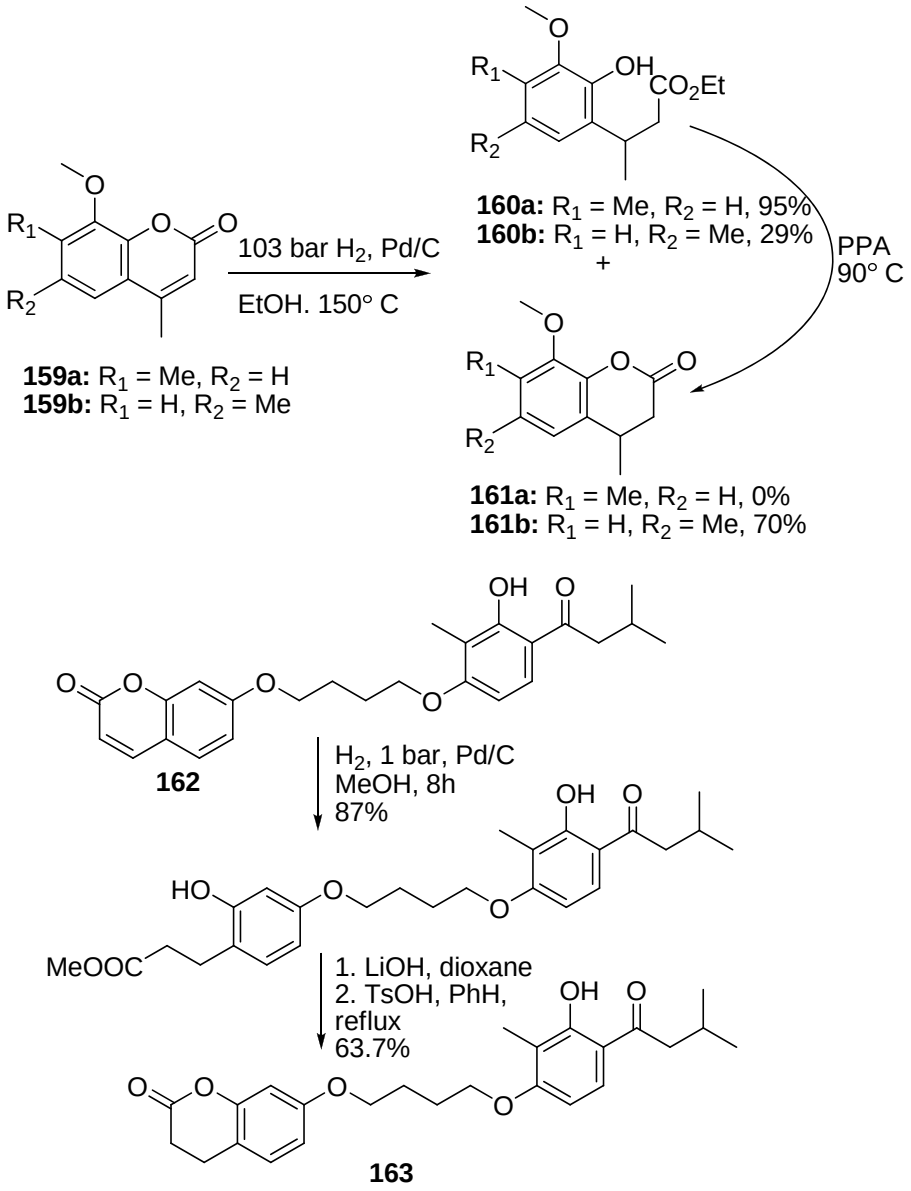
Very often coumarins are hydrogenated through the salts of *o*-hydroxycinnamic acid **140**. This salt is generated *in-situ*, and when the reaction is completed, the reacting mixture is acidified. Acid functions as a cyclizing reagent for *o*-hydroxyphenylpropionic acid. Actually, the process is described as **137**→**140**→**141**→**142**. W. Borsche and P. Hahn-Weinheimer[200] took directly *o*-coumaric acid (*o*-hydroxycinnamic acid) which was reduced to chroman-2-one.

In studying fungi's chemistry, F. M. Dean et al.[201] have reduced a number of coumarin-3-carboxylic acids and 3-acetylcoumarins. It is interesting that 3-acetylcoumarin, 3-acetyl-6-methoxycoumarin and 3-acetyl-7-methylcoumarin could be hydrogenated on Pd/C to the corresponding chroman-2-ones, while 3-acetyl-7-methoxy-, 3-acetyl-7-hydroxy- and 3-acetyl-6,7-dimethoxycoumarin were hydrogenated to 7-R-3-ethylcoumarins. On platinum 3-acetyl-7-hydroxycoumarin was mainly hydrogenated to the corresponding 3-ethylcoumarin, but chroman-2-one was also isolated as a by-product.

F. D. Mills[202] has studied the reduction of 8-methoxy-4,7-dimethylcoumarin **159a** and 8-methoxy-4,6-dimethylcoumarin **159b**. He reports that **159a** could not be reduced at low temperature and under low pressure of hydrogen on Raney-nickel or palladium catalyst. Both coumarins were hydrogenated at higher pressure (higher than 3.1 bar) to give a mixture of chroman-2-one with starting coumarin. The hydrogenation of **159a** in EtOH at 150º C and

under pressure of 103 bar gave **160a,** while the hydrogenation of **159b** gave a mixture of **160b** and **161b**. Both esters **160** were converted to chroman-2-ones by PPA at 90ºC.

The resembling strategy was used by R. V. Cube et al.[203] with reduction of **162** which was opened by hydrogenation on Pd/C, but further converted to **163**.



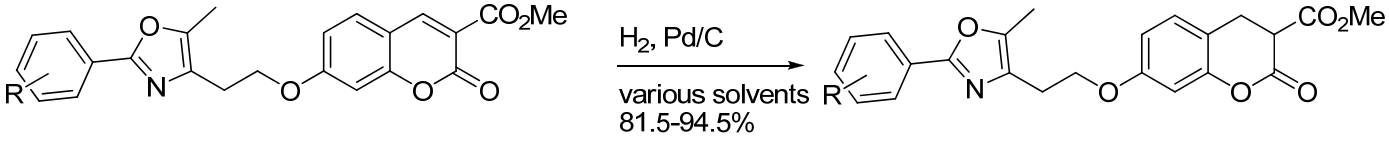
Scheme 36

N. Cohen et al.[204] report about the hydrogenation of 7-hydroxycoumarin in ethanol that gave a mixture of 7-hydroxychroman-2-one and ethyl 2,4-dihydroxybenzenepropanoate. The latter compound was converted to 7-hydroxychroman-2-one by refluxing in PhMe with TsOH.

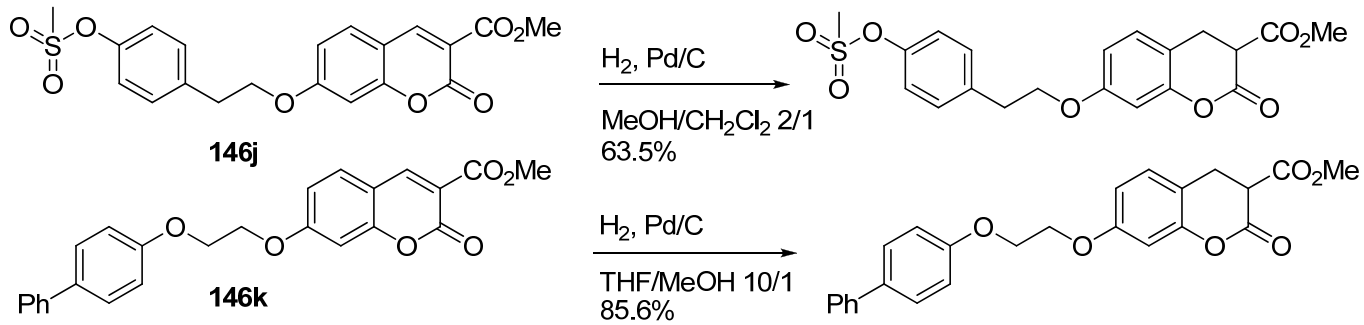
J. Demyttenaere et al.{Demyttenaere, #107} tried to hydrogenate scopoletin (7-hydroxy-6-methoxycoumarin) on Pd/C. They have found that in EtOAc this hydrogenation

goes quantitatively, while in EtOH only ethyl 3-(2,4-dihydroxy-5-methoxyphenyl)propionate was obtained. In 1,2-dimethoxyethane no reduction was observed.

Chinese reseacher[182] have synthesized various coumarins and chroman-2-ones which are active against 3T3-L1 cells and are patented as useful drugs in the treatment of type 2 diabetes. The coumarins **164a-k** were hydrogenated over 5% or 10% Pd/C or over Raney-nickel, but the use of 10% Pd/C is reported to be the most effective one. The hydrogenation reactions were carried out in methanol-containing mixtures of solvents, and afforded the purposeful chroman-2-ones in good or moderate yields.



146a, R = *p*-Ph; **146b**, R = *m*-Me; **146c**, R = *p*-Me; **146d**, R = *p*-tBu; **146e**, R = *p*-MeO; **146f**, R = *m*-MeO; **146g**, R = *m*-F; **146h**, R = *p*-F; **146i**, R = *m*-CF_3

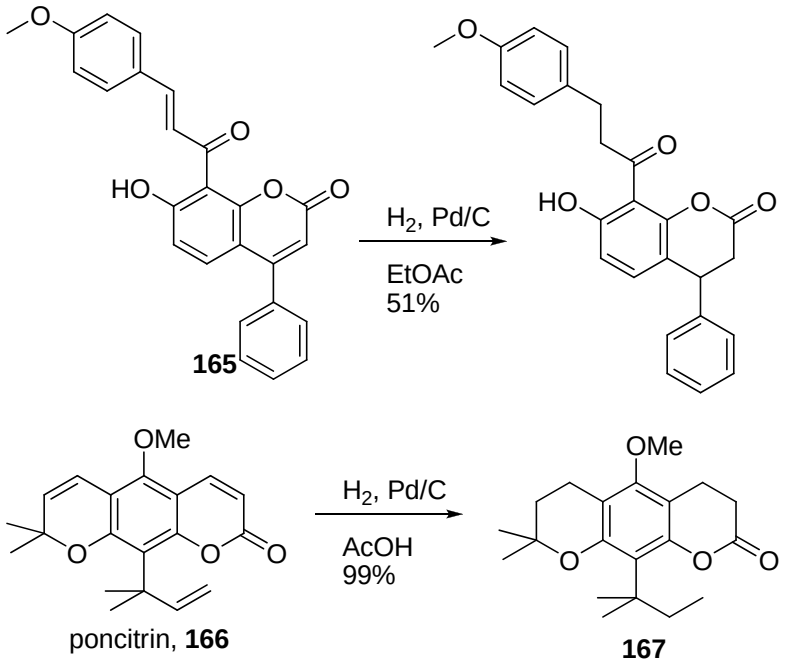


Scheme 37

P. Yates et al.[206] report about a very clean reduction of 6-methyl- and 7-methylcoumarin which gave corresponding chroman-2-ones with a yield of 98.5 and 99%, respectively.

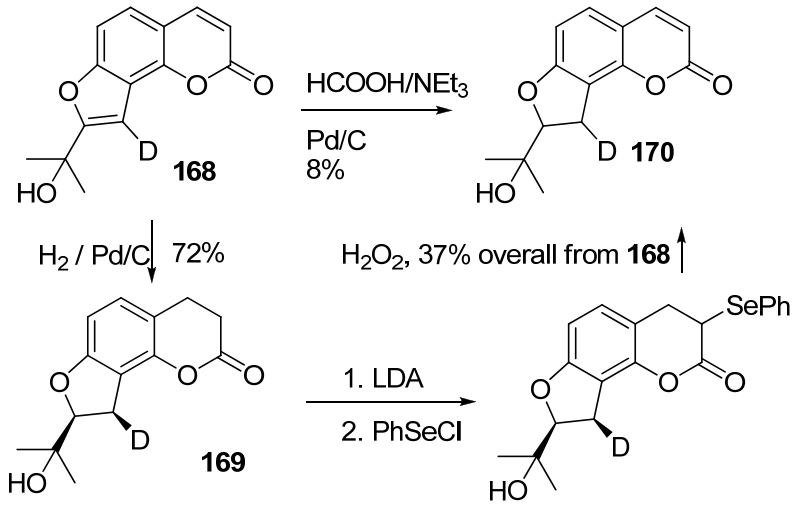
J. Crombie et al.[207] have studied the hydrogenation of 5,7-dihydroxy-8-(2-methylbutyryl)-4-pentylcoumarin. They report that it could not be reduced in ethanol or EtOAc under 35 bar of hydrogen over various heterogeneous catalysts. It was eventually hydrogenated at 100º C in EtOH on Pd/C with a yield of 74% under 50 bar of hydrogen. 5,7-Dihydroxy-8-(2-methylbutyryl)-4-pentylcoumarin was hydrogenated under the same conditions.

V. K. Ahluwalia et al.[208] report about 7-hydroxy-8-(4′-methoxycinnamoyl)-4-phenyl-coumarin's **165** hydrogenation. It has another unsaturated part in addition to the coumarin cycle, both were hydrogenated on Pd/C. The same is valid for poncitrin[209] **166**, which was reduced to hexahydroponcitrin **167**.



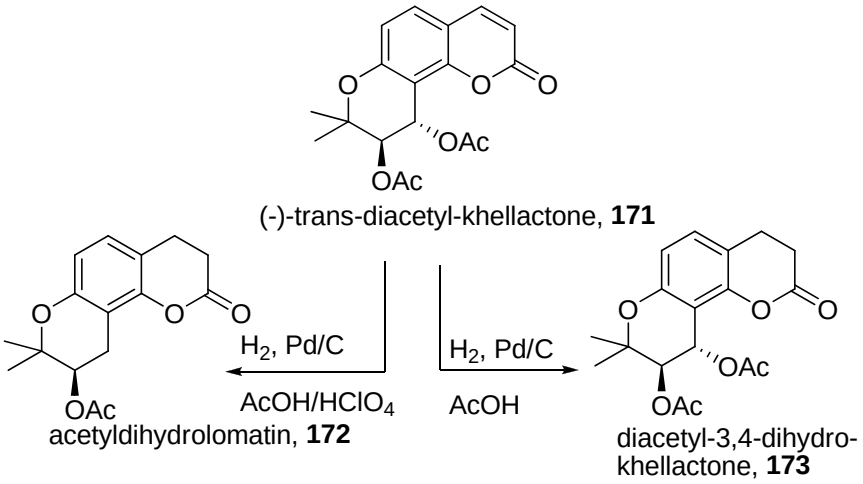
Scheme 38

Compound **168** was hydrogenated to **169** on Pd/C[210]. By catalytic transfer hydrogenation (CTH) only the side-chain was hydrogenated, but with a very bad yield. Since the authors needed **170,** they developed an interesting synthetical procedure (see scheme 39).



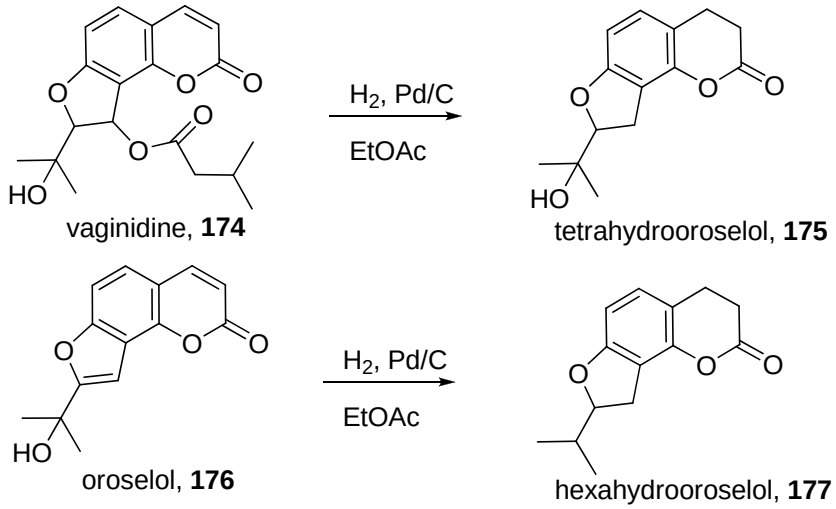
Scheme 39

K. K. Nadrakarni et al.[211] have hydrogenated 6-hydroxy-4,7-dimethylcoumarin in presence of perchloric acid. (-)-Trans-diacetyl-khellactone **171** was found to undergo a partial deacetylation under hydrogenation, activated by $HClO_4$[212].



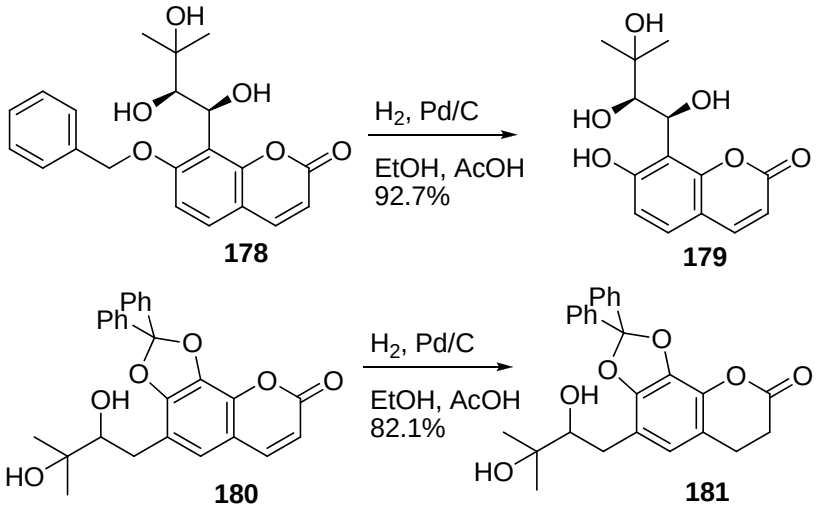
Scheme 40

The similar deacetylaton for vaginidine **174** leading to tetrahydrooroselol **175**, is reported in the article of T.R. Seshadri and Vishwapaul[213]. They also report about hydrogenation of oroselol **176** that proceeded with water elimination thus yielding hexahydrooroselol **177**.



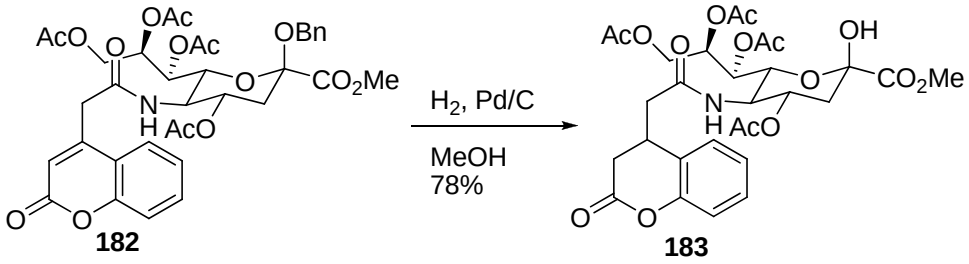
Scheme 41

Mild acidic catalysis (AcOH in EtOH) also was applied by J. Reisch et al.[214]. It is interesting that benzylated coumarin **178** was only deprotected to give **179**, while **180** was hydrogenated to chromanone **181**.



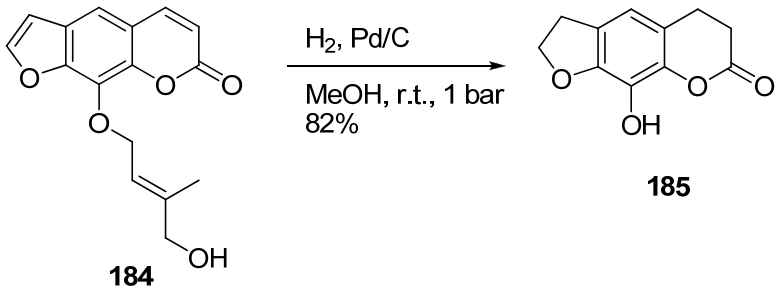
Scheme 42

Patent[215] describes a hydrogenation of **182**, proceeded with removing of benzyl-group and with coumarin-ring reduction, thus giving **183** with the yield of 78%.



Scheme 43

One example of destructive hydrogenation (by analogy to destructive oxidation) of coumarin is found[216]. The compound **184** was converted to **185** by hydrogenation in methanol.



Scheme 44

Table 9. Hydrogenation of coumarins on palladium on charcoal. If otherwise is not stated, 10% Pd/C was used, and the product is the corresponding 2-chromanone.

Substrate	p(H_2), bar	Solvent	yield, %	time	additional information	ref.
umbelliferone (7-hydroxycoumarin)	N/A	AcOH	94	10 h	no synthetis procedure available	[194]
4`-methoxyneoflavone	3.8	EtOAc	89	24 h		[195]

coumarin, 4,7-dimethyl-, 4,6-dimethyl-, 6-methoxy-, 6-methoxy-4,7-dimethyl-, 6-methoxy-7-methylcoumarin	1	AcOH	97-99	12 h		[196]
164a, 164b, 164c, 164e, 164f, 164g, 164h, 164i	1	MeOH/ dioxane 1/3	85.4, 94.5, 87.1, 92.4, 89.6, 90.2, 89.9, 85.0, resp.	N/A		[182]
164d	1	MeOH/ CH_2Cl_2 6/1	81.5	N/A		[182]
164j	1	MeOH/ CH_2Cl_2 2/1	63.5	N/A		[182]
164k	1	THF/MeOH 10/1	85.6	N/A		[182]
coumarin-3-carboxylic acid	4.2	water	62	4 h	Pd/C from 1 g of charcoal and 0.4 g of $PdCl_2$. Na-salt of substrate was hydrogenated	[201]
coumarin-3-carboxylic acid	6.8	MeOH	N/A	N/A	Pd/C from 1 g of charcoal and 0.4 g of $PdCl_2$. Methyl 2-oxochroman-3-carboxylate is isolated	[201]
6,7-dimethoxycoumarin-3-carboxylic acid	4.1	Water	N/A	4 h	20% Pd/C used. Na-salt of substrate was hydrogenated. Crude product was methylated by CH_2N_2 or decarboxylated.	[201]
3-acetylcoumarin, 3-acety-6-methoxylcoumarin, 3-acetyl-7-methylcoumarin	4.1	MeOH	N/A	1 h	Pd/C from 1 g of charcoal and 0.1 g of $PdCl_2$.	[201]
3-acetyl-6,7-dimethoxycoumarin	N/A	N/A	N/A	N/A	no synthetic procedure available. Chroman-2-one is a by-product.	[201]
8-methoxy-4,7-dimethylcoumarin **159a**	3.1	EtOH	13	4 h	50º C, the rest of starting compound recovered	[202]
8-methoxy-4,7-dimethylcoumarin **159a**	6.2	EtOH	70	4 h	100º C, the rest of starting compound recovered	[202]
8-methoxy-4,7-dimethylcoumarin **159a**	41.3	EtOAc	61	4 h	50º C, the rest of starting compound recovered	[202]
8-methoxy-4,6-dimethylcoumarin **159b**	103	EtOH	29	6 h	150º C, also ethyl 3-(2`-hydroxy-3`-methoxy-5`-methylphenyl)butanoate (70%) isolated	[202]
7-hydroxycoumarin	2.7	EtOH	70	N/A	60º C, product – mixture of chromanone and ethyl 2,4-dihydroxybenzenepro-panoate	[204]
scopoletin (7-hydroxy-6-methoxycoumarin)	3.4	EtOAc	96	17 h	in EtOH reaction leads to ethyl 3-(2,4-dihydroxy-5-methoxyphenyl)propio-nate	{Demytt enaere, #107}
6-methylcoumarin, 7-methylcoumarin	3.4	EtOAc	99	3-6 h		[206]
5,7-dihydroxy-8-(2-methylbutyryl)-4-	50	EtOH	74, 62,	night	100º C or 20º C, resp.	[207]

pentylcoumarin, 5,7-dihydroxy-4-pentylcoumarin			resp.			
165	N/A	EtOAc	51	6 h	side-chain also hydrogenated	[208]
poncitrin **166**	1	AcOH	99	N/A	product: hexahydroponcitrin **167**	[209]
168	N/A	Acetone	72	4 h	side-chain hydrogenation, product - **169**	[210]
6-hydroxy-4,7-dimethylcoumarin	N/A	AcOH	61.8	3 h	90º C, with $HClO_4$	[211]
(-)-trans-diacetyl-khellactone **171**	1	AcOH/ $HClO_4$	N/A	N/A	product: acetyldihydrolomatin **172**	[212]
(-)-trans-diacetyl-khellactone **171**	1	AcOH	N/A	N/A	product: diacetyl-3,4-dihydro khellactone **173**	[212]
vaginidine **174**	N/A	EtOAc	N/A	30 h	reduction goes with desacylation, **175** isolated as a product	[213]
oroselol **176**	N/A	EtOAc	N/A	24 h	side-chains also hydrogenated, **177** isolated as a product	[213]
182	1	MeOH	78	over night	patent, side benzyl-group is also removed, **183** is a product	[215]
184	1	MeOH	82	N/A	the product is **185**	[216]
6-fluorocoumarin	N/A	EtOH	25	N/A		[217]
8-isobutyryl-6-isopentenyl-5,7-dihydroxy-4-phenylcoumarin, 8-isobutyryl-6-isopentenyl-5,7-dimethoxy-4-phenylcoumarin	N/A	EtOH	50, 39 resp.	N/A	isopentenyl side-chain also hydrogenated.	[218]
4-pentylcoumarin	4	N/A	62	N/A	no synthetic procedure available	[219]
180	N/A	EtOH	82.1	N/A	AcOH added, product – **181**	[214]
8-methoxy-4,7-dimethylcoumarin	N/A	EtOAc	98	10 h	no synthetic procedure available	[220]
6,8-dimethoxy-4,7-dimethylcoumarin	N/A	EtOAc	98	4 days	no synthetic procedure available	[221]
6-nitrocoumarin	4	THF	83.6; 93,1	5 h; 15 h	r.t. or 50º C, resp. With 3 Å molecular sieves and with di-*tert*-butylcarbonate; *tert*-butyl 2-oxochroman-6-ylcarbamate isolated, patent, reaction is given as an example	[222], [223], resp.
coumarin	5	Without	99.9	8 h	65-75º C, patent, reaction is given as an example	[224]
methyl 7-(2-(5-ethylpyridin-2-yl)ethoxy)coumarin-3-carboxylate, methyl 7-(2-(5-methyl-2-phenyloxazol-4-yl)ethoxy)coumarin-3-carboxylate	N/A	MeOH/ dioxane 3/1	N/A	N/A	No synthetic procedures available in article [225]. Synthetic procedures seems to be present in patent [226]	[225]
tert-butyl 7-(2-(5-methyl-2-phenyloxazol-4-yl)ethoxy)coumarin-3-carboxylate	N/A	MeOH/ dioxane 1/1	N/A	N/A		[225]
methyl 7-(2-(tert-butoxycarbonyl(methyl)amino)ethoxy)coumarin-3-carboxylate	N/A	Dioxane	N/A	N/A		[225]

methyl 7-((2-phenyl)ethoxyl)coumarin-3-carboxylate, methyl 7-(2-(5-methyl-2-phenyloxazol-4-yl)ethoxy)coumarin-3-carboxylate	1	MeOH/ dioxane 3/1; 1/2, resp.	95, 80, resp.	N/A	patent, reaction is given as an example	[226]
methyl 7-[2-(N-tert-butoxycarbonyl-N-methylamino)ethoxyl]coumarin-3-carboxylate, *tert*-butyl 7-(2-(5-methyl-2-phenyloxazol-4-yl)ethoxy)coumarin-3-carboxylate	1	MeOH/ dioxane 1/3, 1/1, resp.	98, 71, resp.	N/A	yield of crude compound, patent, reaction is given as an example	[226]
7-methoxycoumarin	N/A	Benzene	100	4,5 h	50º C	[227]
7-methoxy-6-(3-methylbutanoyl)coumarin	1	AcOH	N/A	N/A	at 65º C, hydrogenatin of side carbonyl-group, 6-isopentyl-7-methoxychroman-2-one isolated as a product	[228]
suberosine (7-methoxy-6-(3-methylbut-2-enyl)coumarin)	1	EtOH	N/A	N/A	side-chain also hydrogenated, 6-isopentyl-7-methoxychroman-2-one was isolated	[229]
ehtyl coumarin-3-carboxylate	N/A	N/A	N/A	N/A	No synthetic procedure available, patent	[230]
7-butoxy-8-fluor-3-[4-(4-*trans*-pentyl-cyclohexyl)-phenyl]coumarin	N/A	THF	77	N/A	patent, reaction is given as an example	
6-ethylcoumarin, 7-isopropylcoumarin	3	EtOAc	96, 98, resp.	N/A		[231]
coumarin	N/A	AcOH with traces of H_2O	84	3 h		[232]
3-phenyl-4-(4-acetoxyphenyl)-7-methoxycoumarin	69	THF	N/A	N/A	60º C, no synthetic procedure available, *cis*-product isolated	[233]

In summary, the heterogeneous hydrogenation of coumarins over Pd/C is quite a good method reported in more then thirty publications. The coumarin-ring is not very sensitive to this type of hydrogenation that allows to hydrogenate selectively C=C-bonds of side-substituents or perform a debenzylation. However, it does not allow to hydrogenate the coumarin ring, leaving side-substituents intact. For hydrogenation in alcohols the transacylation is typical, but should not occur for sure. Sometimes after hydrogenation in alcohols the mixtures consisting of chroman-2-one and transacylated product are isolated. For 9-acyloxy-8,9-dihydro-2H-furo[2,3-h]coumarins reductive deacetylation may take place (as for **174**).

1.2.1.2 With palladium on the other support or elemental palladium

As for Pd/C, hydrogen on $Pd/BaSO_4$ also could hydrogenate only a side-part of the substrate, leaving the coumarin-ring intact[234].

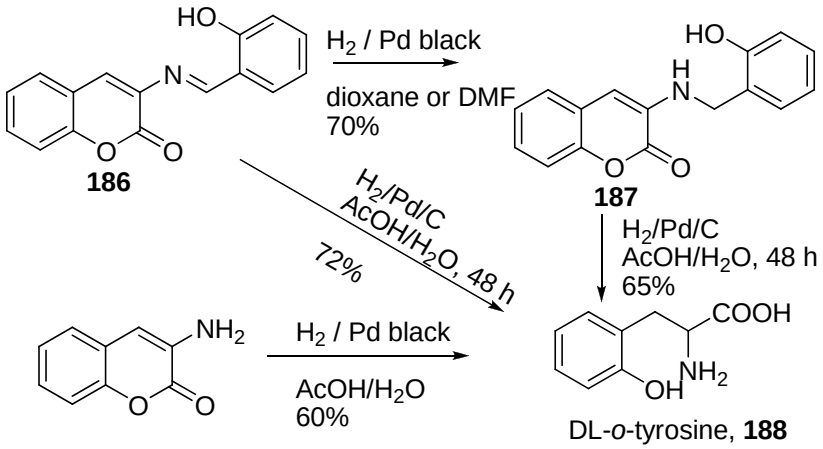
C. Paal and H. Schiedewitz[235] have studied coumarin's reduction on $Pd/BaSO_4$. They note that coumarin could be reduced very slowly (within more than 24 hours) and that this

process needs more catalyst than the other compounds. They have also studied the reduction of sodium and barium salts of coumarin acid (*o*-hydroxycinnamic acid), and these compounds were more active in reduction. The authors note a change in the colour of the solution (from yellow to colourless). Unfortunately, they did not measure the yields of reactions, because their purpose was to determine the rates of cis- and trans-hydrogenation, and coumarin was a specimen of unsaturated compound with cis-arrangement.

L. I. Smith and D. Tenenbaum[236] have hydrogenated in ethanol under 3 bar of hydrogen 3-acetyl-6-hydroxy-, 3-acetyl-6-methoxy- and 3,6-diacetyl-5,7,8-trimethylcoumarin over $Pd(OH)_2/CaCO_3$. The yields exceeded 90%.

D. J. Collins et al.[237] report about the hydrogenation of 7-methoxycoumarin on $Pd/CaCO_3$ under 69 bar of hydrogen at 55º C during 18 h.

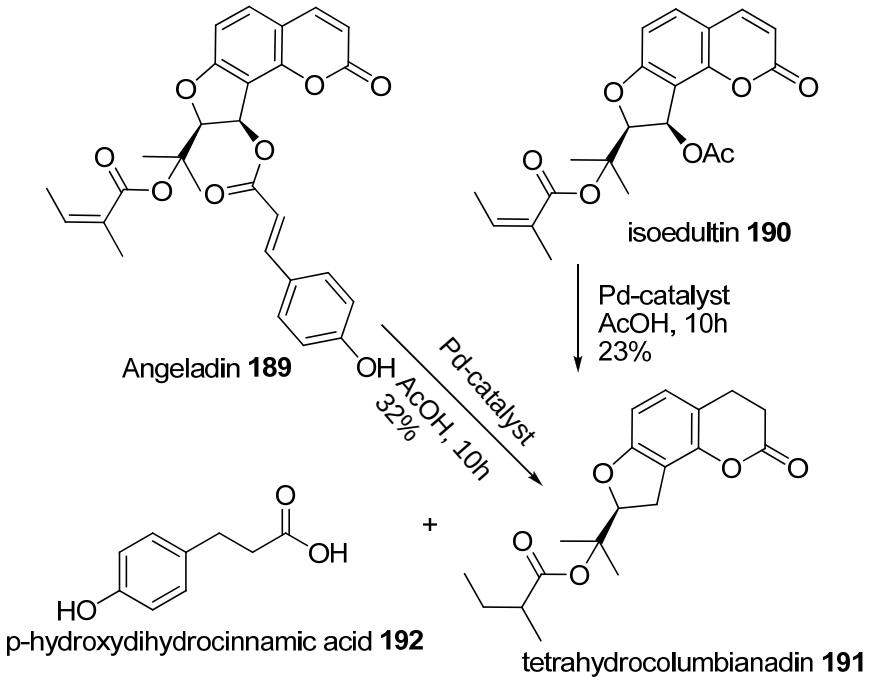
G. Kokotos and C. Tzougraki[232] report about hydrogenation of **186** on Pd black in dioxane which gave **187**. The hydrogenation of **186** or **187** on Pd black in AcOH with traces of water leads to DL-*o*-tyrosine **188**, while hydrogenation of unsubstituted coumarin under the same conditions leads to chroman-2-one with 84% yield.



Scheme 45

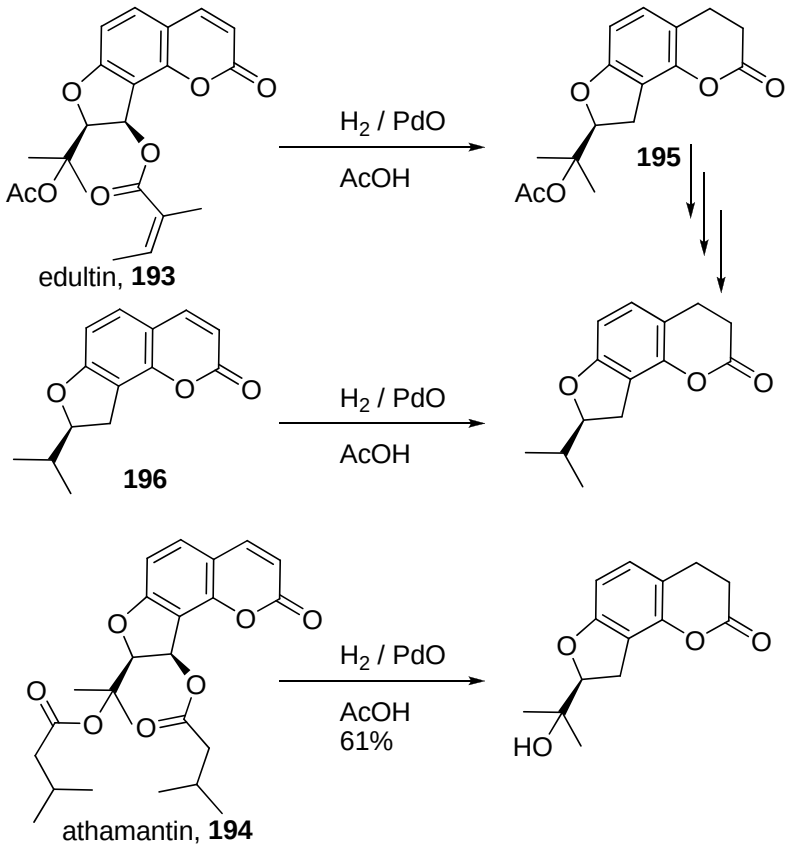
Z. Csuros et al.[238] report about coumarin's hydrogenation on colloidal palladium in aqueous ethanol. However, this article is not synthetical and only kinetic data are available.

The authors of the article[239] have hydrogenated angeladin **189** and isoedultin **190**, both to give tetrahydrocolumbianadin **191**. Thereby, a destruction of a side-chain happened. The *p*-hydroxydihydrocinnamic acid **192** was also isolated, thus proving the substrate/product decomposition. Unfortunately, the authors do not write which catalyst exactly was used, only "paladium catalyst" is stated in the article. Hydrogenation took place in acetic acid for 10 h. The pressure of hydrogen is not given.



Scheme 46

Similar reactions, catalyzed by palladium oxide, are reported for edultin **193**[240] and for athamantin **194**[241]. The formation of **195** is confirmed by hydrogenation of the model coumarin **196**[240]**.**



Scheme 47

In summary, the hydrogenation of coumarins over palladium catalysts, other than Pd/C, has almost the same properties as that over Pd/C. 9-acyloxy-8,9-dihydro-2H-furo[2,3-h]coumarins also undergo reductive deacylation on PdO-derived catalyst.

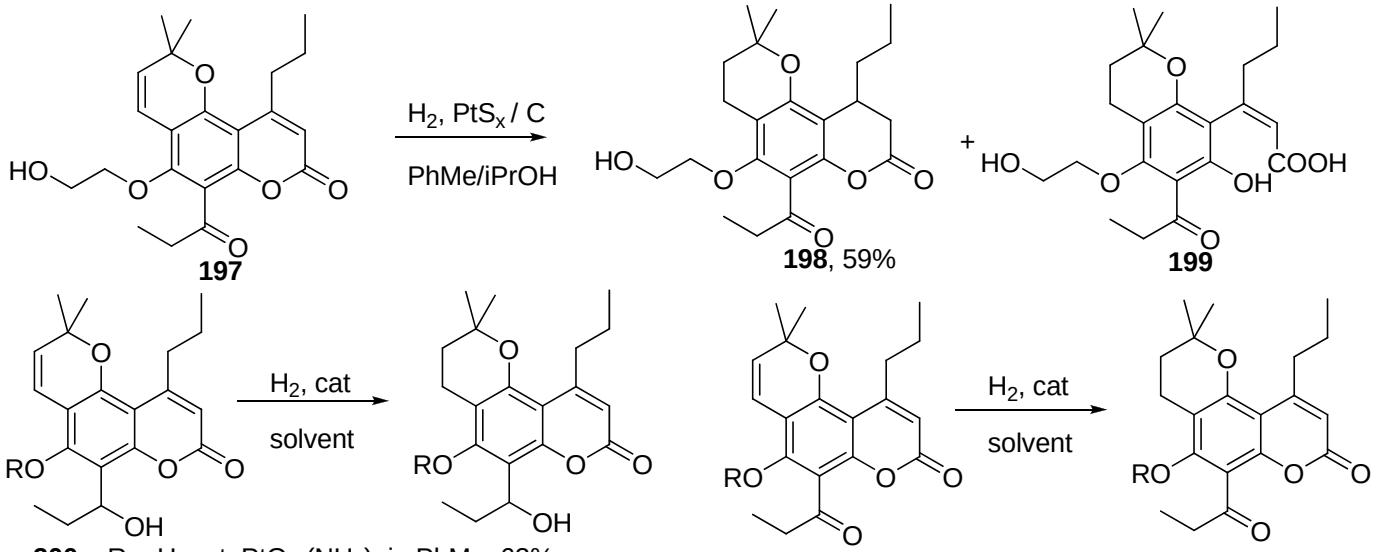
1.2.1.3 With platinum

A few articles on this topic are found. Table 10 represents the information about coumarins' hydrogenation on platinum that gives chroman-2-ones.

In the article[242] it is reported about the selectivity of PtO_2 in hydrogenation of 9-acyloxy-8-(2-acyloxypropan-2-yl)-8,9-dihydrofuro[2,3-h]coumarins, which leaves the coumarin ring intact, and catalyzes only the hydrogenation of the side-chain (with reductive deacylation). With Pd/C this was not observed. The other article[243] also reports about hydrogenation of side-ring without affecting the coumarin.

L. I. Smith and R. O. Denyes report about the hydrogenation of ethyl 5,7,8-trimethyl-6-hydroxycoumarin-3-carboxylate and ethyl 5,7,8-trimethyl-6-acetoxycoumarin-3-carboxylate on PtO_2[244]. The former compound was also reduced by zinc in AcOH (see section 1.2.3).

In patent[245] the use of platinum sulphide, adsorbed on charcoal, is described for reducing of coumarin. Ze-Qi Xu et al.[246] observed a hydrogenation of **197** on 5% PtS_x/C, which gave **198** and **199** as products, although the coumarin-ring of compounds **200a-c** and of **201a-c** was not affected by hydrogenation over this catalyst or over NH_3-poisoned PtO_2.

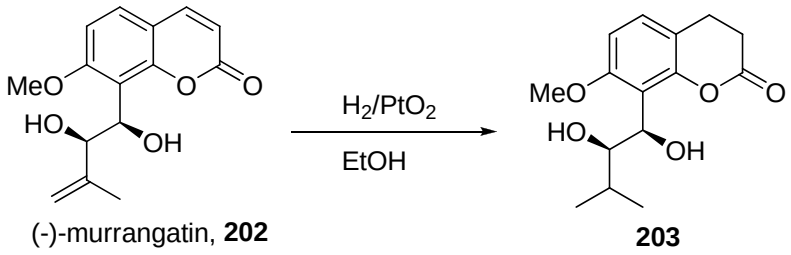


200a, R = H, cat. PtO_2 (NH_3), in PhMe, 63%
200b, R = Me, cat. 5% PtS_x/C, in EtOH, 68%
200c, R = Et, cat. PtO_2 (NH_3), in EtOH, 61%

201a, R = H, cat. 5% PtS_x/C, in PhMe/iPrOH, 53%
201b, R = Me, cat. 5% PtS_x/C, in EtOH, 68%
201c, R = Et, cat. PtO_2 (NH_3), in EtOH, 61%

Scheme 48

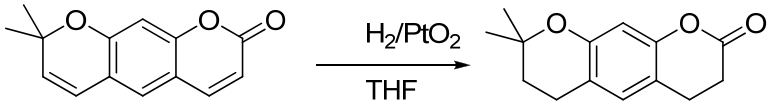
In order to assign the absolute stereochemistry of (-)-murrangatin **202** C. Ito and H. Furukawa[247] have synthesized tetrahydromurrangatin **203** by hydrogenation on platinum oxide. Compound **203** was benzoylated, and stereochemistry of benzoate was assigned with the help of CD by dibenzoate rule.



(-)-murrangatin, **202** **203**

Scheme 49

Y. B. M. Pouliquen et al.[248] have reduced xanthyletin **204**. Like for murrangatin **202**, this reduction goes also to side-chain of coumarin, and **205** was obtained.



xanthyletin, **204** **205**

Scheme 50

Table 10. Summary table of coumarins' hydrogenation on platinum. If otherwise not stated, the product is the corresponding 2-chromanone.

Substrate	p(H_2), bar	solvent	yield, %	time	additional information	ref.
coumarin	N/A	EtOH	N/A	N/A	PtO_2 used.	180
coumarin	48	PhH	N/A	5,5 h	PtS_x/C used, patent, reaction is given as an example	245
197	1	PhMe/ iPrOH	59	16 h	5% PtS_x/C used, products are **198** and **199**	246
(-)-murrangatin **202**	N/A	EtOH	N/A	6,5 h	PtO_2 used, with hydrogenation of side-chain	247
xanthyletin **204**	N/A	THF	98	N/A	PtO_2 used, with hydrogenation of side-chain	248
marmin (7-(3,7-dihydroxy-3,7-dimethyloctyloxy)coumarin)	N/A	EtOH or AcOH	N/A	N/A	PtO_2 used, the product is 7-hydroxychroman-2-one	249
(6S,7S)-6,7-dihydroxy-8,8-dimethyl-7,8-dihydropyrano[3,2-g]coumarin	N/A	AcOH	44	7 h	PtO_2 used, 6-CH(OH) reduced to 6-CH_2, thus yielding (S)-7-hydroxy-8,8-dimethyl-3,4,7,8-tetrahydropyrano[3,2-g]chromen-2(6H)-one as a product (**231**, see later)	250, 251
5-methoxy-4-methylcoumarin	3-4	MeOH	N/A	6 h	PtO_2 used	252
N, N-diethyl coumarin-4-carboxamide, N, N-diethyl coumarin-3-carboxamide, 4-	N/A	EtOH	77, 66, 97, resp.	N/A	PtO_2 used.	92

methylcoumarin						

1.2.1.4 With nickel

Almost every article reviewed in this section reports about coumarins' hydrogenation on Raney-Nickel, although some old articles report about hydrogenation on "plain" nickel. If not stated otherwise, Raney-Nickel was used.

Table 11 represents the information about coumarins' hydrogenation on nickel that gives chroman-2-ones.

P. L. de Benneville and R. Connor[253, 254] have made a research of coumarin's hydrogenation on Raney-nickel and on copper chromite (see later) under pressure of 100-200 bar of hydrogen. The hydrogenation of coumarin at 100º C in ether gives chroman-2-one with a 90% yield, while hydrogenation at higher temperatures (and in the other solvents) gives products of further hydrogenation (e.g. hexa- and octahydrocoumarin and hexahydrochroman).

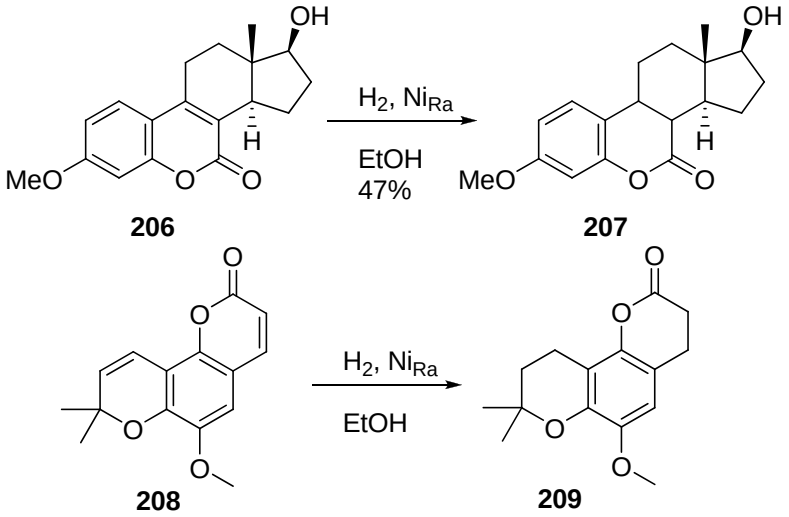
R. F. Armstrong and T. P. Hilditch[255] report about hydrogenation of coumarin on nickel. They have studied the kinetical properties of such a hydrogenation, and their article is not synthetical. However, the name "Raney" does not occur in this article, that suggests that "plain" nickel was used.

V. L. Palfray and S. Sabetay[256] report about coumarin's hydrogenation at high pressure on plain or Raney-nickel. However, they do not report the value of pressure. But in the article[257] V. L. Palfray writes "150 kg" stating the pressure of hydrogen. From this context it is not obvious to what area this weight is referred so that the pressure cannot be distinguished.

F. D. Mills[202] reports that 8-methoxy-4,7-dimethylcoumarin could not be hydrogenated over Raney-nickel under 103 bar in EtOH.

Y. S. Sanghvi and A.S. Rao[258] have reduced 4,7-dimethylcoumarin in hard conditions (aqueous NaOH, Raney-nickel, 100 bar of hydrogen, 180º C) and obtained a series of substituted cyclohexanes and octahydrochromans, i.e. the phenyl-ring was hydrogenated.

Two articles describe the hydrogenation of more complex coumarins over Raney nickel: of compound **206**[259] and of **208**[199].



Scheme 51

Table 11. Summary table of coumarins' hydrogenation on nickel. If not stated otherwise, the product is the corresponding 2-chromanone and Raney-nickel was used.

Substrate	$p(H_2)$, bar	solvent	yield, %	time	additional information	ref.
208	N/A	EtOH	N/A	N/A	with reduction of side-ring. The product is **209**	[199]
coumarin	103	EtOH	N/A	2 h		[237]
4-methylcoumarin	3-4	MeOH	71	7 h		[252]
coumarin	100-200	Et_2O	N/A	0.5 h	100º C	[253]
coumarin	High	N/A	N/A	N/A	plain and Raney-nickel used, no synthetic procedures available	[256, 257, 260]
206	124	EtOH	47	2 days	100º C, product is **207**, 15% of starting material recovered	[259]
coumarin	30	iPrOH	28	1 h	20-120º C, patent, reaction is given as an example	[261]
coumarin	N/A	EtOAc	100	50 min	ultrasonic irradiation	[262]
coumarin	N/A	EtOAc	57	120 min	without ultrasonic irradiation	[262]

1.2.2 Transfer hydrogenation of coumarins

A few articles are found representing this method of hydrogenation for coumarins. For coumarins CTH was catalyzed by palladium (diverse forms) and by Raney nickel[263]. Table 12 represents the information about coumarins' CTH, resulting in chroman-2-ones.

K. Kindler and K. Lührs[264] have studied the reduction of some organic compounds with terpens as reducing agents. They report that only 10% Pd/C was active in such reactions, while Rh/C and Pt black were inactive. Unfortunately, they do not report the yields of reduced compounds. Similar is the method of Sh. Akabori and T. Suzuki[265] who used tetraline. But they used Pd black as a catalyst.

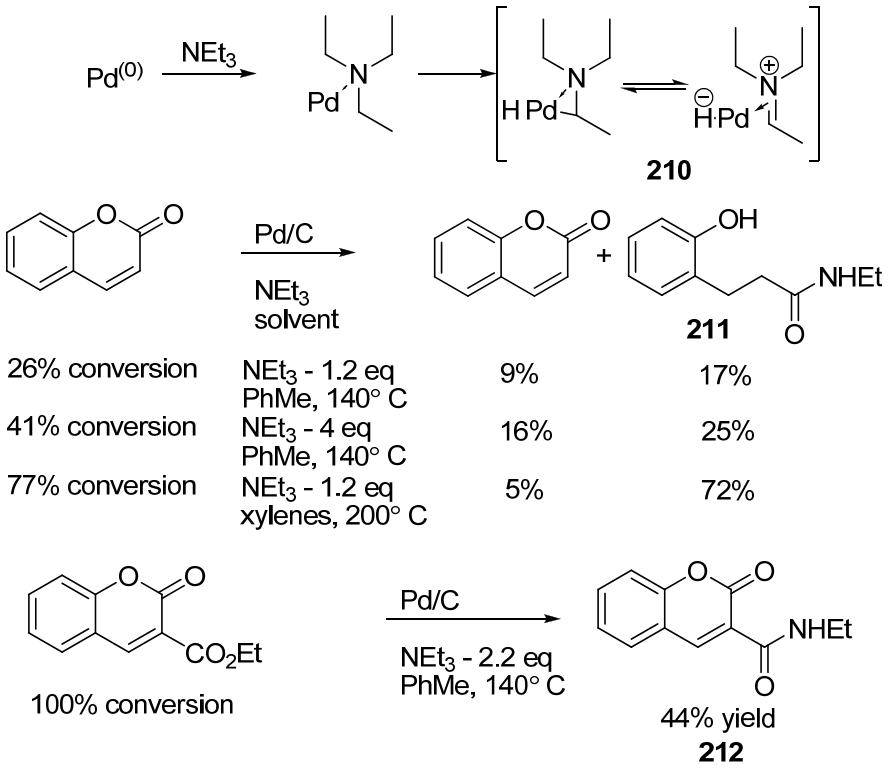
B. J. Hussey and R. A. W. Johnstone[266] have studied reductive cleavage of phenolic hydroxyl groups by CTH. Among Ru/C, Rh/C, Pd/C and Pt/C only the palladium catalyst was active. In order to achieve such a cleavage, the C–O-bond should be weakened. A set of compounds was synthesized to study this process under CTH-conditions. Among the other compounds 7-(1-phenyl-1H-tetrazol-5-yloxy)-coumarin was reduced. The aim was to make a C–O cleavage, not to reduce the coumarin, but traces of croman-2-one were recorded by gas-chromatography.

B. Elamin et al.[267] report about the flow reactor for CTH. Coumarin was reduced with a 100% yield using HCOOH on Pd black.

H. Berthold et al.[268] performed CTH on 10% Pd/C in ionic liquid (BMIM PF_6), assisted by MW-irradiation. When the system NH_4COOH was used from 6-methylcoumarin only 3-(2-hydroxy-5-methylphenyl)propanamide was obtained with a yield 30%. When using NEt_3/HCOOH, no conversion of 6-methylcoumarin was observed.

N.C. Ganguly et al.[269] report about selective deallylation of 6- and 7-allyloxycoumarins by ammonium formate in methanol, catalyzed by 10% Pd/C. At r.t. the coumarin ring was not affected, but under reflux it was also hydrogenated.

French scientists[270] have studied the CTH by triethylamine over 10% Pd/C and over other precious metals, adsorbed on charcoal. The hydrogenation of coumarins was studied only using Pd/C. They show that the system triethylamine-Pd/C probably produces the particle **210**, which can act as reducing agent for various activated C=C-bonds. Applied to coumarin, the chroman-2-one and amide **211** were detected in reaction mixture. Ethyl coumarin-3-carboxylate,however, only gave N-ethyl coumarin-3-carboxamide **212**, probably through Pd/C-catalyzed dehydrogenation.



Scheme 52

The series of 3,4-diarylcoumarins is reduced by CTH with isopropanol on Raney-nickel[263]. The authors report that 2,2-dimethyl-3,4-diarylchromenes could also be reduced with this method. Unfortunately, the authors do not give the yields of the synthesized compounds.

A. Sharma, V. Kumar and A. K. Sinha[271, 272] have studied CTH of α,β-unsaturated carbonylic/carboxylic compounds by formic acid under MW-irradiation. The reaction was catalyzed by $PdCl_2$. The reaction mixture was adsorbed on silica gel, then subjected to MW-irradiation in domestic[271] or in the focussed[272] MW-oven. Coumarin was hydrogenated with a yield of 55% (domestic) or 32% (focussed MW). Additionally, 3-(2-hydroxyphenyl)propanoic acid was isolated (14% or 47%, resp.).

Table 12. Summary table of coumarins' catalytic thransfer hydrogenation. If otherwise not stated, the product is the corresponding 2-chromanone.

Substrate	reducing agent	solvent	yield, %	time	additional information	ref.
6-methyl-3,4-diphenyl-, 7-methoxy-3,4-diphenyl-, 7-methoxy-4-(4-methoxyphenyl)-3-phenyl-, 4-(4-methoxyphenyl)-3-phenyl-, 7-methoxy-4-(4-hydroxyphenyl)-3-phenylcoumarin, 1,2-diphenyl-3H-benzo[f]chromen-3-one, 13-methyl-9H-phenanthro[9,10-c]chromen-9-one	iPrOH	iPrOH/THF 1/8	N/A	0.5 h	Raney-nickel used, 60-65ºC	[263]

coumarin	Limonene	p-menthan	N/A	10 min	10% Pd/C used, 173º	[264]
coumarin	Tetraline	PhMe	N/A	N/A	Pd black used, 115-120º C, synthetical procedure not available	[265]
7-(1-phenyl-1H-tetrazol-5-yloxy)-2H-chromen-2-one	NaH_2PO_2	PhH/EtOH/ H_2O	traces	55 min	10% Pd/C used, aim coumpound, coumarin, isolated with 91% yield	[266]
coumarin	HCOOH	N/A	100	5 min	Pd black used	[267]
7-methoxycoumarin	HCO_2NH_4	MeOH	96	2 h	10% Pd/C used, reflux	[269]
coumarin	NEt_3 (1.2 eq or 4 eq)	PhMe	34, 39 (borsm, resp.).	16 h	10% Pd/C used, 140º C, product was not isolated	[270]
coumarin	NEt_3 (1.2 eq)	xylenes	6 (borsm)	16 h	10% Pd/C used, 200º C, product was not isolated	[270]
coumarin	HCOOH	silica gel/MeOH/ HCOOH/ H_2O	55 (domes-tic MW) or 32 (focused MW)	55 min or 7 min, resp.	$PdCl_2$, MeOH, HCOOH, H_2O (+HCO_2NH_4 in some experiments) and substrate were adsorbed on silica gel, then MW-reaction performed in domestic or focused MW-oven	[271, 272]

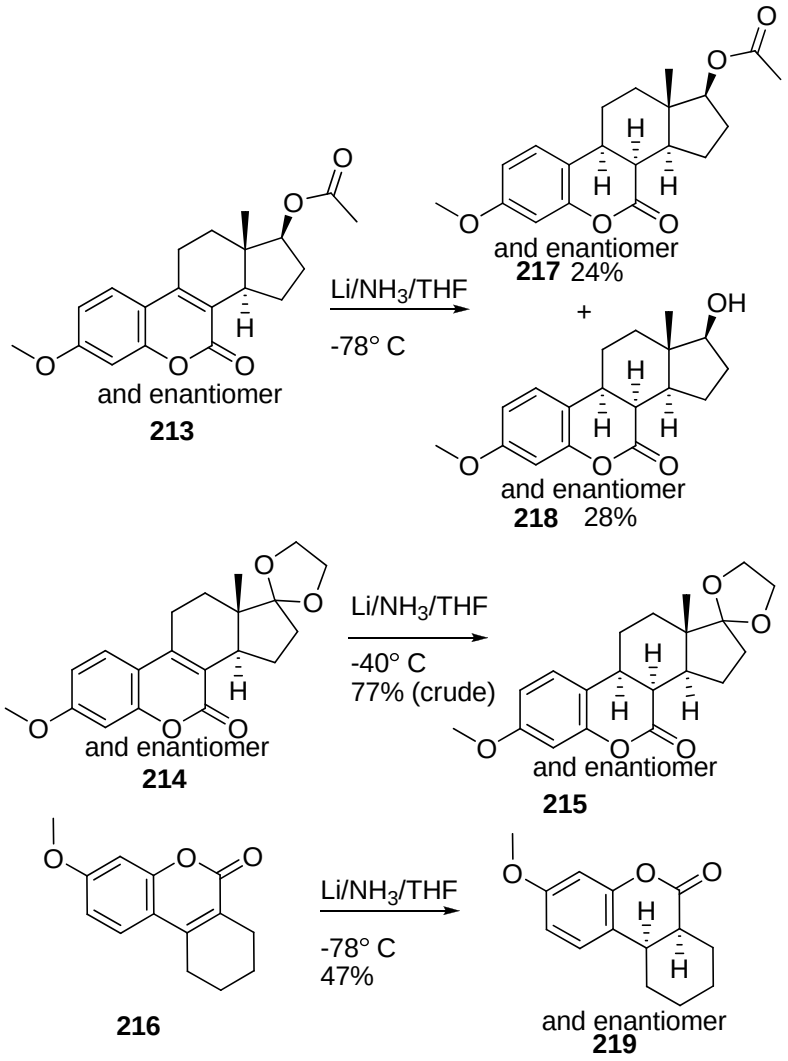
1.2.3 Reduction of coumarins with metals

Reduction with metals was widely applied for coumarins. Essentially it was the reduction with Raney-nickel alloy (Ni/Al) in alkali. Also Zn in AcOH, Zn/Cu couple, sodium amalgam and metals in liquid ammonia were used.

Table 13 shows the information about coumarins' reduction with metals that gives chroman-2-ones.

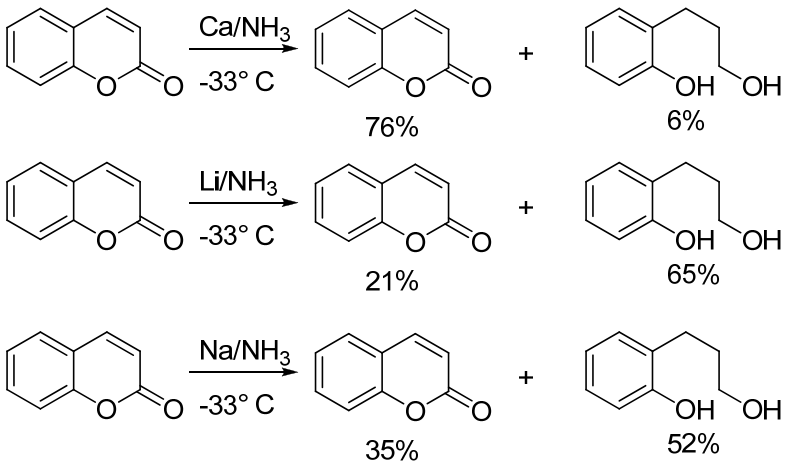
The article[273] reports about hydrogenation of seselin (8,8-dimethyl-2H,8H-pyrano[2,3-f]chromen-2-one) by Li/NH_3 which leaves the coumarin-ring intact. A.J. Birch et al.[274] have found the coumarin ring to stay intact after reduction with Li/NH_3 and Na/NH_3.

Nevertheless, D. J. Collins et al. [259] report about the reduction of steroidal coumarins **213** and **214** by lithium in liquid ammonia. Purposeful compound **215** was partially opened by ammonia to give the corresponding carboxamide, but the yield of chroman-2-one **215** was 77%. The same D. J. Collins and the other group of coauthors[275] report about the reduction of **216** by Li/NH_3.



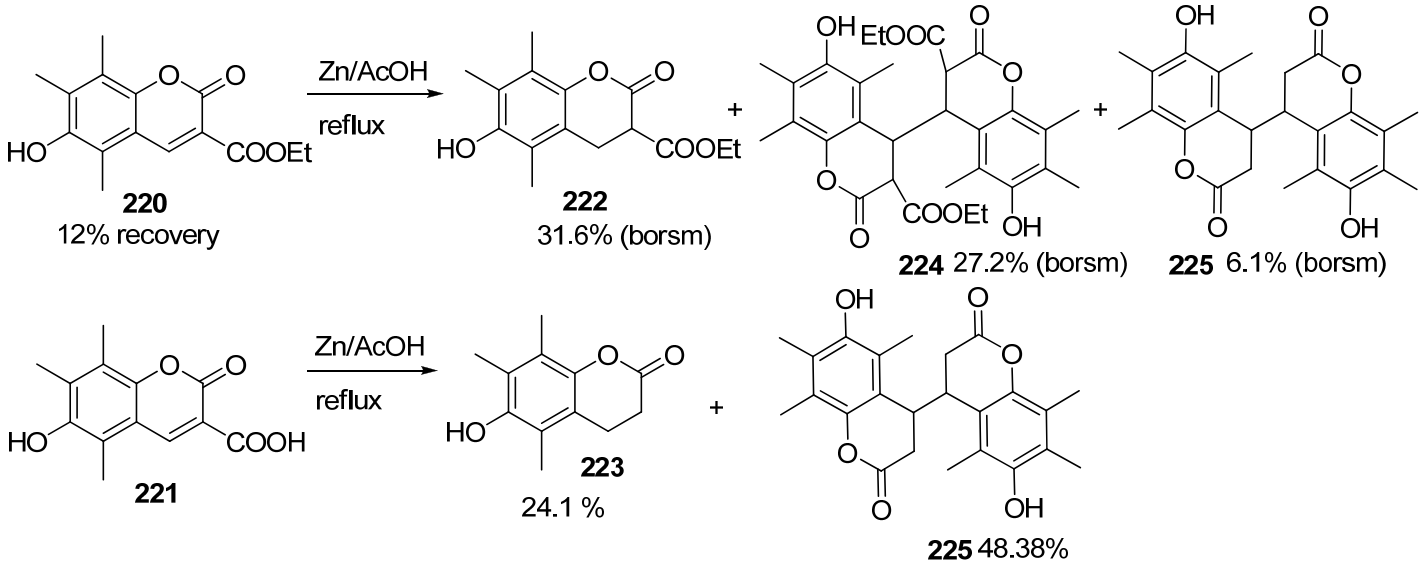
Scheme 53

J. R. Hwu et al.[162] have also studied the reduction with metals in liquid ammonia. The simple coumarin was reduced to the mixture of chroman-2-one and 2-(3-hydroxypropyl)phenol. The application of Ca, Li and Na in liquid ammonia is shown in scheme 54.



Scheme 54

Ethyl 5,7,8-trimethyl-6-hydroxycoumarin-3-carboxylate **220** and 5,7,8-trimethyl-6-acetoxycoumarin-3-carboxylic acid **221** were reduced by Zn in AcOH[244]. This reduction yielded the corresponding chroman-2-ones **222, 223** with dimerized **224** and with dimerized and decarboxylated chroman-2-one **225**.



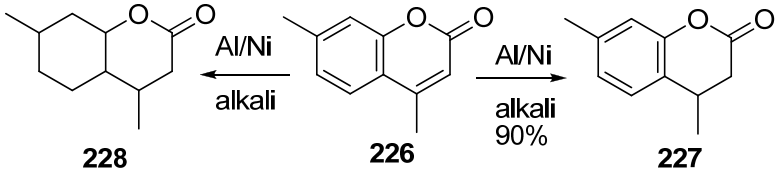
Scheme 55

A. F. Barrero et al.[276] have studied the reduction of α,β-unsaturated carbonyl and carboxyl compounds by Raney nickel (without hydrogenation). They report that Raney-nickel can reduce them selectively, without reducing the unconjugated C=C-bond, if such is present in molecules. Coumarin was also reduced (90%) by Raney-nickel. Unfortunately, they have not tested the reduction of furocoumarins, it could be a method of its reduction without affecting the side C=C-bond and without reductive deacylation.

A. S. Dreiding and A. J. Tomasewski[277] have reduced β-(6-methyl-4-coumarin)-propionic acid in NaOH with Raney-nickel alloy. Essentially they have opened the coumarin

cycle by alkali, which must facilitate the reduction and then the corresponding *o*-hydroxycinnamate was reduced either by hydrogen on Raney-nickel or by Al itself. The mechanism of this reaction was not studied, but for coumarins both mechanisms are possible.

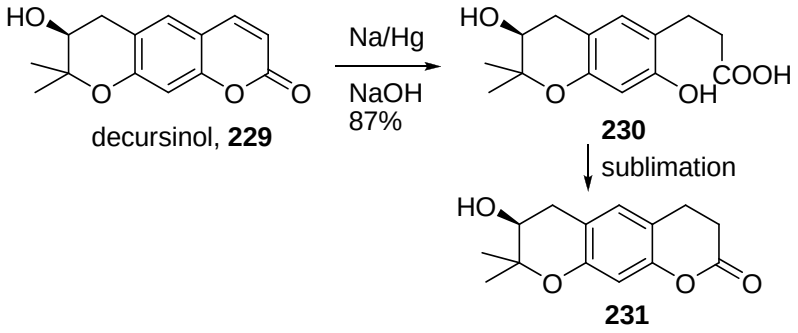
D. G. Talekar et al.[105] report about the reduction of 4,7-dimethylcoumarin **226** by this method. They could obtain either 4,7-dimethylchroman-2-one **227** or 4,7-dimethyloctahydrocoumarin **228** (mixture of stereoisomers).



Scheme 56

A. A. Ranade et al.[278] have reduced 2H-naphto[2,3-b]pyran-2-one, but with benzo[g]chroman-2-one also 3-(3-hydroxynaphthalen-2-yl)propanoic acid was present in the resulted mixture. This mixture was refluxed with TsOH in benzene for 1 hour to give pure 3,4-dihydrobenzo[g]chromen-2-one. The same problems occurred with the reduction of 2H-naphto[1,2-b]pyran-2-one and 3H-naphto[2,1-b]pyran-3-one. All the three 2-cromanones were further reduced by LAH to give chromans.

A few articles are found where coumarins' reduction with sodium amalgam is reported[279-281]. The reduction of decursinol **229** by Na/Hg gave the corresponding **230** which was cyclized to **231** by vacuum sublimation[250]. However, the application of sodium, encapsulated in silica gel, for reduction of coumarin yielded 2-(3-hydroxypropyl)phenol (77%)[282], i.e. the carboxylic-group was also reduced.



Scheme 57

B. L. Sondengam et al.[283] report about the reduction of ethyl coumarin-3-carboxylate in refluxing methanol by zinc-copper couple. For this reduction a presence of two electron-withdrawing groups is required. Coumarin was not reduced by such a method, but recovered with 95% yield.

Table 13. Summary table of coumarins' reduction with metals. If not stated otherwise, the product is the corresponding 2-chromanone.

Substrate	reducing reagent	solvent	yield	time	additional information	ref.
ethyl 5,7,8-trimethyl-6-hydroxycoumarin-3-carboxylate	Zn/AcOH	AcOH	28	N/A	reflux, 12% of starting material recovered	[244]
7,8-trimethyl-6-acetoxycoumarin-3-carboxylic acid	Zn/AcOH	AcOH	24	N/A	reflux, decarboxylated product isolated	[244]
213	Li/NH_3	NH_3/THF	28	30 min	at -78º C, products: **217** (24%) and **218** (28%)	[259]
214	Li/NH_3	NH_3/THF	77	1 h	-40º C, product **215**	[259]
coumarin	Raney nickel	THF	90	15 min		[276]
216	Li/NH_3	NH_3/THF	47	30 min	-78º C, product **219**	[275]
coumarin	Ca/NH_3	THF/NH_3 1/4	76	2 h	-33º C	[162]
coumarin	Li/NH_3	THF/NH_3 1/4	21	2 h	-33º C	
coumarin	Na/NH	THF/NH_3 1/4	35	2 h	-33º C	
β-(6-methyl-4-coumarin)-propionic acid	Ni/Al	NaOH	57	5 h	heating	[277]
4,7-dimethylcoumarin	Ni/Al	Alkali	90	N/A		[105]
2H-naphto[2,3-b]pyran-2-one, 2H-naphto[1,2-b]pyran-2-one, 3H-naphto[2,1-b]pyran-3-one	Ni/Al	NaOH	85	85	mixture of chromanone and phenylpropanoic acid obtained, the latter was cyclized by TsOH in PhH	[278]
dicoumarin (2H,2'H-3,3'-bichromene-2,2'-dione)	Na/Hg	Alkali	N/A	N/A		[279]
3-coumarincarboxylic acid	Na/Hg	N/A	N/A	N/A	no synthetic procedure available	[280]
1-phenyl-2,3-dihydrochromeno[4,3-b]pyrrol-4(1H)-one	Na/Hg	EtOH	28	24 h		[281]
ethyl coumarin-3-carboxylate	Zn-Cu	MeOH/H_2O	94	6 h	reflux	[283]
coumarin	Ni/Al	NaOH	85	1.5 h	90º C	[284]

As can be seen in Table 13, the reduction of coumarins with metals is quite a good method, surely not free from some drawbacks. As usual, the drawbacks are connected with the decomposition of the coumarin ring, hence the formation of diverse products.

1.2.4 Reduction of coumarins with complex hydrides

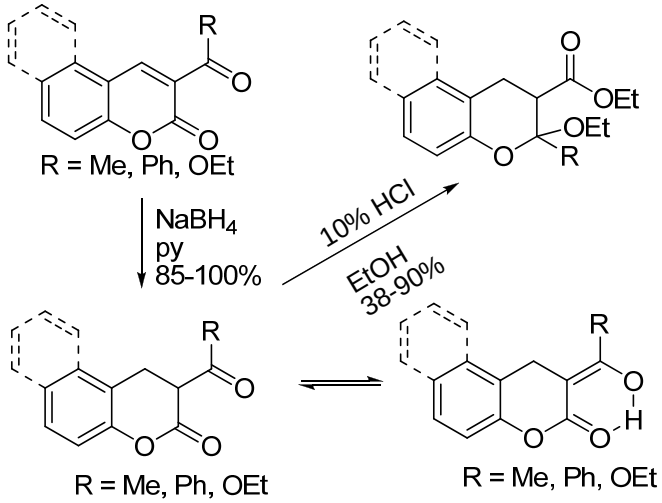
Table 14 represents the information about coumarins' reduction with complex hydrides that gives chroman-2-ones.

Several authors report that the coumarin-cycle is broken by LAH[285]. P. K. Arora[263] reports about cycle-breaking by LiAl(O*t*-Bu_3)H.

Some derivatives of ethyl coumarin-3-carboxylate are proven to be broken by $NaBH_4$ in MeOH[286]. The system $CoCl_2$/$NaBH_4$ reduces neoflavanone and 6-methylneoflavone to 2-(3-hydroxy-1-phenylpropyl)phenol and 2-(3-hydroxy-1-phenylpropyl)-4-methylphenol, resp.[287].

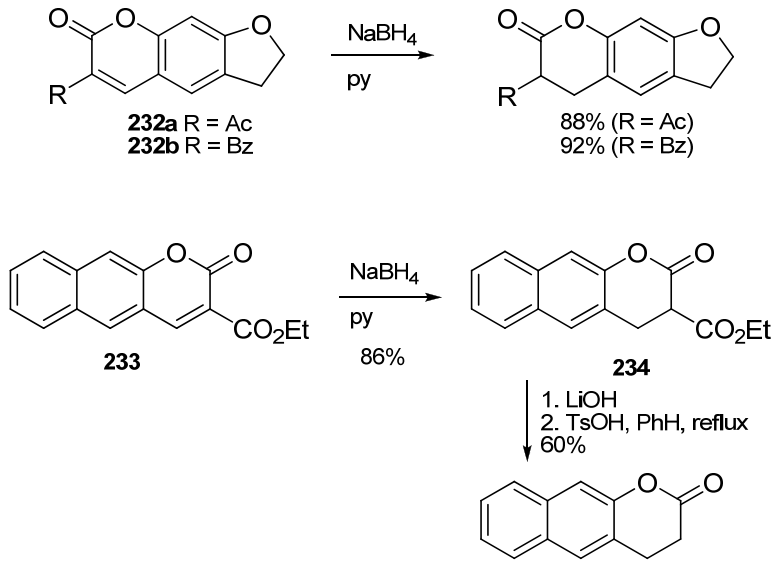
Like the other reducing-reagents, sometimes $NaBH_4$ can leave the coumarin-ring intact[288]. Many coumarins, bearing the unsaturated side-chains, were reduced by $NaBH_4$ or by $NaBH_4/CeCl_3$ without reduction of the coumarin-ring[246]. These coumarins have 3-H and 4-alkyl substituents, i.e. not bearing an EWG in the 3rd position.

$NaBH_4$ in pyridine is proven to be a very selective reducing reagent for the coumarins, bearing 3-acyl- or 3-carboxyl-group[289] (see scheme 58). The chroman-2-ones obtained are found to be very enolizable. An interesting rearrangement inherent for such compounds was found (see scheme 58).



Scheme 58

The same authors report about a reduction of 6-acyl-2,3-dihydrofuro[3,2-g]chromen-7-ones **232a-b**[290]. A similar reduction of ethyl 2-oxo-2H-benzo[g]chromene-3-carboxylate **233** and of ethyl 3-oxo-3H-benzo[f]chromene-2-carboxylate is described in article[291]. Compound **234** was further saponified and decarboxylated. Very similar compounds are reduced by $NaBH_3CN$ in presence of HCl[292].



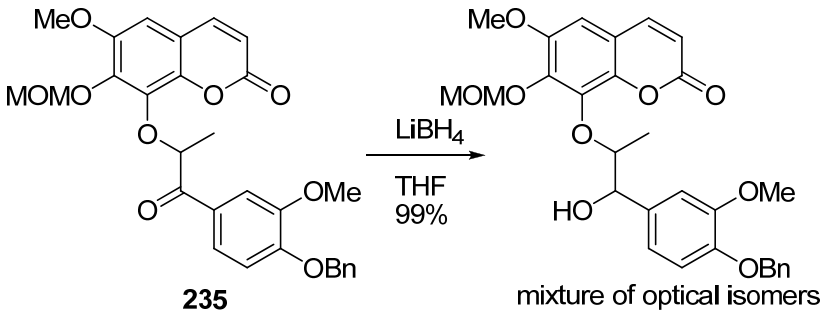
Scheme 59

G. Kokotos with C. Tzougraki[232] report about the synthesis of 3-acetamido-6-amino-, 3-acetamido-8-amino and 6-aminocoumarin by reduction of the corresponding nitrocoumarin by $NaBH_4$ in presence of 10% Pd/C in aqueous methanol. The coumarin-ring was not affected.

M. Lissel et al.[293] have studied several hydrydoboranes in the reduction of coumarin-3-carboxylic- and thiocarboxylic acid ethyl esters: diborane (BH_3), borane/dimethyl sulphide, 9-borabicyclo[3.3.1]nonane (9-BBN), bis[*t*-butylthio]ethane-diborane (BTED). With ethyl coumarin-3-carboxylate all these boranes were tested, while with the other coumarin-3-carboxylates only 9-BBN was tested. All these boranes give the corresponding chroman-2-ones with yields of 45-57%.

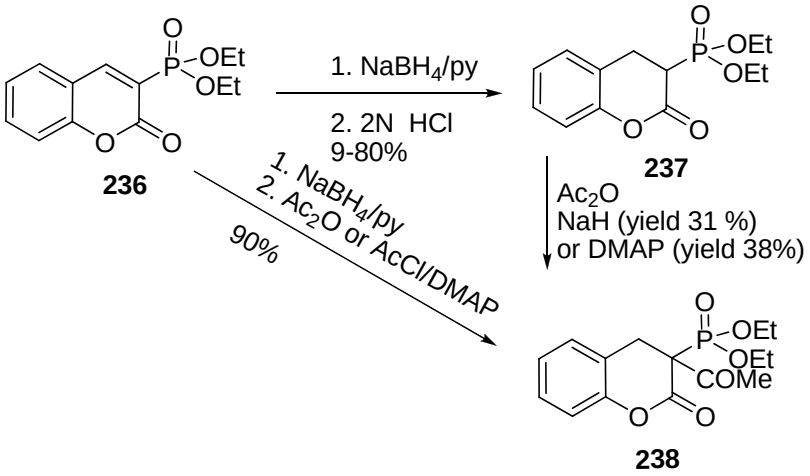
Article[294] describes the reduction of 3-nitrocoumarin with $NaBH_4$ in water at room temperature. 3-Nitrochroman-2-one was isolated with a yield of 75%.

The use of $LiBH_4$ is described in article[295]. It has reduced the carbonyl in the side-chain of the substituted coumarin **235**, without affecting the coumarin ring.



Scheme 60

Diethyl 2-oxo-2H-chromen-3-ylphosphonate **236** was reduced and acetylated in one-pot synthesis[296]. The authors did not prepare pure **237** from **236**, but have made these reactions consecutive: the crude **237** was acetylated. After a two-step reaction the highest yield of **237** was 80%, which is linked with the problems during acetylation. In the best run the yield of **237** was 9% while that of **238** was 90%. This means, that the initial yield of **237** was 99%.



Scheme 61

Table 14. Summary table of coumarins' reduction with complex hydrides. If not stated otherwise, the product is the corresponding 2-chromanone.

Substrate	reducing reagent	Solvent	yield	time	additional information	ref.
3-acetyl-, 3-benzoylcoumarin, ethyl coumarin-3-carboxylate, 2-acetyl-3H-benzo[f]chromen-3-one, 2-benzoyl-3H-benzo[f]chromen-3-one, ethyl 3-oxo-3H-benzo[f]chromene-2-carboxylate	$NaBH_4$	Pyridine	N/A, 92, 88, 93, 100, 85, resp.	3-4 h	products are very enolizable	[289]
232a, 232b	$NaBH_4$	Pyridine	88, 92 resp.	30 min	products are very enolizable	[290]
3-benzoyl-, 6-methoxy-3-benzoyl, 6-nitro-3-benzoylcoumarin	$NaBH_3CN$	EtOH	57,81, 86 resp.	4, 1.5, 1.5 h resp.	in presence of HCl and bromcresol green as pH-indicator	[292]
ethyl 2-oxo-2H-benzo[g]chromene-3-carboxylate **233**, ethyl 3-oxo-3H-benzo[f]chromene-2-carboxylate	$NaBH_4$	Pyridine	86, 85, resp.	1.5 h	0ºC, then r.t.	[291]
ethyl coumarin-3-carboxylate	BH_3, 9-BBN, BMS, BTED	THF	54, 57, 45, 45 resp.	4 h	0ºC	[293]
ethyl coumarin-3-thiocarboxylate, 5,7-dimethoxycoumarin-3-carboxylate, 5,7-dimethoxycoumarin-3-thiocarboxylate, 8-methoxycoumarin-3-carboxylate, ethyl 3-oxo-3H-benzo[f]chromene-2-carboxylate	9-BBN	THF	55,55, 55,45, 52, resp.	4 h	0ºC	[293]
3-nitrocoumarin	$NaBH_4$	Water	75	1,5 h		[294]

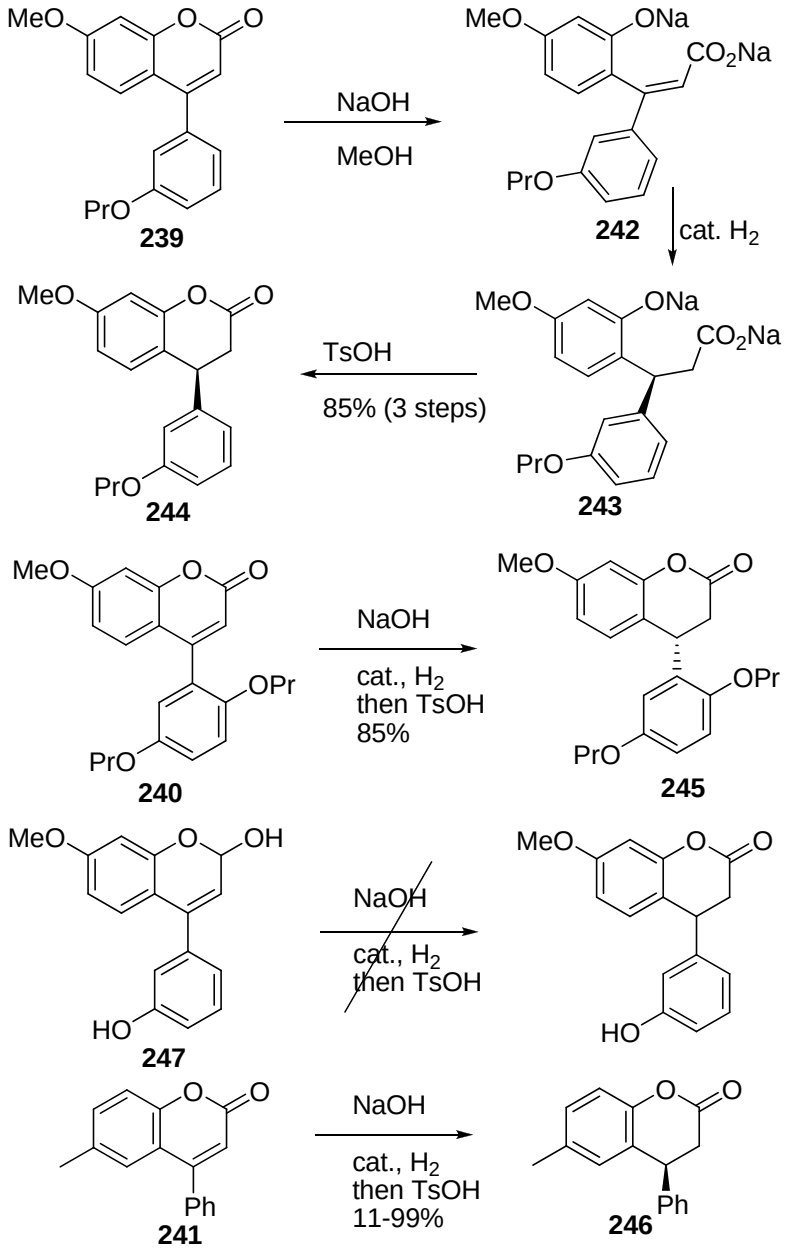
diethyl 2-oxo-2H-chromen-3-ylphosphonate **237**	$NaBH_4$	Pyridine	80	20 h	the highest yield of isolated chroman-2-one. Yileds of not isolated chromanones were higher.	[296]
3-benzoylcoumarin	$NaBH_4$	Pyridine	79	30 min		[297]

As a summary, $NABH_4$ in pyridine or in the other solvent is a very efficient reagent for the reduction of coumarin, but the latter should have an EWG in the 3rd position.

1.2.5 Homogeneous hydrogenation of coumarins

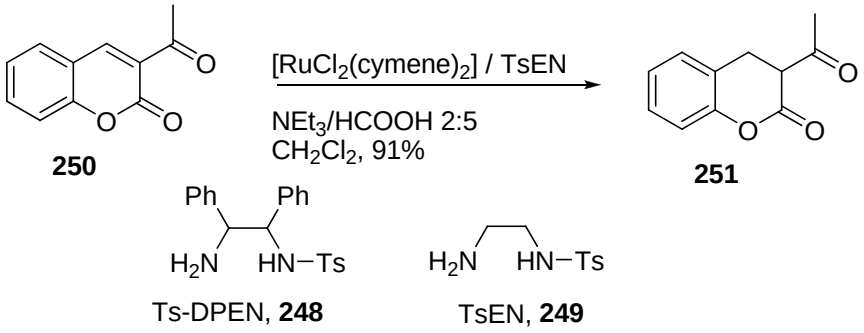
Table 15 presents the information about coumarins' homogeneous hydrogenation that gives chroman-2-ones.

Several articles[191, 192] and patents[298, 299] describe homogeneous hydrogenation of coumarins. Neoflavones **239, 240,** and **241** were decomposed by NaOH (or by the other hydroxides) to give the corresponding bis-sodium salts (**242** and similar). The latter were homogeneously hydrogenated with moderate to high ee in good yield. The subsequent salts of chiral carbonic acids (**243** and similar) were lactonized by using TsOH to give the corresponding chroman-2-ones **244**, **245,** and **246**. The catalyst, which gave the highest ee, was found to be an *in situ* prepared complex from $[Rh(COD)Cl]_2$ and Chiraphos ligand. All attempts to hydrogenate **247** were in vain, probably because of the coordination of catalyst to phenol-oxygen.



Scheme 62

D. Xue et al.[300] report about the transfer hydrogenation (using NEt_3/HCOOH 2/5) of α,β-unsaturated carbonyl compounds, catalyzed by Ru-complexes of tosylated diamines. TsDPEN **248** is known to be a ligand that can switch Ru to hydrogenate a carbonyl-group even in presence of double carbon-carbon bond[24, 300]. The autors of the article[300] have synthesized the substance **249** and coordinated it to Ru. This system hydrogenated the C=C bond when the latter was conjugated with the carbonyl from the first and with the benzene-ring from the other side. Unfortunately, this ligand is not chiral, so that such a hydrogenation could not be asymmetric. Among the other compounds 3-acetylcoumarin **250** was hydrogenated to give **251** with a 91% yield.



Scheme 63

Also coumarin was reduced by the known procedure hydrosilation/desilylation[24]. Coumarin was hydrosilated with triethylsilane in presence of Wilkinson's catalyst ($[Rh(PPh_3)_3Cl]$)[301]. After chromatography on silica gel chroman-2-one was isolated with a yield of 87%. The authors note that trisubstituted double-bond could not be reduced by such a method, e.g. hydrosilation of 7-dimethylamino-4-methylcoumarin leaves this coumarin intact.

Table 15. Homogeneous hydrogenation of coumarins. If not stated otherwise, the product is the corresponding 2-chromanone.

Substrate	Catalyst	solvent	yield, % (ee, %)	time	additional information	ref.
7-methoxy-4-(3-propoxyphenyl)-coumarin **239**	[RuCl((S)-BINAP)(p-cymene)]Cl	MeOH, iPrOH,	85 (39-85)	18 h	activation by hydroxide, hydrogenation at 50º C under 1.2-5.5 bar of H_2, then lactonization	191, 299
7-methoxy-4-(3-propoxyphenyl)-coumarin **239**	[RuCl((S)-BINAP)(p-cymene)]Cl	MeOH/ CH_2Cl_2	85 (46)	18 h	activation by hydroxide, hydrogenation at 25º C under 5.5 bar of H_2, then lactonization	191, 299
7-methoxy-4-(3-propoxyphenyl)-coumarin **239**	[RuCl((S)-TolBINAP)(p-cymene)]Cl	MeOH	85 (84)	18 h	activation by hydroxide, hydrogenation at 50º C under 1.2 bar of H_2, then lactonization	191, 299
7-methoxy-4-(3-propoxyphenyl)-coumarin **239**	$[RuBr_2(S\text{-}TolBINAP)]_n$	MeOH	85 (64)	18 h	activation by hydroxide, hydr. at 50º C under 1.2 bar of H_2, then lactonization	191, 299
7-methoxy-4-(3-propoxyphenyl)-coumarin **239**	[Rh(COD)(Et-DuPhos)]OTf	MeOH	85 (78)	18 h	activation by hydroxide, hydr. at 50º C under 27.5 bar of H_2, then lactonization	191, 299
7-methoxy-4-(3-propoxyphenyl)-coumarin **239**	$[Rh(NBD)(P\hat{}P)]ClO_4$	MeOH	85 (43-85)	18 h	activation by hydroxide, P^P: R-Prophos, S,S-Skewphos, S,S-Chiraphos, hydrogenation at 50º C under 27.5 bar of H_2, then lactonization	191, 299
7-methoxy-4-(3-propoxyphenyl)-coumarin **239**	$[Rh(COD)Cl]_2$ + S,S-Chiraphos	MeOH	85 (91-95)	18 h	activation by hydroxide, hydrogenation at 50º C under 5.5-12.4 bar of H_2, then lactonization	191, 299
4-(2,5-dipropoxyphenyl)-7-methoxycoumarin **240**	[RuCl((S)-BINAP)(p-cymene)]Cl	MeOH	85 (84)	48	activation by hydroxide, hydrogenation at 50º C under 1.3 bar of H_2, then lactonization	191, 299
6-methylneoflavone **241**	$[Rh(CODCl]_2$ + (S,S)-Chiraphos; $Ru(TFA)_2$ + (+)-TMBTP	MeOH	96 (80)	24 h	activation by hydroxide, hydrogenation at 50º C under 12 bar of H_2, then lactonization	192, 298
6-methylneoflavone **241**	[Rh(nbd)((S,S)-Chiraphos)]BF_4;	MeOH	11(20), 99(0),	24 h	activation by hydroxide, hydrogenation at 50º C under 12 bar	192, 298

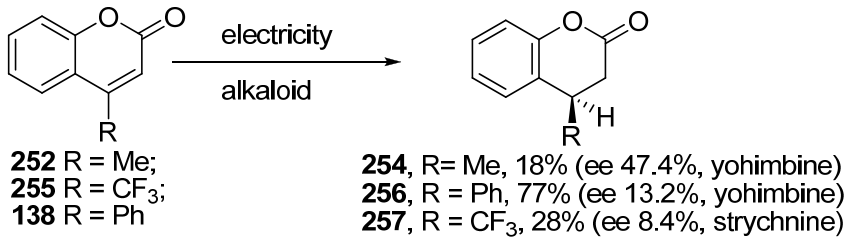
	$[Rh(COD)Cl]_2$ + (R)-Prophos; $[Ru((S)\text{-}BINAP)(OAc)_2]$		22(44), resp.		of H_2, then lactonization	
3-acetylcoumarin **250**	[Ru(p-cymene)(TsEN)Cl]Cl, prepared from $[Ru(p\text{-}cymene)Cl_2]_2$ + TsEN **249**	CH_2Cl_2	91 (0)	2 h	without activation by hydroxide, hence, without lactonisation, transfer hydrogenation, NEt_3/HCO_2H complex used as hydrogen source	[300]
coumarin	$[Rh(PPh_3)_3Cl]$	PhH	87	16 h	without activation by hydroxide, hence, without lactonisation, hydrosilation by Et_3SiH, then desisilation on silica gel	[301]

1.2.6 Electrochemical reduction

R. N. Gourley et al.[302] report about the electrochemical reduction of coumarin and of 4-methylcoumarin **252** in presence of organic bases in aqueous methanol (see scheme 65). As organic bases some alkaloids were used (catalytically). The best yield of chroman-2-ones was when yohimbine was added. The other compound is proven to be dimerized chromanone **253,** mixture of stereoisomers. Chirality of alkaloids has induced the stereoselectivity in coumarins' reduction. 4-Methylchroman-2-one **254** was obtained with ee 19% (when yohimbine was used). Simple coumarin was reduced in the similar conditions with yield of 56.6%.

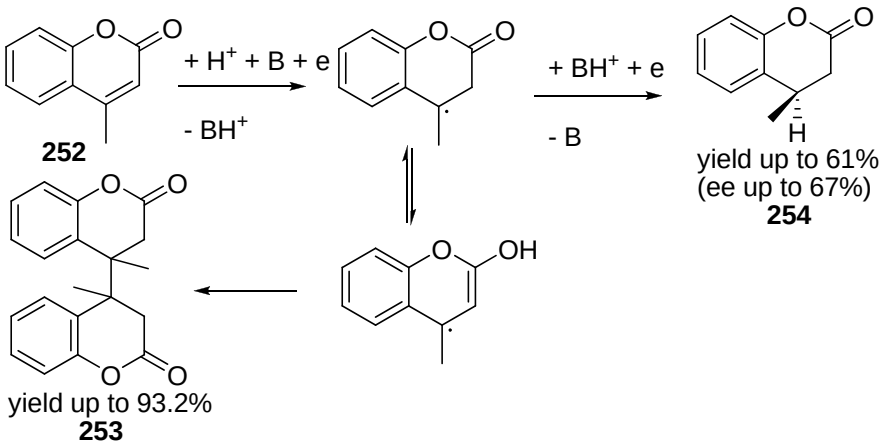
In their next article[252] the yield of chroman-2-one was improved to 66.9%. Additionally 4,7-dimethylcoumarin and 5-methoxy-4-methylcoumarin were electrochemically hydrogenated in presence of various alkaloids. 4,7-Dimethylchroman-2-one was obtained in yield of 24.2% (codeine as base), and the best yield of 5-methoxy-4-methylchroman-2-one was 84% (emetine as base). The products have shown optical activity, but enantiomeric excesses of the reduction reactions were not measured.

Later N. Schoo and H.-J. Schäfer[303] have studied the reduction of coumarins **138, 252** and **255**. They have optimized the conditions (alkaloid, pH, electrode potential, solvent, carrier electrolyte) to have the highest ee. The best yield of 4-methylchroman-2-one **254** was 18% (ee 47.4%), of neoflavanone **256** 77% (ee 13.2%), and of 4-trifluoromethylchroman-2-one **257** 28% (ee 8.4%). Although neoflavone **138** is reduced with quite a good chemical yield, **255** and **257** undergo a partial elimination, thus producing 4-CF_2H-, 4-CFH_2 and even 4-CH_3-coumarin and similar 4-substituted chroman-2-ones.



Scheme 64

The mechanism of the electrochemical reduction of **252** was established by German scientists with the help of quantum-chemical computations, voltammetric and kinetic measurements[304]. The simpified mechanism, which leads to the products **253** and **254**, is shown on the scheme 65. Eventually the (R)-4-methylchroman-2-one was obtained electrochemically in presence of yohimbine with a yield of 36% (the best ee 67%) and with the best yield of 61% (63% ee).



Scheme 65

In some cases the electrochemical reduction of coumarins has not affected the coumarin ring[305].

1.2.7 Other methods for the reduction of coumarins

Table 16 presents the information about coumarins' reduction by the other methods that give chroman-2-ones.

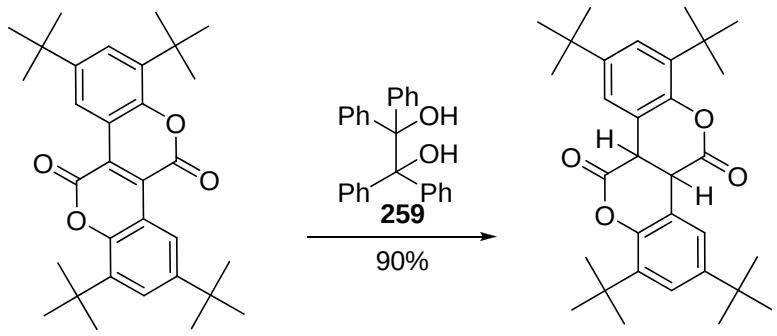
One article is found where preparation and use of Raney-copper is described[306]. Murrey Raney invented the skeletal nickel which is prepared from Ni/Al alloy. The procedure of preparing the catalyst from Cu/Al/Zn alloy by dissolving it in alkali is described in this article. The skeletal Cu obtained was tested to catalyze the reduction of coumarin and of the other compounds. This catalyst is active in reducing coumarin, dihydrocoumarin was synthesized in

45 min at 140-160ºC under 110 bar of hydrogen with a 100% yield. More active Raney-Cu at higher temperatures (210-240ºC) leads to *o*-hydroxycinnamic alcohol.

Some articles inform about the hydrogenation of coumarin under conditions of industrial hydrogenation of fuels. Coumarin was hydrogenated on copper chromite under 100-200 bar of hydrogen[253]. The formation of chroman-2-one was shown by pressure drop, but hydrogenation was not interrupted and chroman-2-one was not isolated. The hydrogenation of coumarin on WS_2 under 100 bar of hydrogen at 280ºC leads to propylbenzene (47% yield)[307]. The hydrogenation on ferric catalyst under 300-350 bar of hydrogen leads to the substituted benzenes[308].

Sodium hydrogentelluride is proven to be a very selective reducing reagent for α,β-unsaturated carbonyls[309]. M. Yamashita et al. have reduced several compounds with this reagent. Coumarin was reduced with 99% yield in EtOH within 4-5 hours. The following patterns are determined in this article: the overreduction of the carbonyl group is negligible, the isolated double bond is not reduced, aromatic groups are not affected, the operation is very simple. In most cases the reduction was also almost quantitative. G. Geethamalika et al.[310] report about the same reduction of coumarin, but it was carried out with a yield of 85%. The very similar system of 2-quinolone is reported not to be hydrogenated by NaHTe[311].

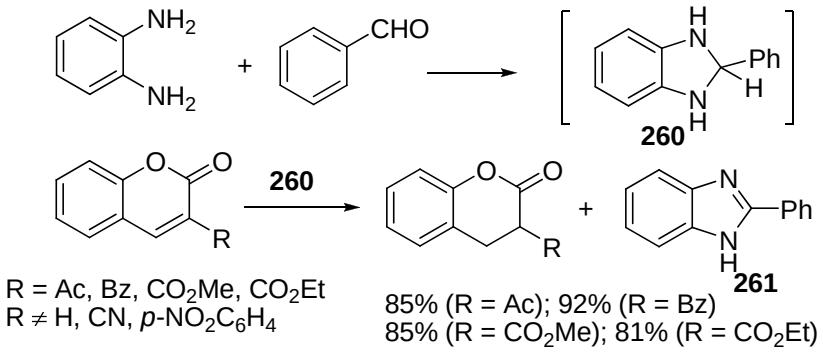
1,3,7,9-tetra-*tert*-butylchromeno[4,3-c]chromene-5,11-dione **258** was reduced by benzpinacol **259** in DMF [312].



258

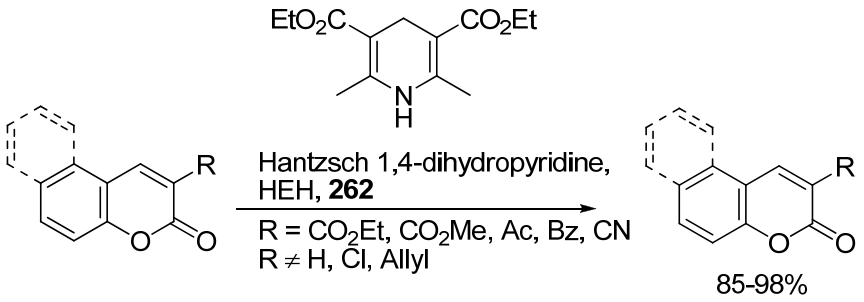
Scheme 66

F. Risitano et al.[313] describe a very interesting method of coumarins' reduction. 2-Acylcoumarins were reduced by 2-phenylbenzimidazoline **260**, formed *in situ* from *o*-phenylenediamine and benzaldehyde (see Scheme 67). **260** is oxidized to 2-phenylbenzoimidazole **261**. 3-Cyanocoumarin could not be reduced by this method.



Scheme 67

A number of coumarins, which have an electron withdrawing group in the 3rd position, were reduced by Hantzsch 1,4-dihydropyridine (HEH) **262**[314]. The coumarins with a 3-electron-donating substituent were not reduced by this method.



Scheme 68

B. S. Kirkiacharian[315] reports about the conversion of coumarin into chroman-4-one *via* addition of diborane to coumarin with further oxidation to 4-flavonol and oxidation of the latter compound with Cr (VI) to chroman-4-one. Also intermediate chroman-4-ylborane could be directly oxidized by Cr (VI) to chroman-4-one.

One patent[316] and article[317] describe a biochemical reduction of coumarin. Diverse microorganisms reduce coumarin to a mixture of chroman-2-one and melilotic acid (3-(2-hydroxyphenyl)propanoic acid). The latter can be dehydrated by citric acid to give chroman-2-one.

The ionic hydrogenation by the system $HSiEt_3/CF_3CO_2H$ was found to be inapplicable for 4-hydroxycoumarin, and 3-acetyl-4-hydroxycoumarin was reduced by this system to give 3-ethyl-4-hydroxycoumarin with a yield of 35%, or ethylbenzene in case of prolongued reaction time[318].

Alane (generated *in situ* from $LiAlH_4$ and BnCl) is reported to reduce coumarin and 7-methoxycoumarin to the corresponding 2-(3-hydroxyprop-1-enyl)phenols, thus C=C-bond was not affected[319].

Table 16. Summary table of coumarins' hydrogenation by the other methods. If not stated otherwise, the product is the corresponding 2-chromanone.

Substrate	reducing reagent	solvent	yield, %	time	additional information	ref.
coumarin	biochemical reduction	H_2O/ EtOH	various	48 h	reduction by *Bacillus cereus, Pseudomonas orientalis, Sacharomices cerevisiae*, then dehydratation by citric acid	[316, 317]
coumarin	Raney-copper/H_2	MeOH	100	45 min	140-160ºC	[306]
coumarin	CuCrO	EtOH	N/A	N/A	140-160ºC, product was not isolated	[253]
coumarin	NaHTe	EtOH	99	4-5 h	NaHTe generated from $NaBH_4$ and Te in EtOH, reduction goes at r.t.	[309]
coumarin	NaHTe	EtOH	85	4-5 h	NaHTe generated from $NaBH_4$ and Te in EtOH, reduction goes under reflux	[310]
258	benzpinacol **259**	DMF	90	N/A		[312]
3-acetyl, 3-benzoylcoumarin, methyl, ethyl coumarin-3-carboxylate	**260**	EtOH	85, 92, 85, 81, resp.	0.5 h		[313]
methyl, ethyl coumarin-3-carboxylate, 3-acetyl-, 3-benzoylcoumarin	HEH **262**	EtOH	95, 95, 96, 98, resp.	1-1.5 h	procedure, suitable only for 3-EWG-substituted coumarins	[314]
ethyl 3-oxo-3H-benzo[f]chromene-2-carboxylate, 2-acetyl-, 2-benzoyl-3H-benzo[f]chromen-3-one	HEH **262**	EtOH	98, 94, 98, resp.	1-1.5 h	procedure, suitable only for 3-EWG-substituted coumarins	[314]
3-cyanocoumarin	HEH **262**	MeCN,THF or PhMe	85, 88 or 94, resp.	1-1.5 h	3-cyanochroman-2-one was trans-esterified in ethanol	[314]

1.2.8 Conclusion

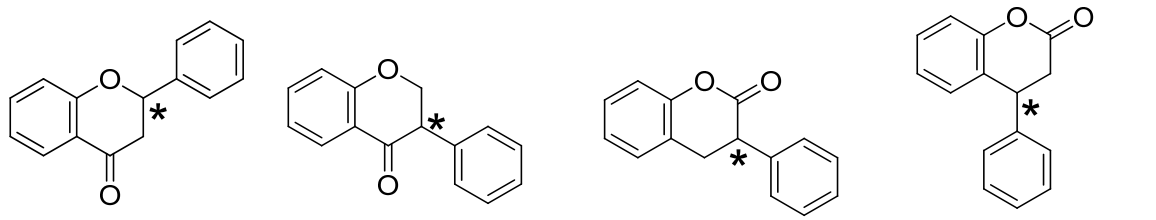
The reduction of coumarins represents an important method of chroman-2-ones' synthesis. Many methods of selective or unselective reduction of such compounds are reported. Although the reduction can lead to a mixture of compounds, presumably with a broken chroman ring; it can easily be lactonized by acids.

The coumarins can be divided into two groups, concerning their activity towards reduction: coumarins bearing 3-EWG and coumarins without such a group. For the first group a number of chemoselective methods are available, while the reduction of the second-group's representatives is more difficult. One of the reasons why the reduction of the 3-EWG-substituted coumarins is simpified is a sterical functionalization of the C=C double-bond (see acrticle[313] and section 1.4).

Unfortunately, enantioselective homogeneous hydrogenation which is quite well developped for various substrates[24, 25] is represented here only by four publications.

1.3 Biologically active compounds: racemates *versus* pure enantiomers.

As mentioned in sections 1.1 and 1.2, the chroman-4-ones and chroman-2-ones have a wide spectrum of biological activity. If these compounds have substituents in 2nd or in 3rd position (for chroman-4-ones) or in 3rd or 4th position (for chroman-2-ones), they become chiral. The chiral atoms of model flavanone **263**, isoflavanone **264**, 3-phenylchroman-2-one **265** and neoflavanone **266** are denoted with a star on the scheme 69.

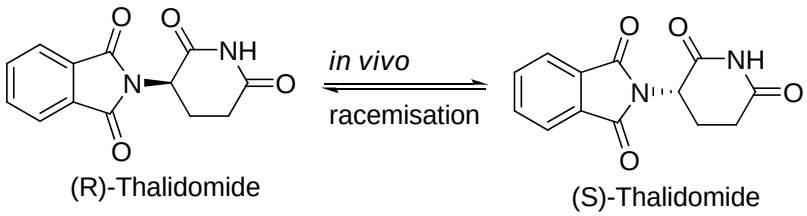


Scheme 69

The targets for biologically active substances are usually considered to be proteins, receptors, nucleic acids (and their complexes with proteins) and lipids[320]. All these targets are chiral *in vivo*, hence the enantiomers of biologically active compounds could be discriminated.

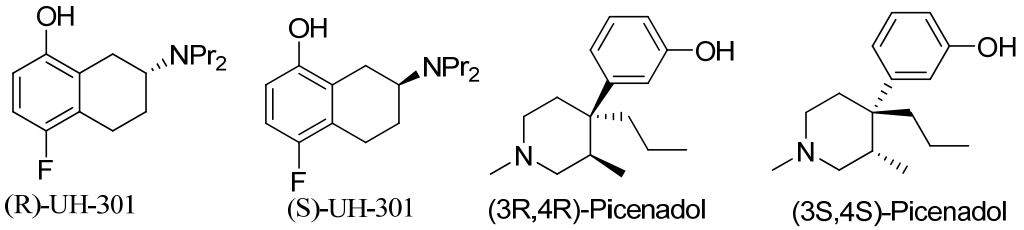
In the book of R. B. Silverman[320], as well as in "FDA's policy statement for the development of new stereoisomeric drugs"[321] the examples of such a discrimination could be found. In the following I give details to some of them.

Well known is a substance called thalidomide: (R)-Thalidomide is sedative, while (S)-Thalidomide intercalates in DNA thus having teratogenic effect. Unfortunately, the enantiomerically pure thalidomide is racemized *in vivo*. (S)-Thalidomide has additionally antiangiogenic, anticancer and leprastatic effect. Since 1998 is has been used again as a drug (but not by pregnant women).



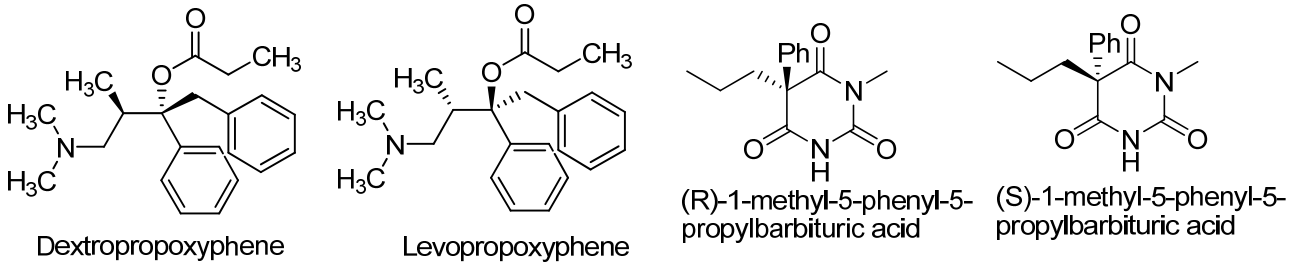
Scheme 70

(R)-UH-301 is an agonist of 5-HT_{1A} receptors while its enantiomer is an antagonist of the same receptors. (3R,4R)-Picenadol is an agonist of μ- and δ-opiate receptors while (3S,4S)-Picenadol is an antagonist of these receptors[322].



Scheme 71

Dextropropoxyphene has an analgesic and narcotic effect while its enantiomer Levopropoxyphene is an antitussive. (R)-1-methyl-5-phenyl-5-propyl-barbituric acid is narcotic while its (S)-enantiomer is a convulsant.



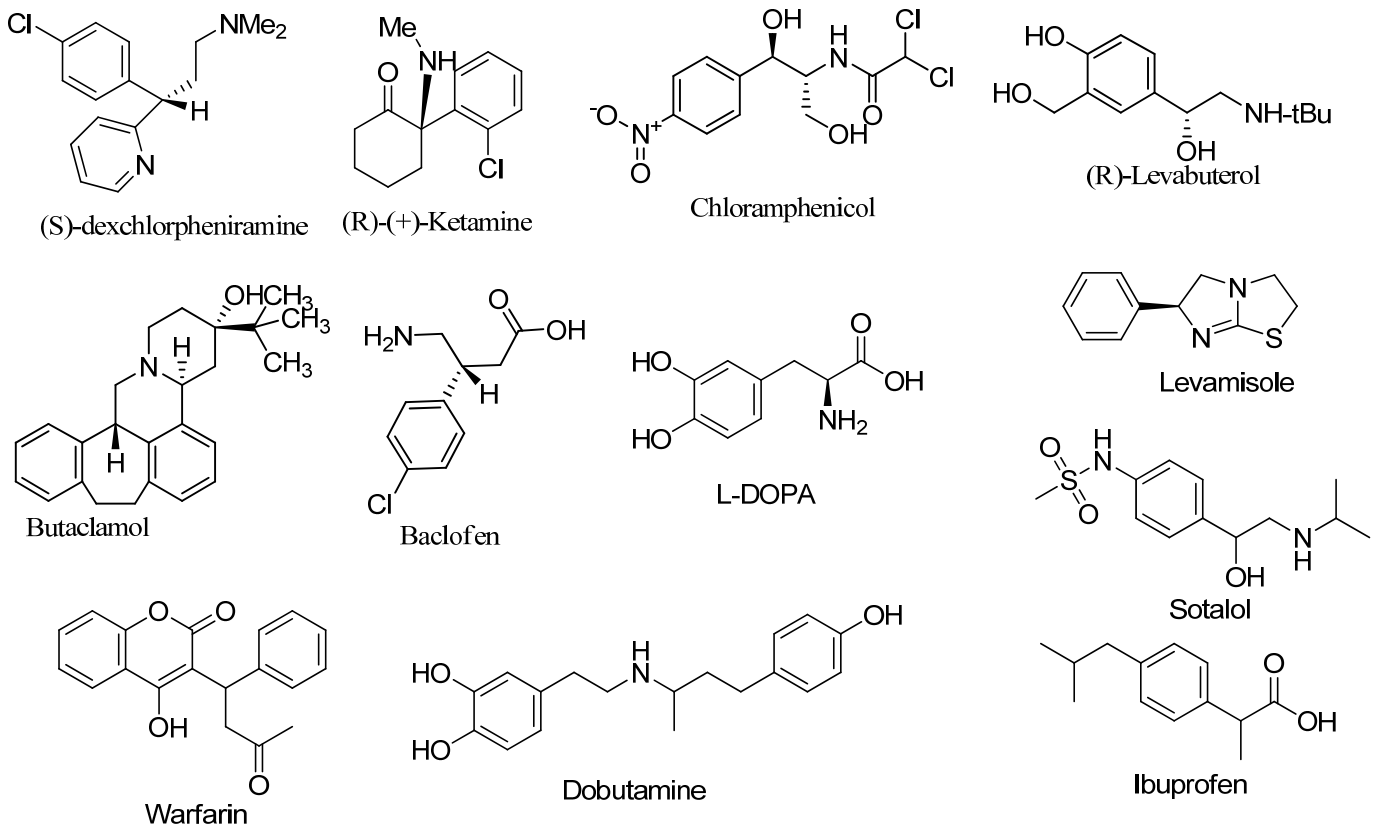
Scheme 72

(S)-Dexchlorpheniramine has an antihistamine activity, while that of (R)-Dexchlorpheniramine is weaker. (R)-Ketamine is hypnotic and analgesic, while (S)-Ketamine has additional side-effects (psychic emergency reactions, pain, disorientation). Chloramphenicol is bacteriostatic (antibiotic), while its three optical isomers are not; nevertheless all four stereoisomers of chloramphenicol contribute to its toxicity[323]. (R)-Levabuterol is bronchodilator, while its enantiomer contributes to side-effects (pulse-rate increase, tremors, decrease of blood glucose and K^+ levels). Butaclamol is D1-, D2- and α-agonist, its enantiomer is inactive. Baclofen is a $GABA_B$-agonist, its enantiomer is inactive. L-DOPA is a precursor of dopamine while R-DOPA causes granulocytopenia. Levamisole is antihelminthic and an interferon inducer, its enantiomer causes vomiting.

On the other hand, both enantiomers of warfarin are anticoagulants and it is sold as racemate. Both enantiomers of dobutamine are positive inotropes; and both isomers of ibuprofen are anti-inflammatory agents.

An interesting case is that of sotalol. R-Sotalol is a type III antiarrhytmic (K^+-channels blocker), while S-sotalol is a β-blocker. Since both effects are useful in the treatment of

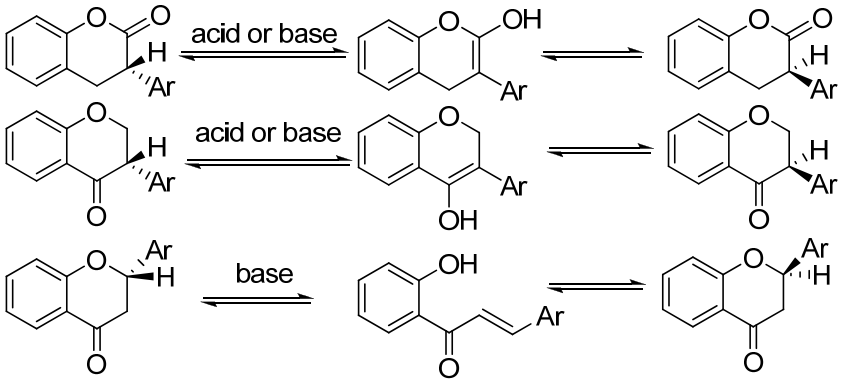
ventricular tachycardias as well as atrial fibrillation, the synergism of the actions of both enantiomers is observed.



Scheme 73

According to FDA's requirement[321], the chiral drug should be tested in form of pure enantiomer (both enantiomers should be tested), as well as racemate. In case of fast racemization *in vivo* (as for thalidomide), this should be proven. The known old racemic drugs can be substituted with the enantiomerically pure ones (chiral switch), and the latter could be patented, hence protected from the rivals. The examples of chirals switches are that of Omeprazole to Esomeprazole by AstraZeneca[324] and that of rac-Metolachlor to (S)-Metolachlor by Syngenta[325].

Flavanones and Isoflavanones as well as 3-arylchroman-2-ones are very racemization-sensitive[23]. The pathways to racemization are drawn on the scheme 74. Neoflavanones are stable towards racemization.



Scheme 74

Among the natural flavanones and isoflavanones sophorol **15**[326] and silybin **21** were isolated enantiomerically pure from plants. Some isoflavanones, isolated from the heartwood of *Dalbergia parviflora*, have shown an optical activity (enantiomeric purity was not measured) while certain isoflavanones were isolated racemic[327]. The chroman-4-ones are biosynthesized enzymatically, hence enatiospecifically in plants[36, 328], and the application of the enzyme 2′-hydroxydaidzein oxidoreductase, isolated from elicitor-challenged soybean cell cultures[168], also results in enantiospecific synthesis of isoflavanones *in vitro*. The sensivity towards racemization of flavanones and isoflavanones results in isolation of racemic compounds from the plant material[23, 329]; this is why the majority of compounds on the scheme **3** is drawn in racemic form.

Here it should be mentioned, that racemic flavanones and isoflavones were resolved with the help of HPLC on chiral stationary phases[330].

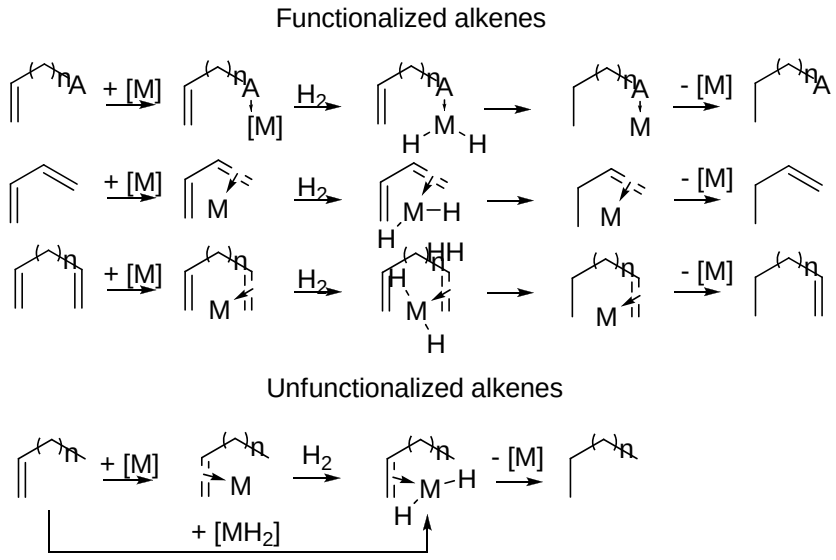
1.4 Homogeneous catalytic hydrogenation of alkenes

The homogeneous catalytic hydrogenation has been studied thoroughly. The 3-volume "Handbook of Homogeneous Hydrogenation"[25] and "Modern reduction methods"[331] where all the features of this method are described have been published only recently. Since a complete review of literature is not necessary, I shall give here the data important for further undertanding of the dissertation. Since a synthesis of chromanones was important for my work, I restrict this topic to homogeneous hydrogenation of alkenes.

Homogeneous hydrogenation can be easily confused with the heterogeneous one. For example, the metal complex can be reduced by hydrogen to form the colloid solution of the metal, which is catalytically active. But, in fact, the microheterogeneity changes the catalysis to be heterogeneous. One way to test if the hydrogenation is homogeneous, the poisoning of

the catalyst by thiophene[332]. While the heterogeneous catalyst is usually poisoned by the thiophene, the homogeneous one remains active (although the activity can change).

The alkenes can be divided in two large groups: functionalized and unfunctionalized ones[24, 333] (see scheme 75). The former have a heteroatom near the alkene double-bond. The metal can coordinate to this heteroatom, then add and transfer hydrogen, thus reducing the C=C-bond. In case of unfunctionalized alkene such a directional heteroatom is absent, hence a metal should coordinate directly to the C=C-bond. The dienes also belong to the class of functionalized alkenes.



Scheme 75

In any case, the complexes with coordinatively unsaturated metals do not exist since they coordinate a solvent molecule, build labile clusters, etc. In the worst case they are destroyed, thus interrupting the catalytical cycle. If not stated otherwise, the "free coordination site" is really saturated by the solvent. On the other hand, the latter complexes are usually very labile and can recoordinate the other ligands. Thereby, solvent-coordination is a masking of the coordinatively unsaturated complex. On the schemes, the solvent molucule is denoted as "S".

The mechanisms of homogeneous hydrogenation are strongly dependent on metal, on ligand, on solvent and on substrate.

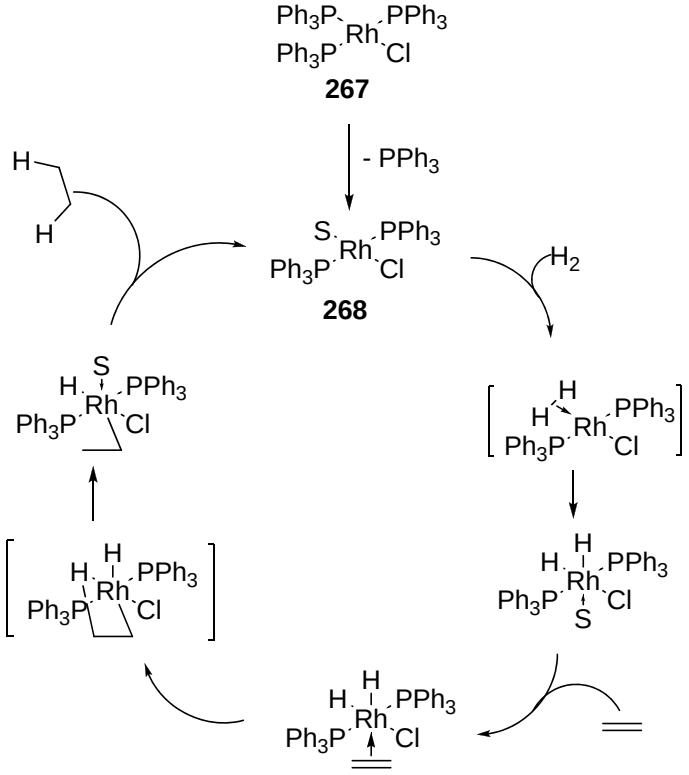
.

1.4.1 Homogeneous hydrogenation of alkenes: rhodium catalysis

The Wilkinson's catalyst, $[Rh(PPh_3)_3Cl]$ **267** is a good catalyst for alkenes hydrogenation[334]. The mechanism of hydrogenation was studied by NMR and is given on scheme 76. The species in brackets are assumed, the other were detected by NMR.

This catalyst needs the one ligand to be dissociated, then **268** is formed and the catalytic cycle can proceed. The analogous complex of iridium is not catalytically active since triphenylphosphine ligand has too strong binding to the metal. Analogous complex that does not need the predissociation is $[Rh(COD)(PPh_3)_2Cl]$. It can be prepared *in situ* from $[Rh(COD)(\mu\text{-}Cl)]_2$ and triphenylphosphine (COD is removed by hydrogenation).

The trans-arrangement of phosphine ligands is proven, but if a chelate diphosphine is used (e.g. BINAP of DPPB), it stays cis-arranged. The other peculiarities of the mechanism are not changed (i.e. chelate-cycle is not destroyed in order to achive the trans-arrangement). The complexes of type $[Rh(P)_2(\mu\text{-}Cl)]_2$ of $[Rh(P\text{^}P)(\mu\text{-}Cl)]_2$ are not catalytically active, and their formation results in catalyst deactivation.



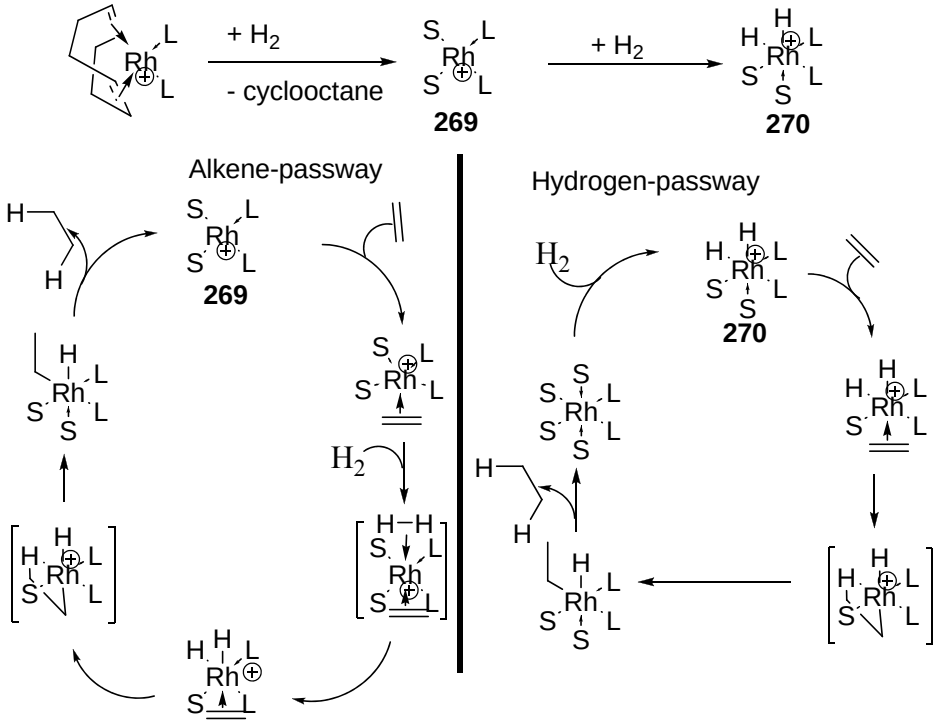
Scheme 76

The mechanism contains an oxidative addition of hydrogen on the first stage. Then an alkene is coordinated and an insertion of hydrogen proceeds. The reductive elimination of alkane regenerates the catalytically active **268**.

The described mechanism represents the hydrogenation by neutral rhodium-complex, and proceeds by hydrogen-passway (first hydrogen is coordinated, then alkene). More active are cationic complexes. Instead of halogen, they have an anion that pretends to be non-coordinating (or weak coordinating). Various weak coordinating anios (WCAs) exist[335], but in

case of Rh-catalysis even OTf^-, BF_4^-, PF_6^- and similar are weak enough to produce the cationic complexes.

The mechanisms of hydrogenation by cationic complexes of rhodium are presented on the scheme 77. Here hydrogen- and alkene-pathways are possible, i.e. first hydrogen or alkene is coordinated. The first mechanism presumes the catalytically active particle **269**, while the latter – **270**. The precatalyst is usually a complex of rhodium with COD, COE, NBD and similar. The coordinated alkene is hydrogenated, thus liberating the coordinatively unsatured species. The latter instantly coordinate solvent, forming labile complex **269** or **270**.

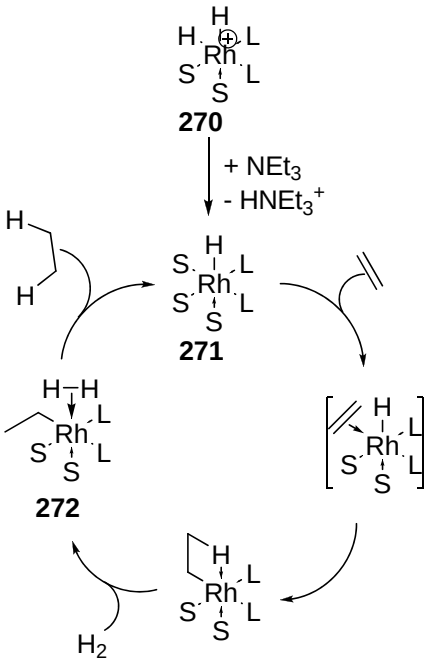


Scheme 77

Since the functionalized alkenes coordinate fast to the metal, for such substrates alkene-pathway is preferable, while for the unfunctionalized one it is the hydrogen-pathway. The alkene pathway is also preferable for triarylphosphines and diarylalkylphosphines as ligands. In case of trialkylphosphine (e.g. BisP, see section 1.4) as a ligand, the reaction always goes through hydrogen pathway[334, 336]. It emphasizes the strong dependence of the mechanism on the ligand.

One proton can be abstracted from the cationic complex **270**, e.g. by base. As such a base triethylamine can be used. This produces the neutral highly unsaturated complex **271**, which is also an active hydrogenation catalyst[334, 337]. The hydrogenation goes through alkene pathway (scheme 78). This mechanism is analogous to that, estabiliched for metallocenes (see section 1.4.4). The complex **272** is given here because of analogy of these two mechanisms.

The existence of complex with π-coordinated hydrogen molecule was proven for metallocenes. The similar mechanism is inherent for hydrogenation, catalyzed by $[RhH(CO)(PPh_3)_2]$. After dissociation of a triphenylphosphine ligand, complex **271** is formed ($L_1 = CO$; $L_2 = PPh_3$).



Scheme 78

As ligands for rhodium-catalyzed homogeneous hydrogenation phosphines, phosphites NHCs and amines are used, but two amines as ligands produce an inactive complex while one amine and one phosphorus-ligand (or NHC) for one rhodium atom produce the active complex. The overwhelming majority of ligands are chelating diphosphines although monodentate ligands are proven to be also very effective (see section 1.4).

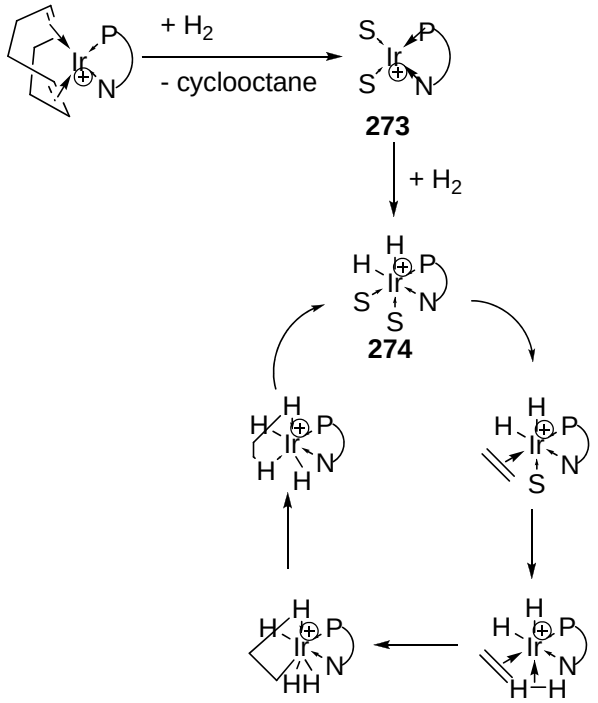
Rhodium catalyzed hydrogenation is effective in case of functionalized and unfunctionalized alkenes[24, 333]. The rate of hydrogenation depends on the number of substituents and theirs arrangement[334], i.e. monosubstituted alkene is hydrogenated faster than the disubstituted one. The cis-alkenes are hydrogenated faster than the trans-substituted ones. The tri-substituted alkenes are hydrogenated quite slow, and tetra-substituted are not hydrogenated.

1.4.2 Homogeneous hydrogenation of alkenes: iridium catalysis

Iridum tends to bond the ligands much more stronger than rhodium, hence the complexes, which require prior ligand dissociation, are usually catalytically not active[338]. Even a complex with solvent (e.g. methanol) can be very stable, thus decelerating the

hydrogenation. Reaction deceleration is usually not wished, since a parallel reaction of catalysts' destruction can take place.

The catalytical cycle is absolutely different from that of rhodium[339]. It is studied for phosphinooxazoline ligand with the help of DFT-calculations and involves the cationic complex of iridium (scheme 79). First the complex of Ir(+1) loses COD (in a form of cyclooctane), then the complex **273** is oxidized by hydrogen to form a complex of Ir(+3) **274**. The latter, analogous to **270**, is a catalytically active particle. The oxidation of Ir(+1) by molecular hydrogen is actually not an oxidation but a reduction. Formally it leads to Ir(+3) complexes but the electron-density is enhanced on the Ir-atom. The reductive addition of hydrogen was studied by R.H. Crabtree and Sh. M. Morehouse[340].

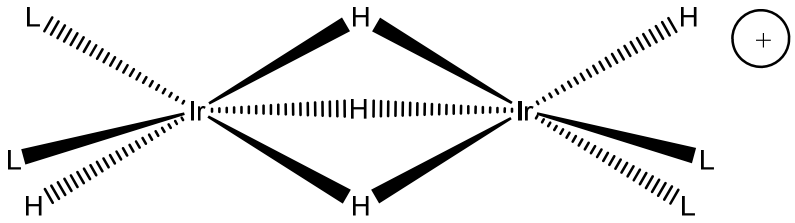


Scheme 79

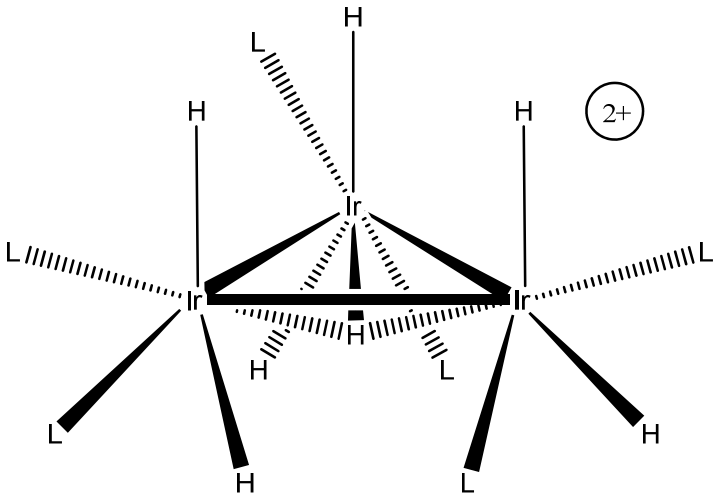
In contrast to rhodium, the addition of organic base (e.g. NEt_3) inactivates the hydrogenation[338, 341]. In case of hydrogenation of the complex $[Ir(COD)(PPh_3)_2]PF_6$ in presence of NEt_3 the pantahydrido-complex $[IrH_5(PPh_3)_2]$ was isolated[342]. The latter was not catalytically active. On the other hand, the corresponding pentahydrido complexes were not isolated for the complexes with P^P and with P^N ligands, and the complex $[IrH_5(PCy_3)_2]$ was prepared by hydrogenation of $[Ir(COD)(PCy_3)(Py)]PF_6$ in presence of NEt_3 and PCy_3, i.e. pyridine was eliminated.

Iridium catalysts are very active, they do not discriminate the alkenes according to their substitution and can hydrogenate even tetrasubstituted ones. On the other hand, they are

deactivated quite fast by forming the hydride-bridged catalytically inactive clusters **275** and **276** (L denotes P or N ligand) [338, 342-344]. Recently it was reported about four-nuclear hydride-bridged clusters of iridium[345].



275



276

Scheme 80

The most famous catalyst from this family is a complex of Crabtree, $[Ir(COD)(Py)(PCy)_3]PF_6$. It is usually used in CH_2Cl_2 under pressure of hydrogen over 50 bar. Very effective are the catalysts with Phox and other P^N ligands (see section 1.5). The substitution of phosphine ligands with NHCs enhances its activity even more[346, 347].

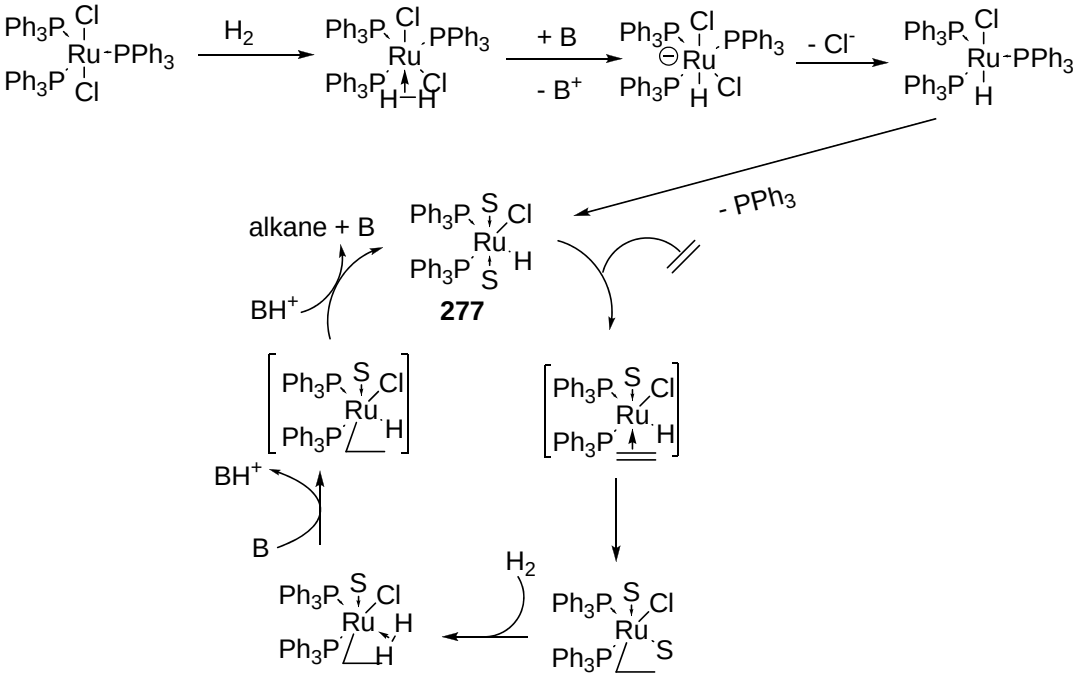
As far as iridium complexes tend to coordinate also bad ligands, thus forming inactive species, the use of counter WCAs is proven to be important for efficiency of catalyzing. The most used counter-ion for iridium complexes is BARF, since it is air and thermally stable, and relatively easy obtainable. The catalysts, bearing different counter-ions were compared[341, 347, 348], showing the WCAs to be superior.

1.4.3 Homogeneous hydrogenation of alkenes: ruthenium and osmium catalysis

The mechanism of Os-catalyzed homogeneous hydrogenation is similar to Ru-catalyzed, but the osmium complexes are usually less active and more expensive, hence are used quite rarely.

There are several types or Ru-complexes, used in alkenes' hydrogenation. Each type has its own mechanism of hydrogenation and often such mechanisms are only speculated, not proven. The disposition of ruthenium to form clusters and polynuclear complexes complicates its chemistry.

The complex $[Ru(PPh_3)_3Cl_2]$, synthesized by Wilkinson, is a potent hydrogenation catalyst. It discriminates effectively differently substituted alkenes and is effective especially for functionalized alkenes (but can also hydrogenate unfunctionalized ones). It requires a base which is involved in catalytical cycle, but even an alcohol (which is commonly used for Ru-catalyzed homogeneous hydrogenation) can serve as a base. In case of benzene as a solvent, external base (e.g. triethylamine) should be added. At first, $[Ru(PPh_3)_3Cl_2]$ is converted to $[Ru(PPh_3)_3HCl]$ which looses triphenylphosphine and generates the active intermediate **277**. Then a catalytic cycle is similar to that of metallocenes (see section 1.4.4)[24, 349].

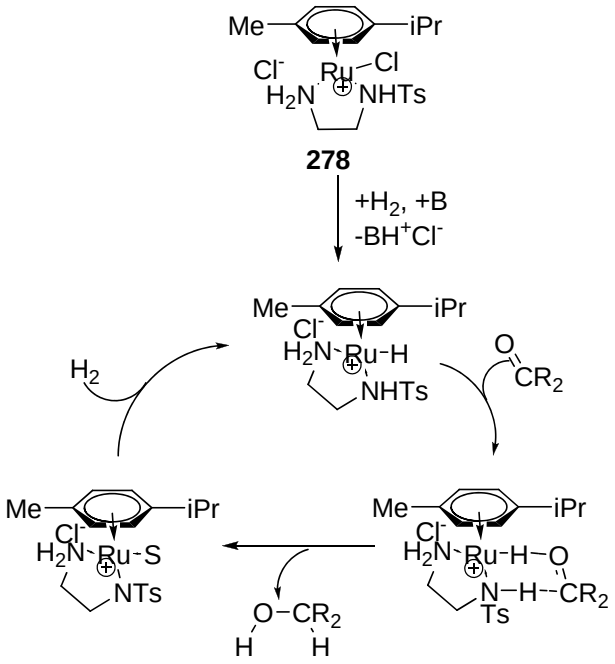


Scheme 81

Similar to rhodium, the ratio phosphine/ruthenium 2/1 is more effective since ligand dissociation is not necessary. Such complexes are represented by $[Ru(BINAP)Cl_2]_n$ and similar (with the other phosphines). They can be generated *in situ* from $[Ru(BINAP)Cl(\mu\text{-}Cl)_2Ru(BINAP)(NEt_3)Cl]$ or from $[Ru(COD)(Metallyl)_2]$, ligand (e.g. BINAP) and HHal[349]. $[Ru(BINAP)_2HCl]$[350] represents the active catalyst, that does not require activation.

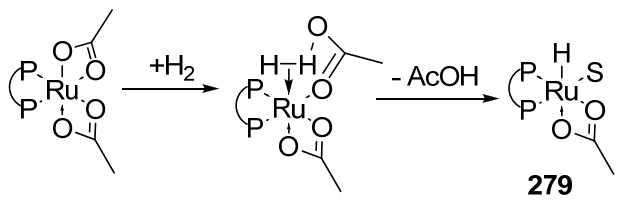
The complexes of type [Ru(Arene)(amine)Cl]Cl (e.g. **278**) are designed by Ryoji Noyori for hydrogenation of the carbonyl-group but are found to catalyze the transfer hydrogenation of some electron-poor alkenes (e.g. 3-acetylcoumarin)[300]. On the scheme below the

mechanism for the carbonyl-group hydrogenation is shown. It can be speculated that the mechanism for electron-deficient C=C-group hydrogenation is analogous. Instead of hydrogen, any other source of hydrogen (HCO_2H or iPrOH) can be used. The mechanism is analogous (presumes CO_2 or acetone elimination, respectively).



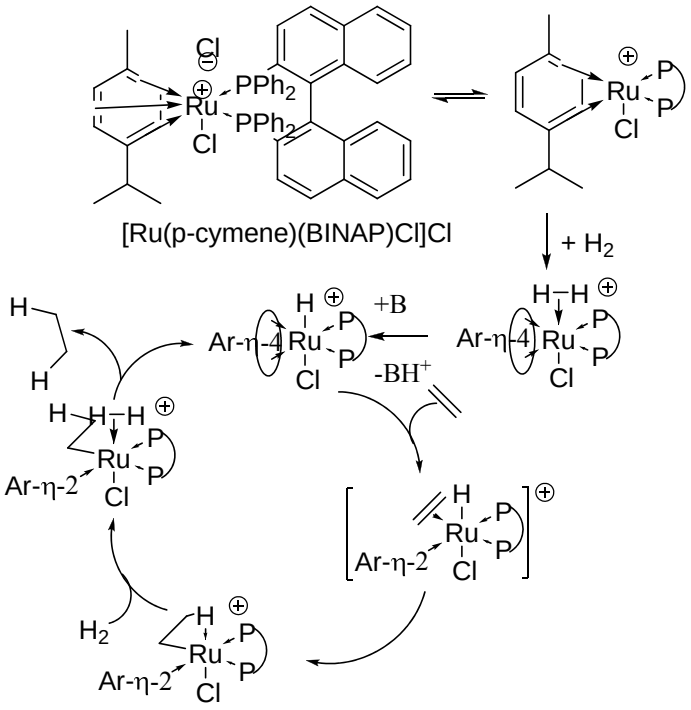
Scheme 82

Very active are dicarboxyl complexes of ruthenium, e.g. $[Ru(BINAP)(OAc)_2]$. In contrast to the other complexes of Ru, these can be further activated by strong acids (e.g. HBF_4 or $HClO_4$). The acetate (or other carboxylate ligand) should be dissociated and its protonation facilitates the dissociation. Reduction catalyzed by the above-mentioned complexes is usually carried out in alcohols. The mechanism of activation is given below. The complex **279** contains hydride hydrogen near the free coordination site. It is similar to **277**, and the further catalytic cycle goes like that characteristic for metallocenes (see section 1.4.4). The complex **279** can then lose the second acetate (especially after acid-activation), thus liberating two free coordination sites which are useful for the precoordination of functionalized alkene.



Scheme 83

Another catalytic system represents the cationic complexes of type [Ru(η-6-Arene)(diphosphine)Cl]Cl. As arene usually comes p-cymene (*p-iso*-propyltoluene), BINAP is the most used diphosphine for this type of complexes. Unfortunately, I cannot find the mechanism of hydrogenation catalyzed by this complex. I can only assume, that an aryl ligand rearranges to η-4-coordination, thus liberating a free coordination site, where hydrogen can coordinate. This assumption and the proposed catalytic cycle are shown below.



Scheme 84

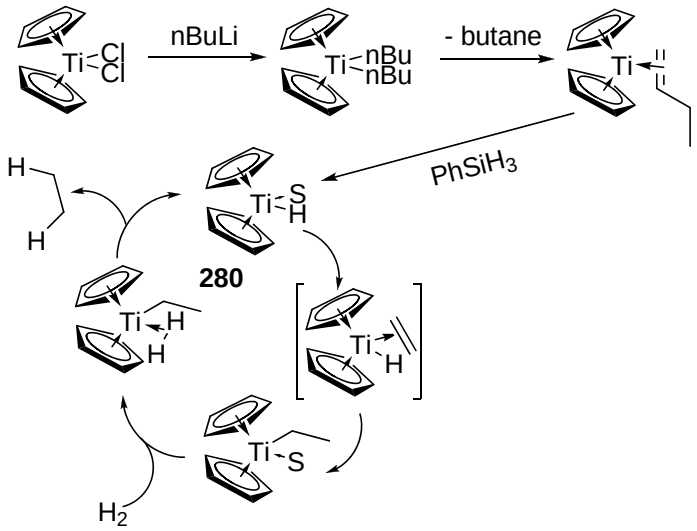
There are many other ruthenium complexes which serve as catalysts/precatalysts for homogeneous hydrogenation. These are $NH_2Et_2[Ru(BINAP)Cl(\mu\text{-}Cl)_3Ru(BINAP)Cl]$, and various other bi- and multinuclear complexes. The mechanisms of hydrogenation for such complexes were not found in literature.

1.4.4 Homogeneous hydrogenation of alkenes: metallocenes

Here the mechanism of hydrogenation, catalyzed by Cp_2TiCl_2 will be described[351, 352]. This mechanism is relevant for the similar complexes of zirconium, hafnium, yttrium, lantanoids and actinoids.

The key step of the hydrogenation, catalyzed by metallocenes, is the activation. The complex of type **280** should be formed, otherwise the hydrogenation is not possible. A high pressure of hydrogen is also significant. The particle **280** represents a catalytically active particle of Ziegler-Natta polymerization, hence under low pressure of hydrogen, the

polymerisation of alkene is a preferable process. Although the Ti(IV) complexes are the precatalysts, the particle **280** is a complex of Ti(III).



Scheme 85

1.4.5 Homogeneous hydrogenation of alkenes: other metals

Very many metal complexes are proven to perform homogeneous hydrogenation. In the periodic table (Figure 1) the elements marked in dark are involved (in form of their complexes) in catalytic homogeneous hydrogenation. It is possible that new reactions would be found and the list of such metals will be extended. The readers who are interested in catalytic homogeneous hydrogenation by the other metals are welcome to refer to the "Handbook of Homogeneous Catalysis"[25] and to "Modern reduction methods"[331]. The overwhelming majority of this metals catalyze the hydrogenation through the formation of unsaturated hydrido-complexes, hence the catalytic cycle is similar to that of metallocenes. Another mechanism is the ionic hydrogenation which proceeds through coordinatively saturated hydrido-complexes and is typical for the hydrogenation of carbonyl-groups and, as an exception, hydrogenation of alkenes[353].

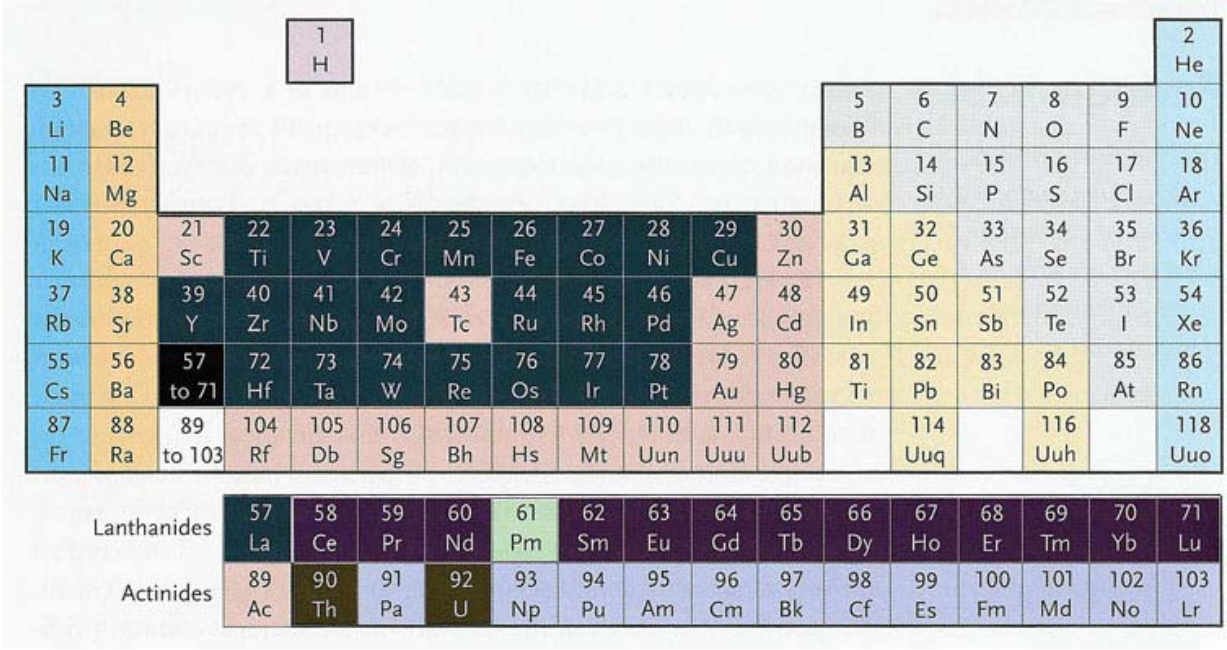


Figure 1

1.5 Enantioselective homogeneous catalytic hydrogenation

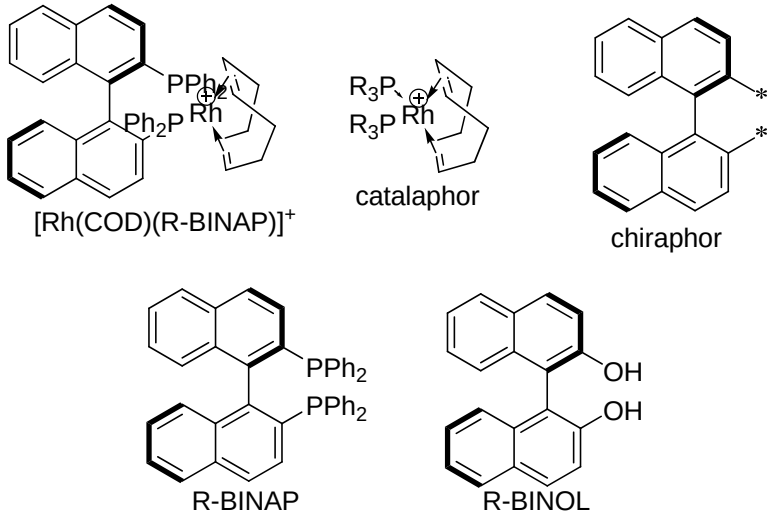
Chiral complexes can be very efficient of enantioselective/enantiospecific hydrogenation, but here the substrate specifity rises even more, resulting in low ee and/or in low conversion caused by minimal changes of the substrate. The similar properties have the enzymes, and there is a far-reaching analogy between metallocomplex catalysts and enzymatic reactions. For identification of the best ligand/catalyst for a certain substrate the techniques of HTS/HTE/HTC are used[354].

Despite the above-mentioned disadvantages, the homogeneous hydrogenation of alkenes makes sense almost only if it is assymetric hydrogenation. The homogeneous catalysts are very expensive and for simple hydrogenation it makes no sense to use homogeneous complexes, since the cheap heterogeneous catalysts are available (e.g. Pd/C). The other disadvantage of the homogeneous catalysis is the necessity of product purification, usually by column chromatography while the heterogeneous catalyst could be simply filtrated and re-used. This problem is partially solved by applying immobilized (heterogenized) homogeneous catalysts[355].

The price of catalyst does not matter in case of "pure science", i.e. if only academical interest is important. The Wilkinson's complexes $[Rh(PPh_3)_3Cl]$ and $[Ru(PPh_3)_3Cl_2]$ are used because they can effectively discriminate the double-bonds with a different number of substituents and even the arrangement of substituents.

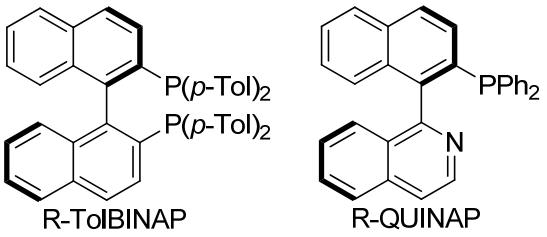
The enantioselective homogeneous hydrogenation is widely used in laboratory and even in industry[356].

The concepts of catalaphor and chiraphor were introduced for asymmetric catalysis[24]. The catalaphor is the metal atom and its near and remote environment which is responsible for the catalysis. The chiraphor is the chiral environment of the atom, responsible only for the stereochemistry of the products. The best understanding of these concepts could be made by the examples. The Wilkinson's catalyst $[Rh(PPh_3)_3Cl]$ has no chiraphor, and its catalaphor is $[Rh(P)_2Cl]$. The complex $[Rh(COD)(R\text{-}BINAP)]BF_4$ has the catalaphor $[Rh(P\text{^}P)]^+$, while its chiraphor is the core of (R)-BINAP. The BINOL and BINAP have the same chiraphor while BINOL being coordinated to rhodium will, of course, not form the catalyst for homogeneous hydrogenation (wrong catalaphor).



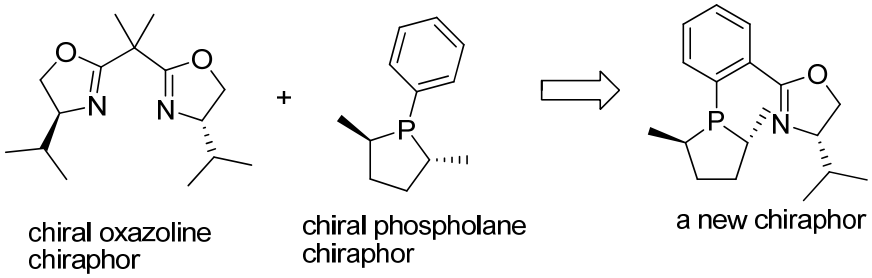
Scheme 86

The limits of two concepts are very inexact. For example, the complexes of rhodium with BINAP, TolBinap and QUINAP (scheme 87) should have the same chiraphor, but will give the different rates and enantiomeric excesses in hydrogenation of some model substrate. In case of QUINAP one atom of the catalaphor is N, but it is still the chiral core of binaphtalene. On the other hand, addition of methyl-groups in not chiral part of BINAP (thus generating TolBINAP) introduces the steric hindrances near the rhodium atom, resulting in different ee and slower reaction rate (comparable to the complex of BINAP). Although it does modify neither chiraphor, nor catalaphor, it changes both rate and ee of the reaction.



Scheme 87

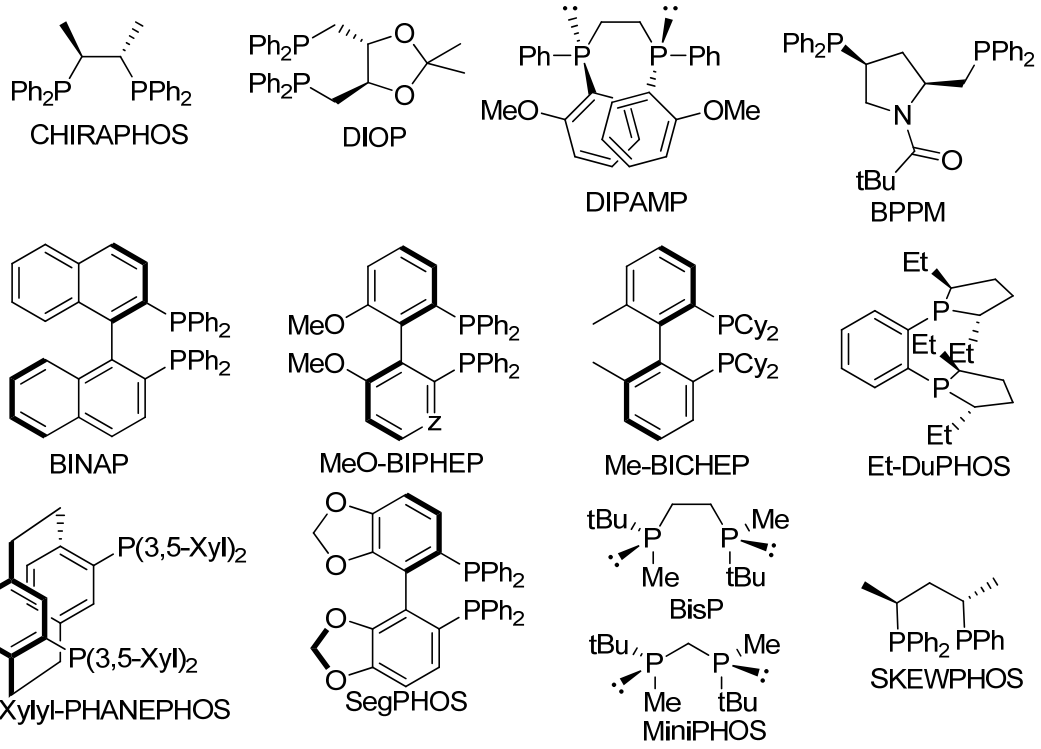
In literature the statement "combination of chiraphors" can be found. It means that chiraphors of some old ligands are combined in a new one. The example is shown on scheme 88.



Scheme 88

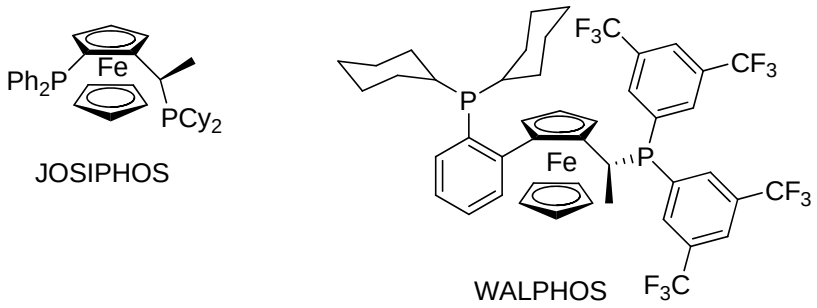
Actually, the asymmetric homogeneous hydrogenation consists in the use of known catalaphors and combination with various chiraphors, thus obtainig chirally pure/enriched products. A very useful book which describes this field of chemisry is the recently published "Phosphorus ligands in asymmetric catalysis: synthesis and applications"[357].

The majority of chiral ligands are bidentate diphosphine ligands with various types of chirality (central, axial and planar). Some examples of such ligands are given below:



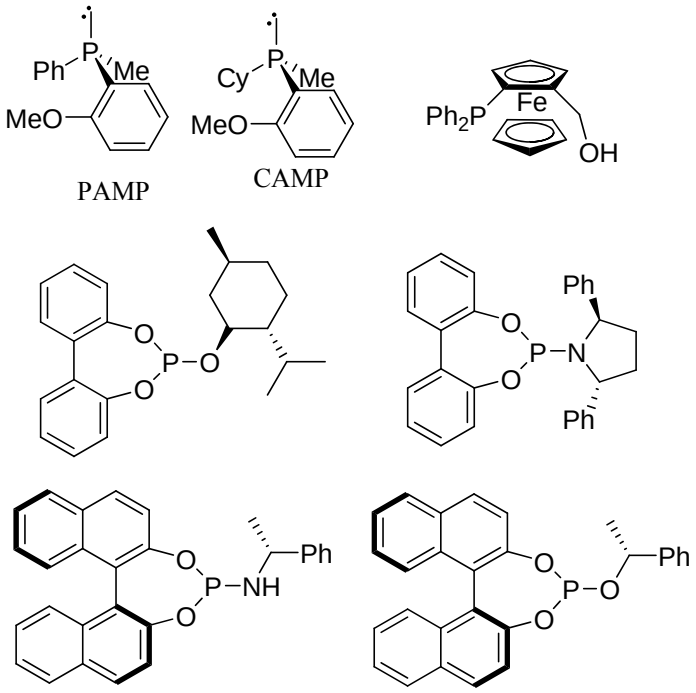
Scheme 89

Both sterically and electronically unsymmetric diphosphine ligands are known, for example:



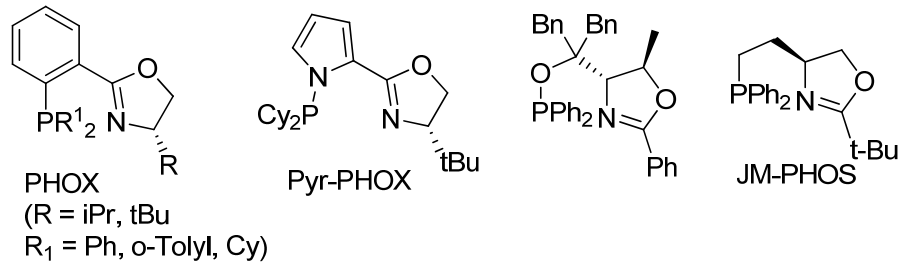
Scheme 90

Monodentate ligands can be very effective for asymmetric homogeneous hydrogenation[358]. Manfred Reetz have suggested the use of mixtures of monodentate ligands that changes the stereochemical outcome of the hydrogenation reactions, compared with the use of pure monodentate ligands[359]. Some examples of widely used monodentate ligands are shown in scheme 91:



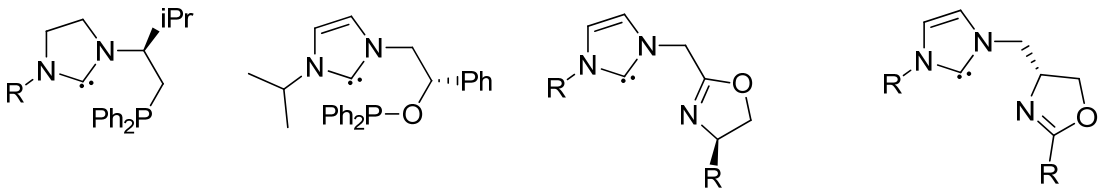
Scheme 91

P^N ligands are widely used for Ir-catalyzed hydrogenation[24, 333], although are very effective also for rhodium[360] and ruthenium[24, 333]. The examples:



Scheme 92

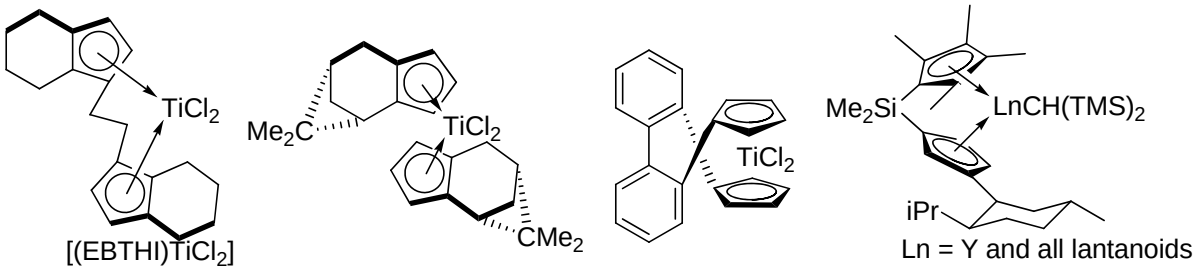
Very effective are C^P and C^N ligands for Ir-catalyzed asymmetric hydrogenation[346, 361, 362]:



Scheme 93

A large quantity of chiral N^N ligands are known, but they are ineffective for hydrogenation of alkenes, although effective for Ru-catalyzed hydrogenation of ketones.

The chiral metallacenes are widely used for asymmetric hydorgenation of unfuctionalized alkenes:


TiCl2
[(EBTHI)TiCl2]
Me2C
TiCl2
CMe2
TiCl2
Me2Si
LnCH(TMS)2
iPr
Ln = Y and all lantanoids

Scheme 94

2 OBJECTIVES

As shown in the introduction, the chromanones are potentially biologically active compounds. Since a certain biological activity is usually associated with one enantiomer, the objective was to design a method of enantioselective hydrogenation/reduction of flavonoids. The work should be focussed on flavonoids and not generally on chromanones because the flavonoids have a better perspective as biologically active compounds. Although the motif of 3-arylcoumarin is rarely found in nature, it is isosteric to isoflavone-motif. The reduction of 3-arylcoumarins was also a part of the objectives.

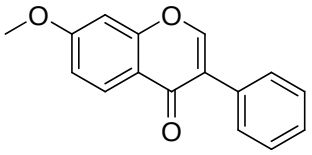
The chroman-4-ones and 3-R-chroman-2-ones are very sensitive to racemization and asymmetric hydrogenation could be an appropriate method of chiral chomanones' synthesis since the reaction usually occurs in very mild condition and the separation of the catalyst does not need acidic/alkaline treatment.

Later, after the discovery of activation of Iridium-complexes by base, the objective was complemented with the necessity to study this reaction (later it is named "nucleophilic hydrogenation", see section 3.3 and further).

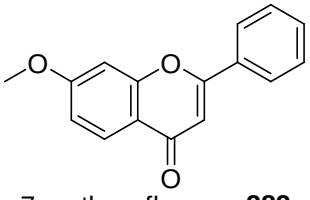
3 RESULTS AND DISCUSSION

3.1 Attempts to hydrogenate model flavonoids

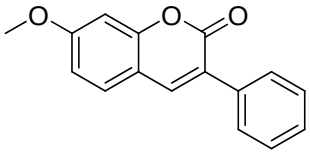
The 7-methoxyisoflavone **281**, 7-methoxyflavone **282**, 7-methoxy-3-phenylcoumarin **283** and 7-methoxyneoflavone **284** were chosen as model substrates. They fly readily in GC/MS that makes the analysis of reaction mixture extremely simple and fast, contain no additional coordination sites, which can change hydrogenation mechanism or interrupt the hydrogenation, and are easily obtainable.



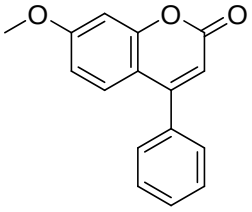
7-methoxyisoflavone, **281**



7-methoxyflavone, **282**



7-methoxy-3-phenylcoumarin, **283**



7-methoxyneoflavone, **284**

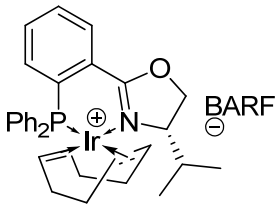
Scheme 95

The first task was the determination of the catalaphor, necessary for the hydrogenation of these flavonoids.

The complexes of rhodium: $[Rh(PPh_3)_3Cl]$ (**general procedure B**), [Rh(rac-BINAP)(COD)Cl] (generated *in situ*, **general procedure C**), [Rh(COD)(rac-BINAP)]OTf (**general procedure D**) were tested to perform the hydrogenation under 100 bar of hydrogen. Toluene, CH_2Cl_2, THF, DMF, propanol-2 or methanol was used as solvent. The 7-hydroxyisoflavone **285** was additionally tested in aqueous propanol-2 (H_2O/iPrOH 1/20) with Wilkinson's complex $[Rh(PPh_3)_3Cl]$. All the exepiment failed, and no conversion was observed by GC/MS or by NMR. The solvents were degased or absolutized (see experimental section). The educts were isolated intact after column chromatography, hence no other transformation took place. Addition of the base (triethylamine) to the reaction mixture resulted in metallic rhodium formation and heterogeneous hydrogenation of the substrates. Addition of triethylamine and thiophene, which represses the heterogeneous hydrogenation, resulted in no conversion of the educts. Hydrogenation of ethyl cinnamate with above

mentioned catalysts in toluene, CH_2Cl_2 ot THF under 100 bar of hydrogen showed the formation of ethyl 3-phenylpropanoate, hence all operations were made properly. The conclusion was made, that the model flavonoids are inert towards homogeneous hydrogenation, catalyzed by above mentioned complexes.

The complexes of iridium: [Ir(COD)(rac-BINAP)Cl] (generated *in situ*, **general procedure C**), [Ir(COD)(rac-BINAP)]BARF, [Ir(COD)(iPr-Phox)]BARF **286c** (**general procedure D**, for the preparation of **286c** see section 7.4) were tested to perform the hydrogenation under 100 bar of hydrogen. Toluene, CH_2Cl_2, THF or methanol was used as a solvent. All the exeperiments failed, and no conversion was observed by GC/MS or by NMR. The solvents were degased and absolutized (see experimental section). The educts were isolated intact after column chromatography, hence no other transformation took place. Hydrogenation of stilbene with [Ir(COD)(iPr-Phox)]BARF **286c** under 100 bar of hydrogen showed the formation of 1,2-diphenylethane. Suprisingly, [Ir(COD)(rac-BINAP)]BARF could hydrogenate stilbene neither in CH_2Cl_2, nor in toluene, and its activity was checked on benzylideneaniline[363], which was reduced to benzylaniline. Hydrogenation of ethyl cinnamate with [Ir(COD)(rac-BINAP)Cl] in CH_2Cl_2 or in THF under 100 bar of hydrogen showed the formation of ethyl 3-phenylpropanoate, hence all operations were made properly. The conclusion was made, that the model flavonoids are inert towards homogeneous hydrogenation, catalyzed by above mentioned complexes.



[Ir(COD)((S)-iPr-Phox)]BARF, **286c**

Scheme 96

The complexes of ruthenium: $[Ru(PPh_3)_3Cl_2]$ and [Ru(S-BINAP)(p-cymene)Cl]Cl (**general procedure E**) were tested to perform the hydrogenation under 100 bar of hydrogen. Toluene, THF or methanol was used as solvent. All the exepiments failed, and no conversion was observed by GC/MS or by NMR. The addition of triethylamine (10 or 100 eq.) was effective only in case of [Ru(S-BINAP)(p-cymene)Cl]Cl in methanol, but this composition could hydrogenat the 7-methoxyisoflavone not catalytically, i.e. the ruthenium complex was not catalyst, but the reagent. The hydrogenation of ethyl cinnamate with above mentioned catalysts in methanol under 100 bar of hydrogen showed the formation of ethyl 3-phenylpropanoate, hence all operations were made properly. The conclusion was made, that

the model flavonoids are inert towards homogeneous hydrogenation, catalyzed by above mentioned complexes.

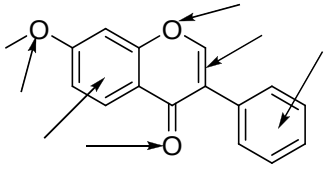
The complexes [Ru(R-BINAP)$(OAc)_2$] and NH_2Et_2[Ru(BINAP)Cl(μ-$Cl)_3$Ru(BINAP)Cl] were tested to perform the hydrogenation under 100 bar of hydrogen (**general procedure F**). Toluene, CH_2Cl_2, THF, DMF, propanol-2 or methanol was used as a solvent. All the exepiment failed, and no conversion was observed by GC/MS or by NMR. The addition of triethylamine (100 eq. for NH_2Et_2[Ru(BINAP)Cl(μ-$Cl)_3$Ru(BINAP)Cl], 1, 2 or 10 eq for [Ru(R-BINAP)$(OAc)_2$], **general procedure E**) was not effective. The addition of acid ($HBF_4 \cdot Et_2O$, solution in MeOH, 1, 2, 10 or 50 eq for [Ru(R-BINAP)$(OAc)_2$]) was not effective too (**general procedure F**). The hydrogenation of nerol under 100 bar of hydrogen with [Ru(R-BINAP)$(OAc)_2$][364] with or without acid-activation showed the formation of 3,7-dimethyloct-6-en-1-ol. The hydrogenation of ethyl cinnamate with NH_2Et_2[Ru(BINAP)Cl(μ-$Cl)_3$Ru(BINAP)Cl] in methanol under 100 bar of hydrogen showed the formation of ethyl 3-phenylpropanoate. Hence all operations were made properly. The conclusion was made, that the model flavonoids are inert towards homogeneous hydrogenation, catalyzed by above mentioned complexes.

The complex [Ru(p-cymene)(Tsen)Cl]Cl (**278**, generated *in situ*) was tested to perform the CTH (with NEt_3-HCO_2H adduct) of the model flavonoids. The complex was generated, then stirred with the substrate and reducing reagent in CH_2Cl_2[365]. No conversion was observed by GC/MS. The CTH of 2-(1-phenylethylidene)malononitrile[365] with above mentioned complex showed the formation of 2-(1-phenylethyl)malononitrile, hence all operations were made properly. The conclusion was made, that the model flavonoids are inert towards CTH, catalyzed by [Ru(p-cymene)(Tsen)Cl]Cl.

In order to explain the inactivity of the model flavonoids, let us examine the structure of the substrate (e.g. of 7-methoxyisoflavone) and reflect on the processes that occur after the precatalyst is activated. This reflexion is, surely, valid also for the other model flavonoids, both chromones and coumarins.

All the precatalysts are activated through formation of coordinatively unsaturated species (stabilized by coordination of solvent molecule). 7-Methoxyisoflavone has several coordination sites: ether oxygens, two phenyl-rings, carbonyl-group and C=C-bond (scheme 97). The methoxy-group is considered to be non-coordinative, since it does not prevent the titanocene-catalyzed hydrogenation and polymerization of alkenes[351]. The same should refer to phenyl-rings, but in this case it was an exception (see later). I speculate, that another ether-oxygen also should not be a good coordination site. The coordination on C=C-bond should

result in its hydrogenation, but it does not take place. Hence, the catalytically active complex coordinates on the carbonyl-group, or attacks the phenyl-ring. The coordination on carbonyl is unproductive, it does not lead to hydrogenation of the substrate.

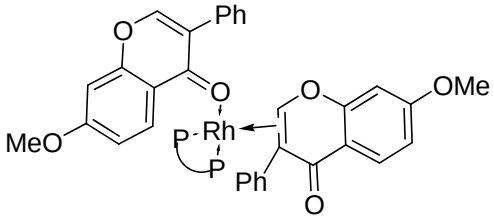


Possible coordination sites of 7-methoxyisoflavone

Scheme 97

This situation can be described in terms of functionalized and unfunctionalized alkenes. As it was described in section 1.3, first a coordination on carbonyl-group should occur, which is inherent for functionalized alkenes. But the geometry of the molecule excludes the further coordination of the metal, which is already coordinated on carbonyl-group, to C=C-bond (hence the latter is unfunctionalized).

The intermolecular coordination is nevertheless possible. If we would assume, that all metallic particles are coordinated on a carbonyl-group of the chromone, then a probability to meet another molecule of chromone is still quite high, and the particle **287** can be formed. In presence of 5 mol-% of catalyst correspondingly 5% of the substrate should be inactivated, and the probability to find the substrate is only 5% lower. The coordination pattern, represented by particle **287**, corresponds to the mechanism of hydrogenation of unfunctionalized C=C-bond. Unfortunately, it does not conform with the reality, since the substrate was not hydrogenated.



287

Scheme 98

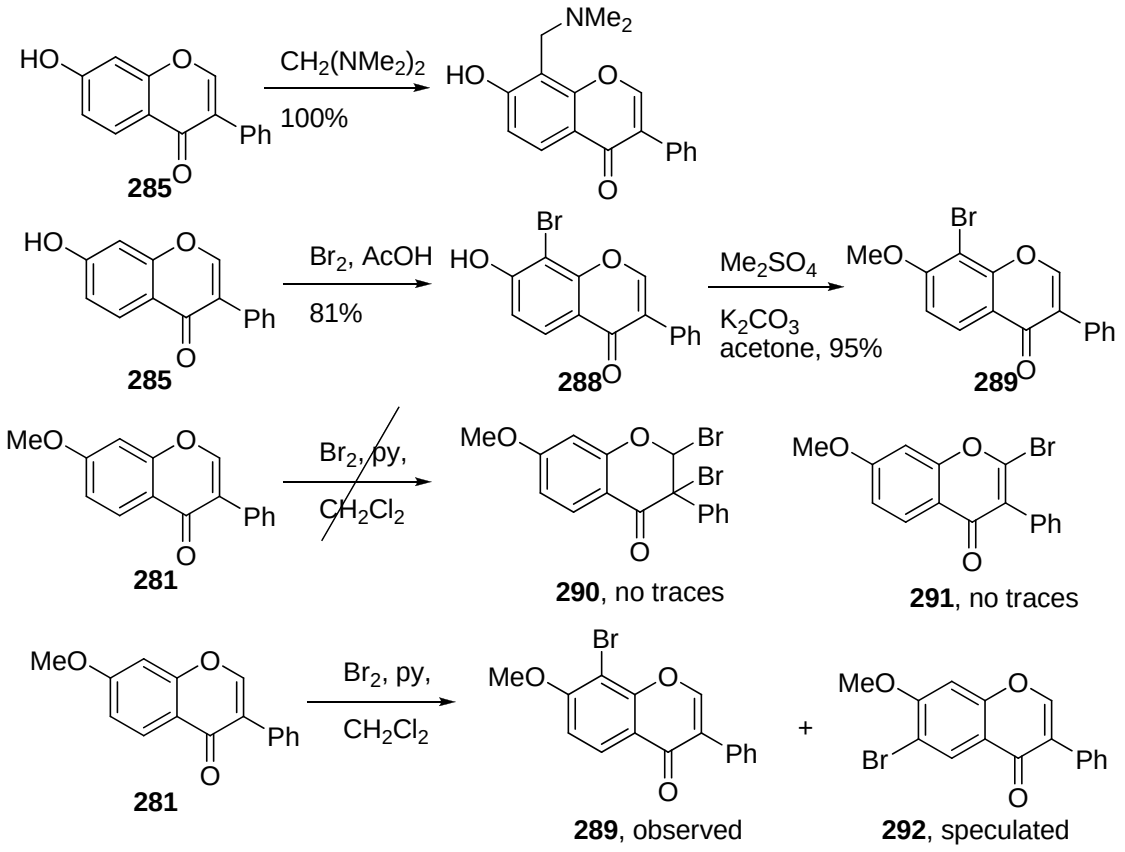
The catalytically active species are cationic or neutral complexes. Obviously, the cationic complexes should be rather electrophilic than nucleophilic, since they have a net charge +1. It corresponds with theirs ability to coordinate (hence hydrogenate) the electron-rich alkenes (e.g. stilbenes)[351].

The complexes of Ir(+1) are known to be nucleophillic (despite the positive charge)[366], which results in the reductive addition of hydrogen[340] (contrary to Rh, which adds hydrogen oxidatively) and involving of Ir(+3) species in the catalytic cycle. "Reductive addition" means that electron density is higher on the metal atom after the addition, i.e. dihydrogen Ir(+3) is more electron reach than parent Ir(+1). Despite this, the cationic complexes of type $[Ir(COD)L_2]$BARF and [Ir(COD)(L^L)]BARF can hydrogenate only electron-rich alkenes (see section 1.4.2 and references there).

7-Oxychromones are known to react with electrophilic compounds, and such reactions represent the normal electrophilic substitution in the aromatic ring[367]. The products are 8-substituted 7-oxychromones. For example, the 7-hydroxyisoflavone is brominated to give 8-bromo-7-hydroxyisoflavone[368]. In conditions of Mannich reaction or under action of bis(dialkylamino)methanes such chromones give the corresponding 8-dialkylaminomethyl-7-oxychromones[369, 370] (example in scheme 99).

The bromination of **285** was reproduced[368], yielding product **288**, which was further methylated to give isoflavone **289**. The latter was used as an authentic sample.

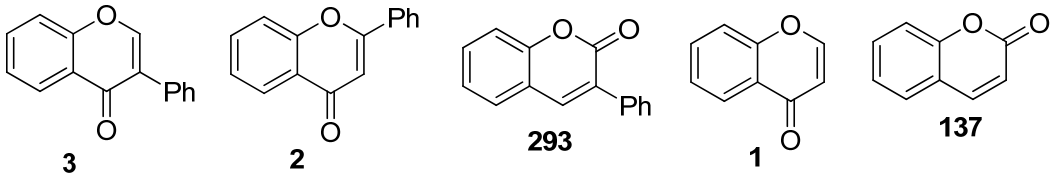
The bromination of **281** in dark leads to a mixture of three compounds: unreacted **281**, **289** (assigned by ^{1}H NMR after comparison with authentic sample), and unidentified compound, which is tentatively **292** (indirect proof see in experimental section). The substances **290** and **291** were not detected.



Scheme 99

On the other hand, plain chromone and many flavones, that do not bear the 7-oxy-group, react with bromine-containing electrophiles forming 3-bromochromones[371, 372] and 3-bromoflavones[372, 373]. The 2,3-dibromochroman-4-one was synthesized from chromone and bromine[374].

In order to exclude the possibility of electrophilic attack to the 8th position, I have checked the hydrogenation of compounds **1-3, 137** and **293** by [Rh(COD)(rac-BINAP)]OTf and by [Ir(COD)(iPr-Phox)]BARF **286c** in THF under 100 bar of hydrogen (**general procedure D**). It should be stated here, that e.g. the simple flavonoids **2-3** are not good model substrates. All natural flavonoids are hydroxylated, and the hydroxy- (or methoxy, glycosyloxy, etc) group is essential for biological activity. The substances **1-3, 137** and **293** were tested as model substrates because of theirs electronic/steric properties, but further as the model flavonoids the methoxylated compounds were used. The compounds **2-3,** and **293** were not hydrogenated *homogeneously*. Metallic rhodium was formed during this process, hence heterogeneous hydrogenation was possible, but the latter was suppressed by thiophene. Probabily, the catalytically active electrophilic complexes are quite weak electrophiles, weaker then bromine, dibromohydantoin or NBS, used for bromination of flavones.



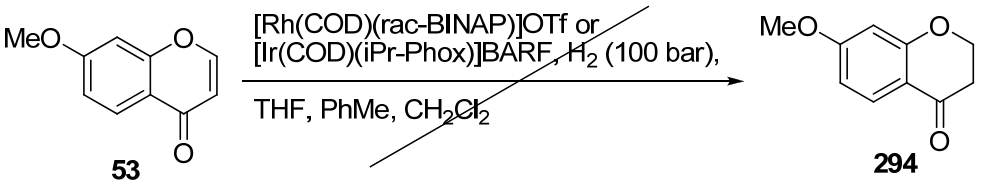
Scheme 100

On the other hand, the sterically unhidered chromone **1** and coumarin **137** were hydrogenated both by [Rh(COD)(rac-BINAP)]OTf and [Ir(COD)(iPr-Phox)]BARF in THF, in presence of 1 mol-% of the catalyst under 100 bar of hydrogen. The conversions are given in Table 17, and the only product is the corresponding chromanone. Although these compounds were hydrogenated, the conversions are quite low, which empasizes the importance of electronic properties of chromone and coumarin ring, but shows that sterical hindrances also play role in their homogeneous hydrogenation. Concerning the nucleophilic hydrogenation of **1** and **137** please refer to the section 3.5.

Table 17. Homogeneous hydrogenation of 1 **and** 137 **in THF (1 mol-% of catalyst)**

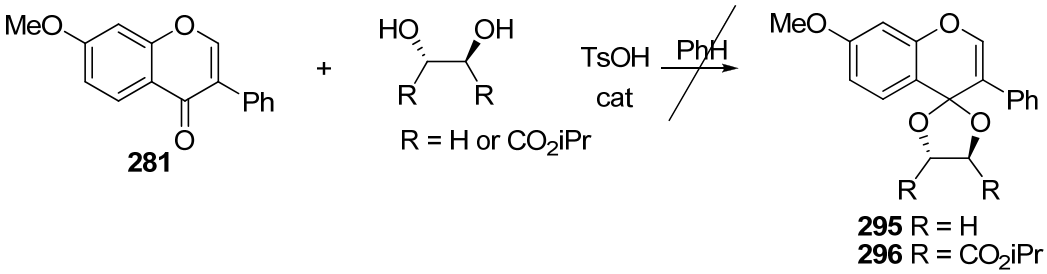
Substrate	Catalyst	Conversion (GC) to the corresponding chromanone
Chromone **1**	[Rh(COD)(rac-BINAP)]OTf	7%
Chromone **1**	[Ir(COD)(iPr-Phox)]BARF	7.5%
Coumarin **137**	[Rh(COD)(rac-BINAP)]OTf	4%
Coumarin **137**	[Ir(COD)(iPr-Phox)]BARF	18%

The most interesting fact is the inability of the catalysts [Rh(COD)(rac-BINAP)]OTf and [Ir(COD)(iPr-Phox)]BARF to hydrogenate the chromone **53** in conditions, effective for **1**. No traces of **297** were detected by GC/MS. This substrate has the same electron and steric environment as **1** around the C=C-bond, but the 7-methoxy-group completely changes the electronic density in annelated Ph-ring. The inability of above mentioned complexes to hydrogenate **53** indirectly proves, that the catalytically active particles, related to the above mentioned Rh- and Ir-complexes, do not atack C=C-bond, but rather react with the phenyl-ring. Concerning the nucleophilic hydrogenation of **53** please refer to the section 3.5.



Scheme 101

The apparent way to make the C=C-bond of **281** nucleophilic is the synthesis of acetals. 7-Methoxyisoflavone **281** was subjected to TsOH-catalyzed reaction with (+)-diisopropyl L-tartrate and with ethyleneglycol with continious separation of water (Dean-Stark receiver). The formation of either **295** or **296** was not observed by GC/MS.



Scheme 102

Chronologically the understanding and the proof, that the electrophilic catalyst attacks phenyl-ring, was made during the 3rd year of the research, and during the 1st it was performed an attempt to "cheat" the catalyst, namely to prepare the heterogenized one (section 3.2).

3.2 Attempts to prepare a heterogenized catalyst

The heterogenized metallocomplexes are effective catalysts for homogeneous hydrogenation[355, 375, 376]. The silica gel is more efective as the other supporters (e.g. polymers)[375, 376], and the complexes, anchored to silica, are shown to be efective catalysts for homogeneous hydrogenation[377, 378]. The reader should not be confused with heterogeneous catalysis. The metallocomplexes, being grafted to a supporter, do a hydrogenation according to the mechanisms, typical for homogeneous hydrogenation. Hence, this is a homogeneous hydrogenation, performed by a heterogeneous catalyst. For the latter a name "heterogenized catalyst" should be used.

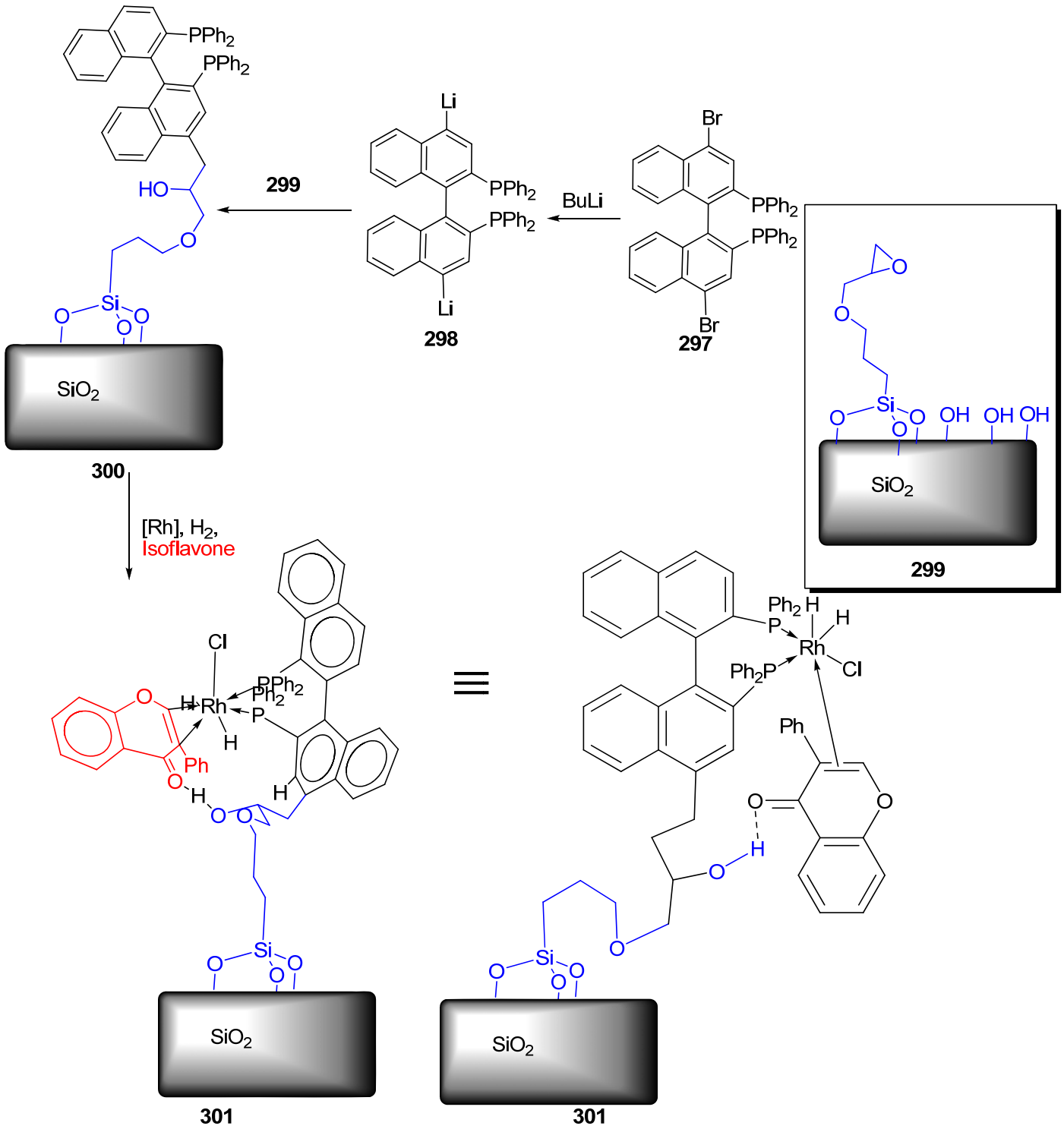
The idea was to graft a chiral ligand (e.g. BINAP) onto silica gel, using a special linker, and coordinate a metal to this ligand. The role of silica gel should be an adsorption of the substrate. The latter should diffuse on the surface of silica till finding of the complex. Then the substrate should coordinate to the metal atom, and this construction should be supported by the linker and, probably, by the silica gel.

2-Cyclohexenone was successfully hydrogenated by silica-grafted Wilkinson's catalyst[378]. Since this substrate has electron-deficient sterically not functionalized C=C-bond, like the flavonoids, the application of heterogenized catalyst could be successful.

As a ligand BINAP was choosed, because its dibromo-derivative **297** is known to be metallated by nBuLi to form the transient dilithium-derivative **298**[379] which can be trapped by various electrophiles. **298** Could be trapped by the epoxy-group, being graphted on silica gel (epoxy-graphted silica gel **299**), thus generating BINAP-graphted silica gel **300**. After forming of **300**, it should be subjected to complexation with rhodium, then a hydrogenation should be tested. The planned reactions are shown on the scheme 103.

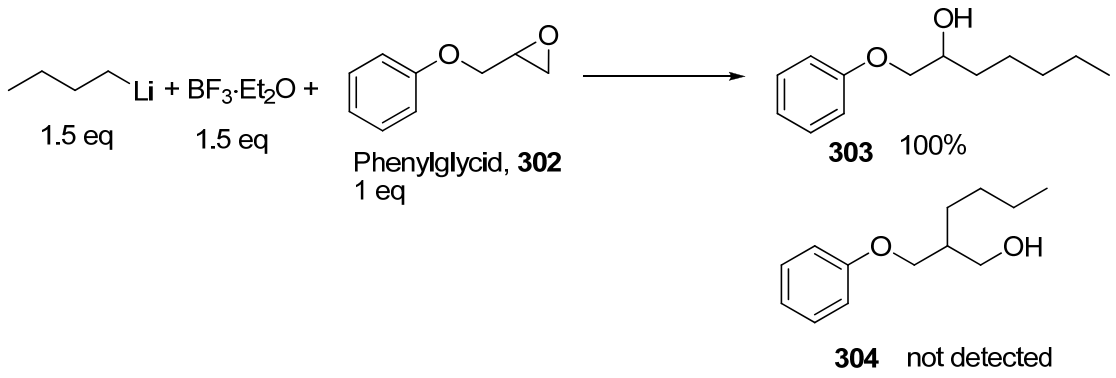
The above mentioned interaction of the linker with the substrate is represented by the structure **301**. This interaction is quite bad visible here, but it was drawn as 3D-structure. The 3D-structure convinced that there are not incompatible sterical hindrances, hence the structure **301** can exist, at least the stereochemistry allows its existence.

In order to find a method for the synthesis of **300**, several test-reactions were performed. As the mimetic of **299** the phenylglycid **302** was chosen. It and its derivatives flow in GC/MS, hence it is quite simple to analyze the reaction mixture. Phenylglycid readily reacts with pure nBuLi, if the latter is activated by $BF_3 \cdot Et_2O$, and produces only one compound **303**. The isomer **304** was detected neither by GC, nor by NMR.



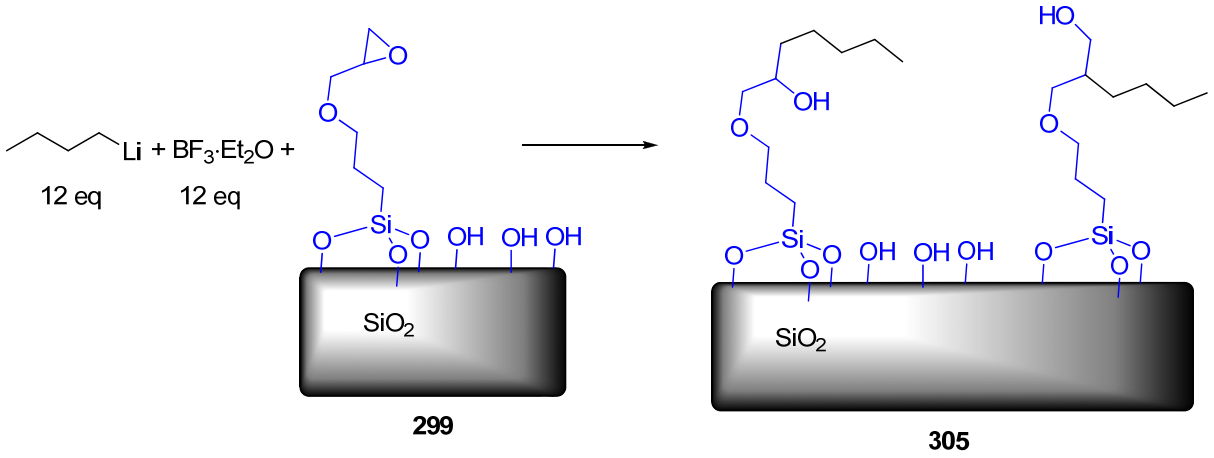
Scheme 103

After several test-reaction, it was found that minimal amount of nBuLi is to be 1.5 equivalents, relative to **302**, and $BF_3 \cdot Et_2O$ should be taken equivalent to organometallics. In such conditions the yield of **303** was quantitative (scheme 104).



Scheme 104

The epoxy-grafted silica gel **299** was prepared according to the known procedure[380], and the content of epoxy-groups was determined by back-titration with thiosulfate[380]. The application of above-mentioned method for the silica gel **299**, with respect to epoxy-group content and with excess of nBuLi and $BF_3 \cdot Et_2O$, gave the silica gel **305** (scheme 105). After washing and soxlet-extraction, **305** was subjected to elemental analysis and to ^{13}C CP/MAS TOSS NMR. The results of elemental analysis were as follows: 4.9% C, 1.47% H.



Scheme 105

The ^{13}C NMR CPTOSS/MAS spectrum (figure 2) of **305** has shown, that there are not epoxy-groups on the surface, but there is a new butyl-group (signal of terminal methyl at 11.3 and methylene groups in region 21-32 ppm). The $SiCH_2$-carbon resonates at 6.5 ppm, and OCH_2/OCH – in region 67-77. The signal at 62.2 can be assigned to CH_2OH, which is produced from hydrolized epoxy-group. Assignemets of the signals is done according to the similar surface compounds, found in literature[381, 382]. Because of high porosity, low packed density and low carbon content relative to the mass of sample, a good NMR spectrum was not obtained even in 67504 transients.

The ^{29}Si NMR CP/MAS spectrum (figure 3) of silica gel **305** is very similar to the corresponding spectra of epoxy- and diol-grafted silica gels[381].

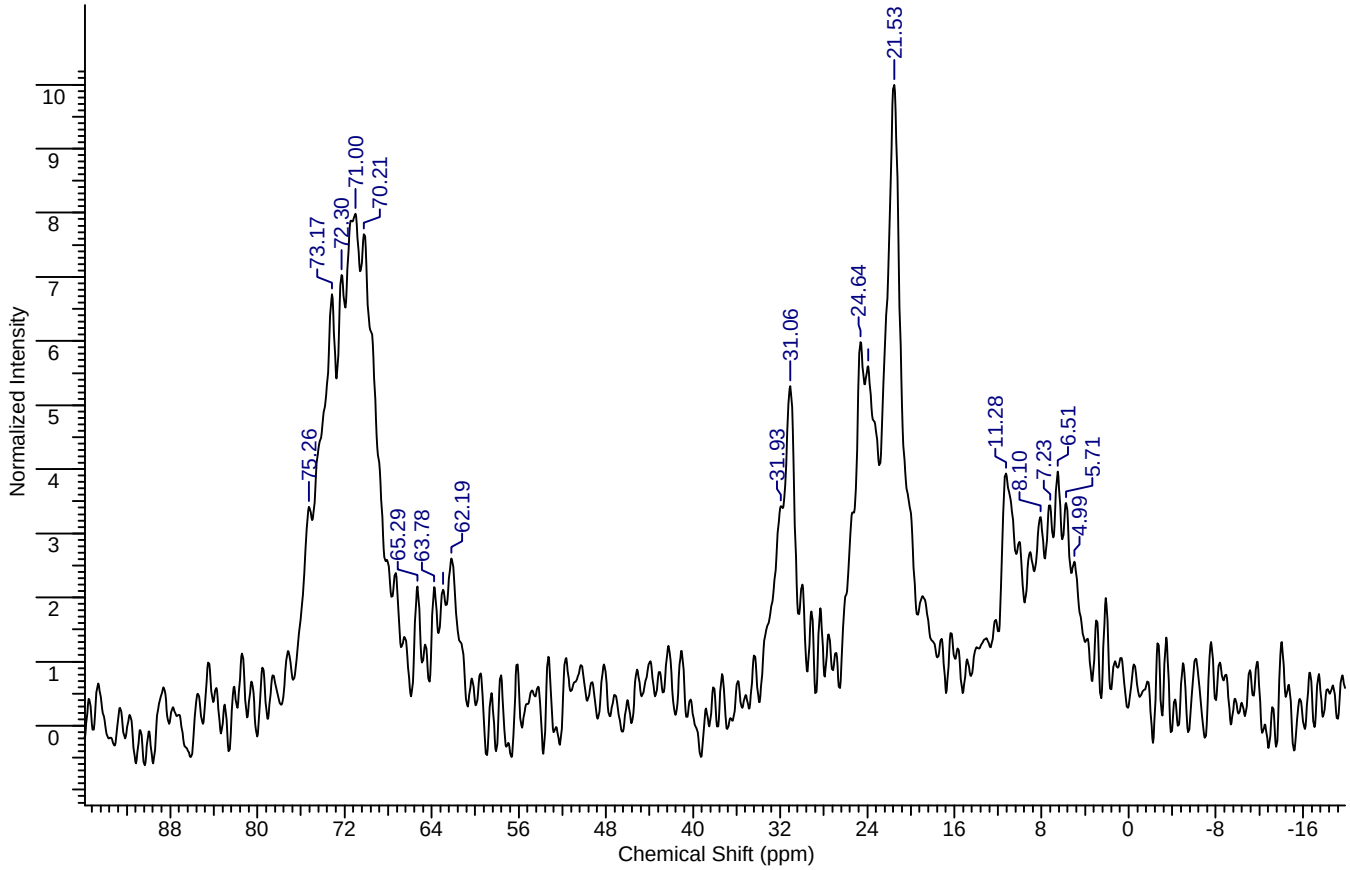


Figure 2

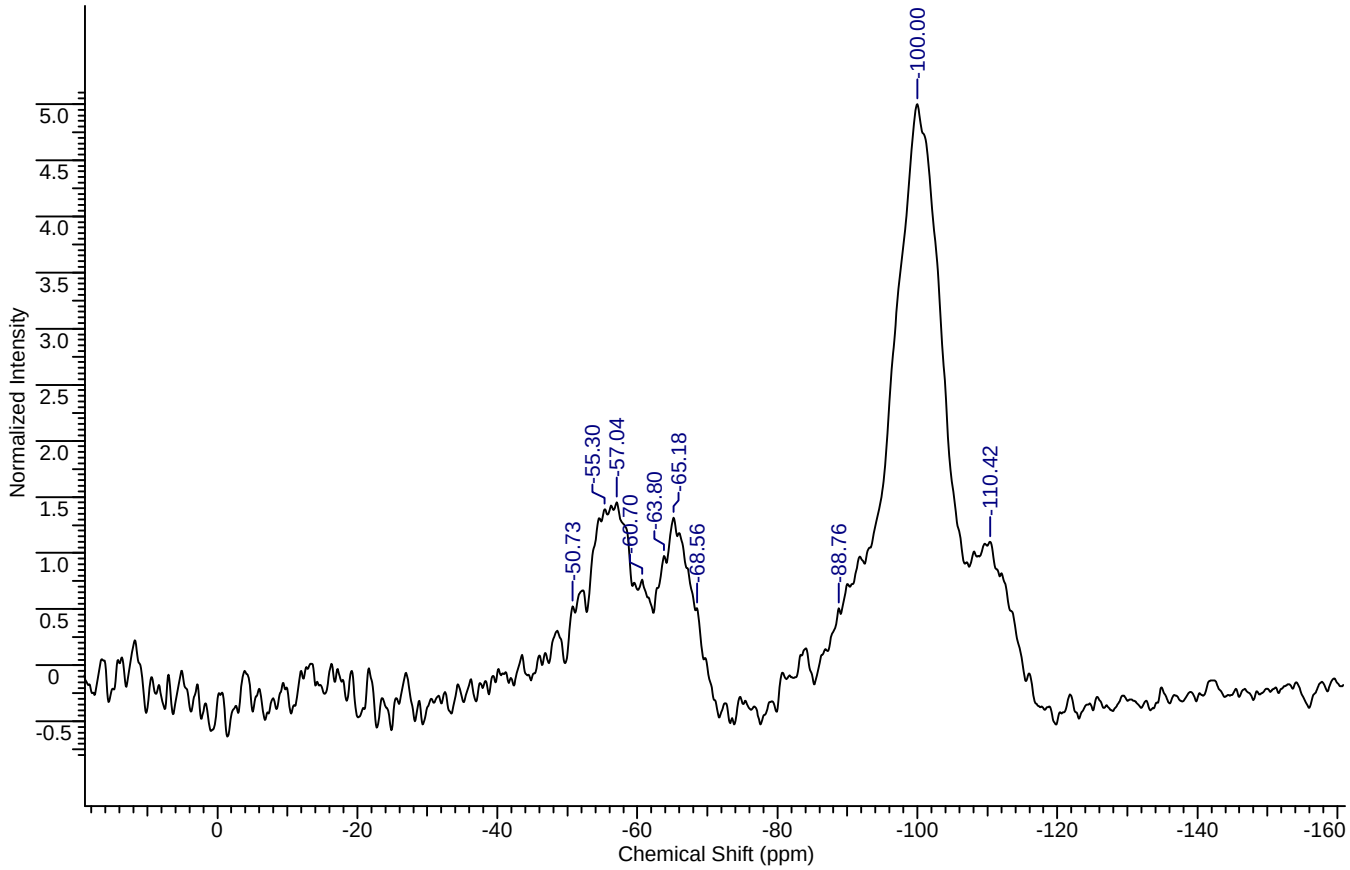
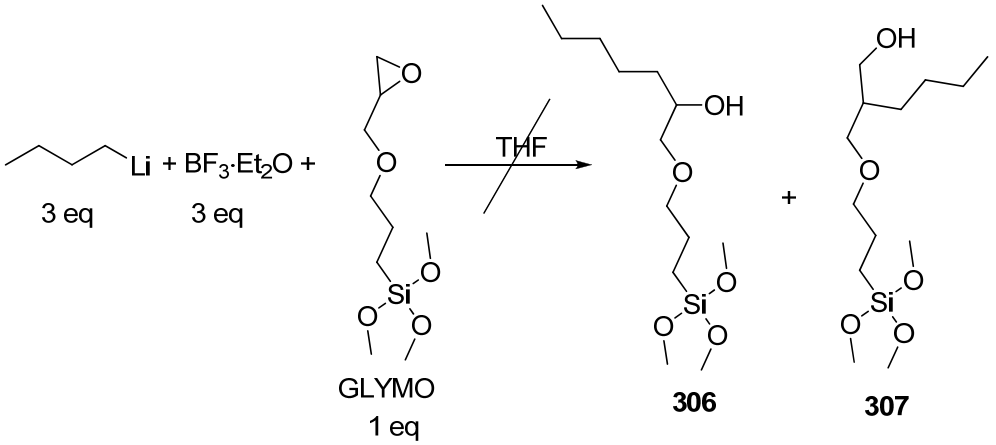


Figure 3

The IR spectrum of the silica gel, used for grafting (without epoxy-groups), is shown in figure 4, while the IR spectrum of **305** in figure 5. After substruction of spectrum of ungrafted silicagel from the spectrum of **305** the spectrum from figure 6 appears. There the low-intensive bands at 2880, 2936 and 2960 cm^{-1} can be observed, which are assigned with valent C-H-vibrations.

Similarly the GLYMO was allowed to react nBuLi, activated by $BF_3 \cdot Et_2O$. The reaction mixture was subjected to ^{29}Si NMR, which showed one doublet at +31.47 ppm (J 287.1 Hz). According to the literature[383], such a signal is characteristic for trialkylfluorosilanes. Hence, this reaction cannot be applied for generation of the purposeful silanes **306** and **307**.



Scheme 106

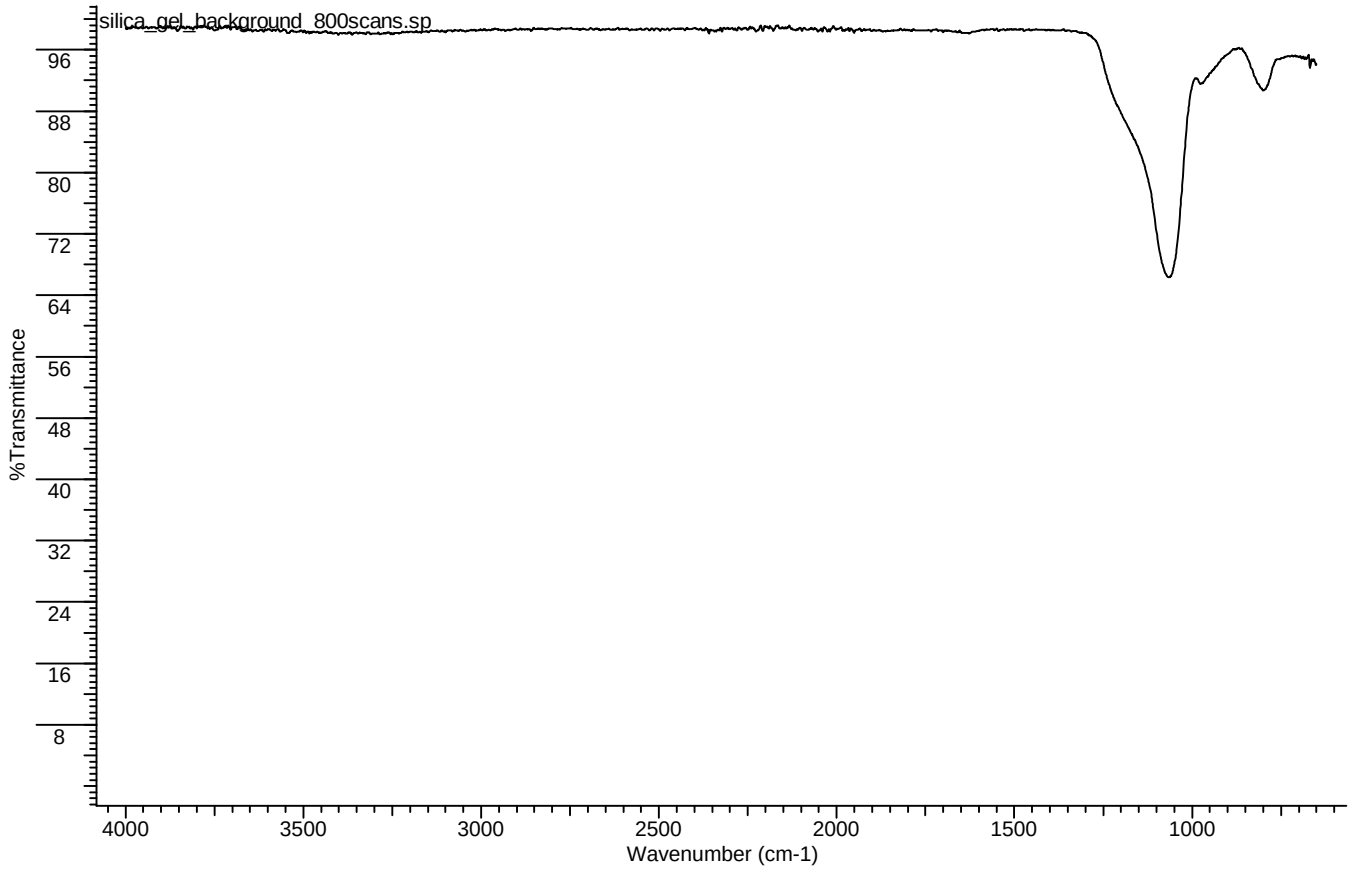


Figure 4

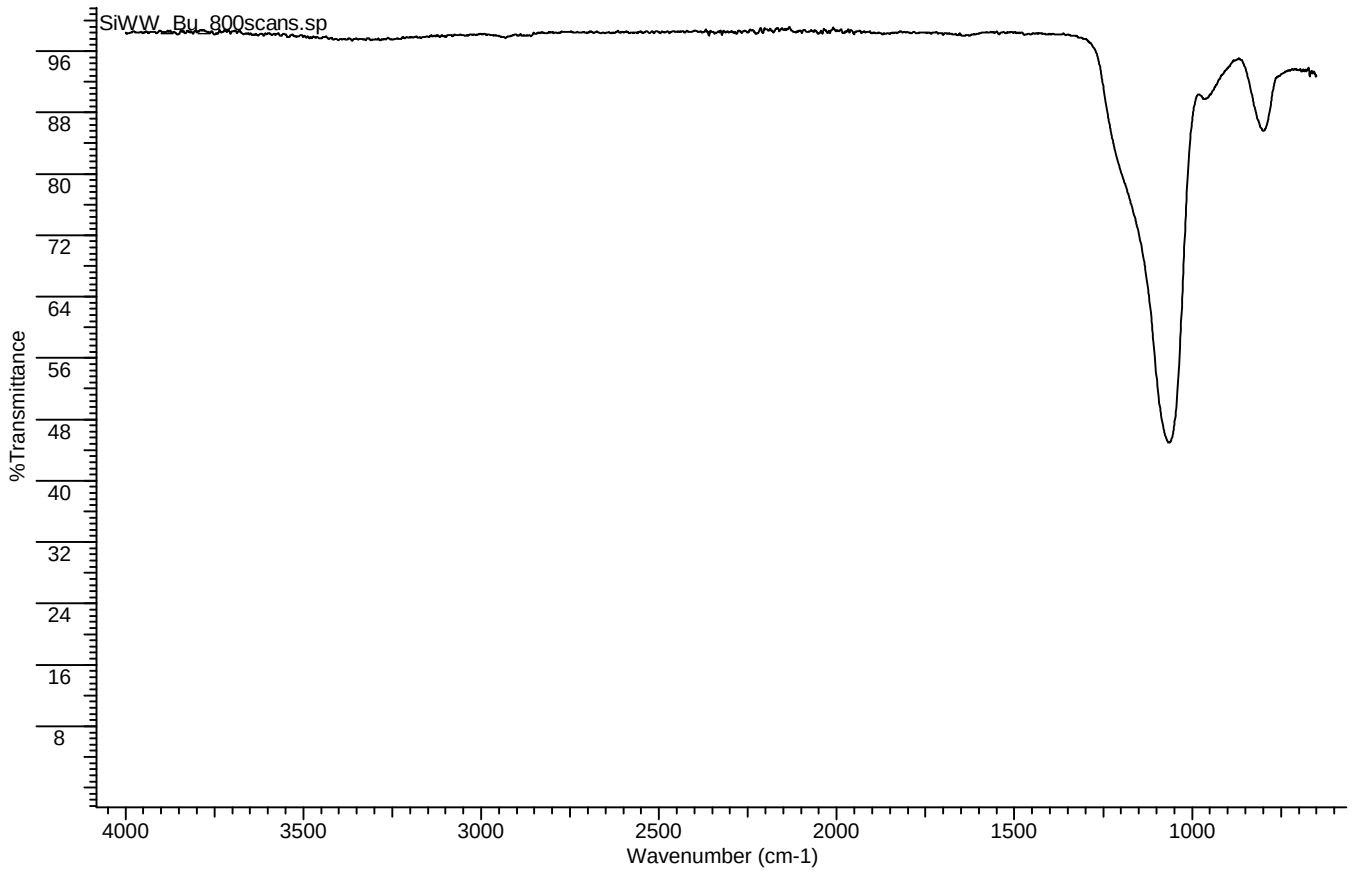


Figure 5

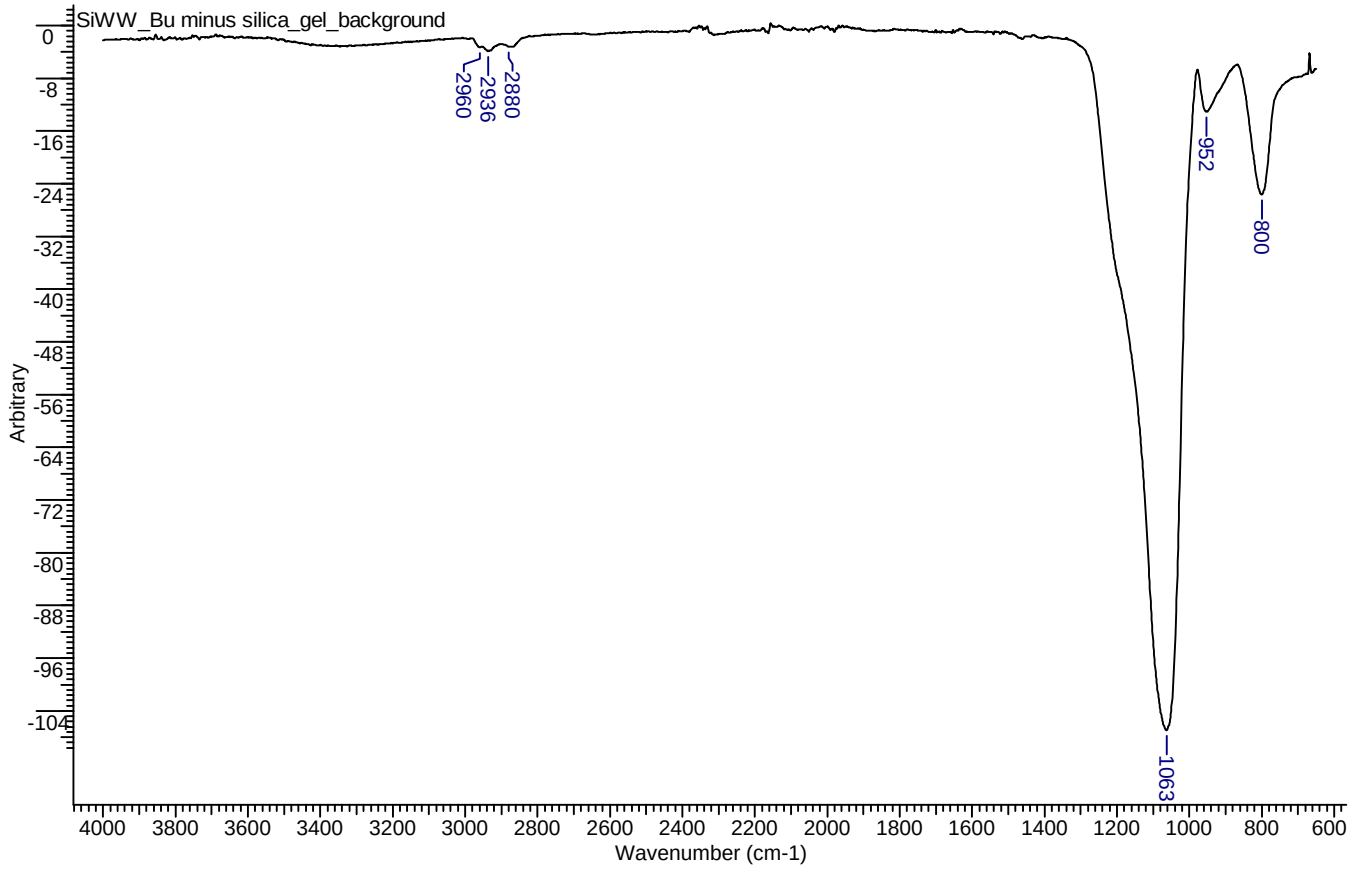
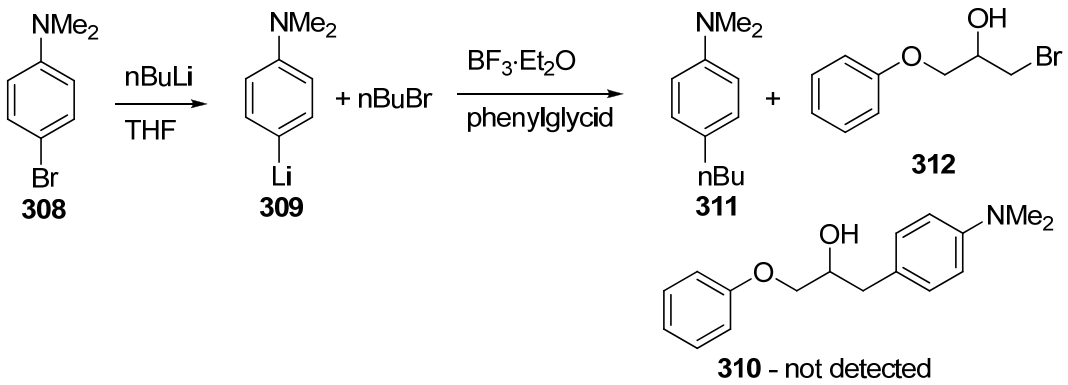


Figure 6

Having a good method of immobilization of butyl-group through butyllithium, it was important to check some other test-compound, resembling the BINAP. Such a compound is *p*-bromodimethylaniline **308**. It was metallated using nBuLi[384], to give **309**, which was allowed to react with $BF_3{\cdot}Et_2O$ and phenylglycid, according to the above mentioned method for synthesis of **303**. Unfortunately, the compound **310** was not detected in reaction mixture. Instead of **310**, the compounds **311** and **312** were detected by GC/MS.



Scheme 107

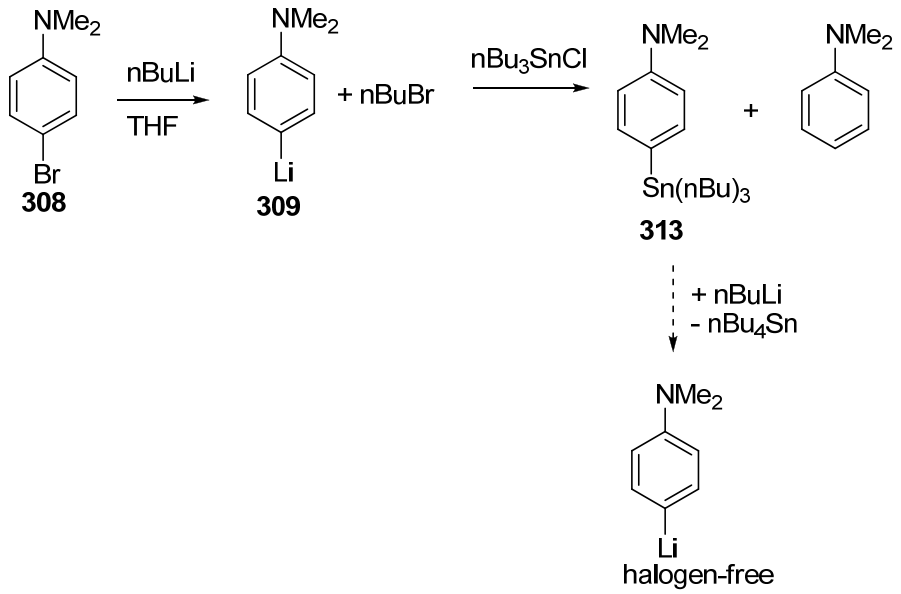
The application of tBuLi instead of nBuLi for generation of *p*-lithiodimethylaniline have suppresed the Wurtz reaction, but the product **310** was even not produced. If **310**·LiBr (generated from *p*-bromodimethylaniline and 2 eq. of tBuLi) was allowed to react with

$BF_3 \cdot Et_2O$ and phenylglycid **302** (at -78º C), and the reaction was quenched in 5 minutes, up to 20% of **310** was detected. But in 10 minutes after quenching **310** was not more detectable. Thus, the compound **310** was formed, but reacted with LiBr and $BF_3 \cdot Et_2O$ to form **312** and dimethylaniline.

The variation of amount of *p*-bromodimethylaniline **308** (1 to 3 eq), $BF_3 \cdot Et_2O$ (1 to 3 eq), of solvents (Et_2O, pentane) and precoordination of BF_3 onto **308** has not changed the outcome of the reaction. This is not surprising, since such a behaviour of LiBr in reactions with epoxides in presence of $BF_3 \cdot Et_2O$ is well known[385], and as long as LiBr is present in the reaction mixture, the compound **310** cannot be synthesized.

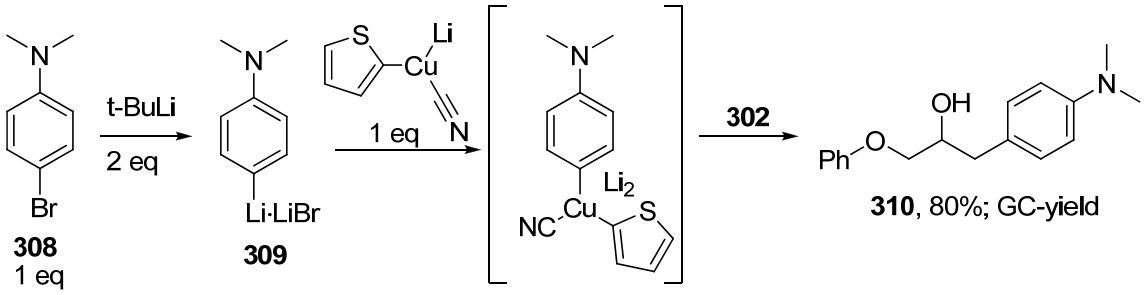
I tried to metallate **308** with EtLi[386] (available from Acros), and then evaporate EtBr without warming of the reaction mixture to r.t. Unfortunately, only p-ethyldimethylaniline was detected after this metallation, and not the product **310**. The precipitation of pure **309** (generated with help of nBuLi) from its THF solution by hexane (leaving nBuBr in solution) was not successful, since **309** is soluble in hexane.

Halogen-free lithio-aryl-compounds were generated from the corresponding stannanes[385, 387]. Unfortunately, the synthesis of stannane **313** was not reproduced[384] (a mixture of **313** with dimethylaniline was formed), hence a generation of halogen-free **309** was not possible. The formation of dimethylaniline is not connected with improper reaction workup, since the monitoring of reaction of **309** with nBu_3SnCl showed not full conversion to **313** even after stirring for 24 h at r.t. in THF. The substance **313** is hydrolized on silica gel, hence column chromatography is impossible on this sorbent. It can be purified by reverse-phase column chromatography[388], but this method is very expensive.



Scheme 108

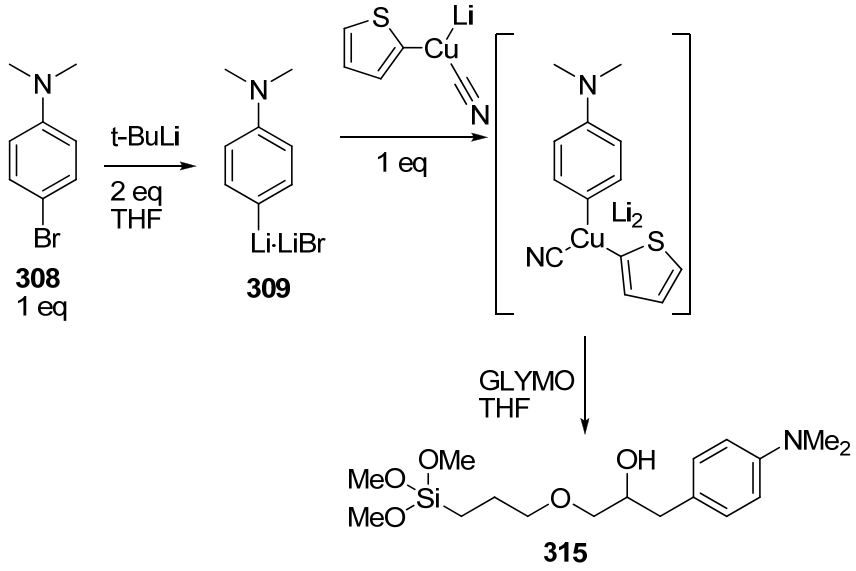
The substance **309**·LiBr (generated from **308** and tBuLi) was found to react with phenylglycid **302** through the corresponding organocuprate. The best GC-yield (80%) was observed if the high-order cuprate, derived from lithium thienylcyanocuprate and **309**·LiBr, was prepared and allowed to react with **302**. The product **310** is stable, it does not disappear in case of prolongoued stirring of reaction mixture.



Scheme 109

The application of organocuprate for coupling with GLYMO gave the purposeful silane **315**, as judged from ^{29}Si NMR of the reaction mixture (resonance at -45.1 ppm), but contaminated with the other Cu-containing compounds. Since **315** cannot be purified by silica gel column chromatography, it should be subjected to grafting being crude. Three different experiments were performed (see section 7.2), but the obtained silica gel was contaminated by Cu, which was indicated by its brown or pale-brown colour, and it cannot be decolorized by washing with saturated aqueous Na_2EDTA, NH_3/NH_4Cl or by saturated solution of LiCl in DMF. I tried to trap this silane as the TMS-derivative, which was quickly washed qith aqueous NH_3/NH_4Cl. It should extract the Cu into aqueous layer, but the grafting of the rest

gave again the coloured silica. Hence, the method *via* organocuprates is unsuitable for grafting.



308 1 eq **309** **315**

Scheme 110

As a summary, a method for successful grafting of dimethylaniline onto silica gel was not found, hence the catalyst with grafted BINAP was not prepared.

3.3 Nucleophilic hydrogenation of 7-methoxyisoflavone

As it was mentioned above, the complex [Ir(COD)(iPr-Phox)]BARF **286c** could not hydrogenate the 7-methoxyisoflavone **281** in standard conditions in dichloromethane (**general procedure D**). The hydrogenation in toluene or in THF also was in vain. Surprisingly, the 7-methoxyisoflavanone was detected after the hydrogenation in toluene, if thriethylamine was added (**general procedure G**).

As it was explained above, the C=C-bond of 7-methoxyisoflavone is electron-deficient, hence inert towards electrophiles and rather apt to react with nucleophiles[367, 389]. Alkali reacts with chromones with attack to the 2-position, resulting in chromone-cycle destruction[23]. Such nuclophiles, as hydrazine, phenylhydrazine, hydroxylamine and guanidine also attack 2-position of chromones, and then the remaining carbonyl-group, thus destroying chromone-ring and building a new one, which is used in synthetic chemistry[390].

An assumption was made, that addition of base to reaction mixture resulted in formation of some new iridium-complex, which attacks the electron-deficien C=C-bond of 7-methoxyisoflavone, and catalyzed its hydrogenation. Because this complex should be nucleophilic, this type of hydrogenation was named “nucleophilic hydrogenation”. The

traditional, base inactivated homogeneous hydrogenation by Ir-complexes, is called here "electrophilic hydrogenation" because of electrophilic Ir-complexes, responsible for hydrogenation of electron-rich alkenes.

In order to optimize reaction conditions base- and solvent-screening experiments were performed under standard conditions (**general procedure G**), and the results are shown in Table 18 and Table 19. 7-Methoxyisoflavone was used as a model substrate and the reaction was run in the presence of 1 mol% of [Ir(COD)(iPr-Phox)]BARF.

Table 18. Base screening (solvent – toluene)

Base	Conversion (GC) of 7-methoxyisoflavone
Triethylamine (NEt_3)	20
Diisopropylamine (DIPEA)	37
LHMDS	0
TMEDA	3
2,6-Di-*tert*-butylpyridine	0

Table 19. Solvent screening (base - DIPEA)

Solvent	Conversion (GC) of 7-methoxyisoflavone
Toluene	37
Methanol	37
Dichloromethane	0
Dichloroethane	0
Chloroform	0
THF	traces of product
MTBE	traces of product
neat DIPEA	traces of product

7-Methoxyisoflavone could be heterogenically hydrogenated in dioxane using palladium on carbon as catalyst. This reaction is completely suppressed by thiophene, which normally poisons heterogeneous catalysts[332]. Hydrogenation catalyzed by [Ir(COD)(iPr-Phox)]BARF readily occurs in the presence of thiophene, thus proving the process' homogeneity. As judged from the results, the coordinating bases LHMDS and TMEDA suppress nucleophilic hydrogenation, while non-coordinating DIPEA activates it more efficiently than triethylamine. Despite the sterical hindrances, the 2,6-di-*tert*-butylpyridine is known to be a

ligand for Pd[391], Au[392] and Ti[393], hence is also a coordinating base. 7-Methoxyisoflavone **281** cannot be reduced in neat DIPEA due to poor solubility. 2-Fold or 10-fold excess of DIPEA (relative to iridium-complex) was not sufficient to run this reaction. In microscale experiment 0.07 ml of base (300-600-fold excess relative to Ir-complex, depends on catalyst load) were directly added to the reaction mixture.

The quality of DIPEA is very significant for the reaction. A very little amount of diisopropylamine could completely inhibit the reaction. Commercial available DIPEA was purified by distillation over ninhydrine, than twice over lithium hydride. Sodium hydride was not effective to make diisopropylamine-free DIPEA.

Chlorinated solvents are widely used[341, 348] for Ir-catalyzed electrophilic hydrogenation but were found to inhibit nucleophilic hydrogenation. The reason behind it is presumably the base-induced decomposition with the formation of trialkylammonium chloride, which subsequently reacts either with catalyst or with catalytically active intermediate. This assumption was confirmed by performing hydrogenation experiments in the presence of tetrabutylammonium chloride. The last compound was chosen because of the fair solubility in toluene and was found to inactivate the nucleophilic hydrogenation reaction.

Another observation is that performing of the reaction in glass vessel sometimes gave a very low conversion. It was associated with the surface OH-groups on the glass, which are quite good ligands for iridium. The use of teflon vessels has disposed of this problem and the experiments became fully reproducible.

The application of 3 mol-% (or more) of the catalyst **286c** gave the full conversion to 7-methoxyisoflavanone, without overreduction or product decomposition. The hydrogenation was performed according the **general preparative procedure H**. 7-Methoxyisoflavanone was isolated with yield of 90% after column chromaography, and its spectral properties were in accordance with the published[5, 394].

It was found, that reaction is not very fast. The hydrogenation of 7-methoxyisoflavone in toluene under 100 bar of hydrogen using 4 mol-% of [Ir(COD)(iPr-Phox)]BARF and 100 mol-% (or 500 mol-%) of DIPEA leads to only 50% conversion in 1 h, but in full conversion after overnight hydrogenation.

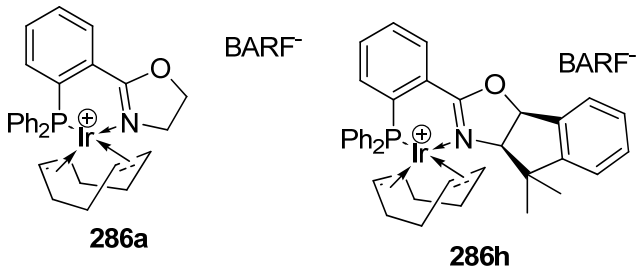
The hydrogenation is identical in concentrated (5 mg of [Ir(COD)(iPr-Phox)]BARF, 25 eq of substrate, 100 eq – 0.05 ml of DIPEA, 0.3 ml of PhMe) and in diluted (5 mg of [Ir(COD)(iPr-Phox)]BARF, 25 eq of substrate, 500 eq – 0.25 ml of DIPEA, 4 ml of PhMe) solution. Full conversion was achieved in both cases after overnight hydrogenation, while hydrogenation during 1 h gave only 50% conversion. Hence, the nucleophilic hydrogenation

is not very fast. If the reaction with 50% conversion is exposed to air and pressurized with hydrogen again, the hydrogenation takes no place. Hence, the catalytically active complex or complexes are air-inactivated.

Racemic 7-methoxyisoflavanone was prepared by the above mentioned hydrogenation using racemic complex **286c** or complex **286a** (preparation see in section 4.4), and subjected to HPLC with chiral column. The isocratic eluation with hexane-ethanol mixture 70/30 resulted in enantiomer separation, hence ee of enantioselective hydrogenation could be measured.

Hydrogenation, catalyzed by enantiomerically pure **286c** was found to proceed with ee 12% in toluene and racemic in methanol. Chirally enriched (12%) 7-methoxyisoflavanone was not racemized by storing in pure methanol, but racemized if one drop of DIPEA was added to the methanol solution. Chirally enriched 7-methoxyisoflavanone was not racemized by overnight stirring in toluene containing 10% DIPEA. Hence, a very low ee achieved in toluene is not connected with the base-induced racemization, but is a property of this reaction. Hydrogenation in methanol, of course, was accompanied by base-induced racemization.

Hydrogenation, catalyzed by **286h** (preparation see in section 4.4), gave ee of 34%, but only 10% conversion. Unfortunately, the screening of many Ir-complexes did not allow to improve ee and conversion of this reaction.



286a **286h**

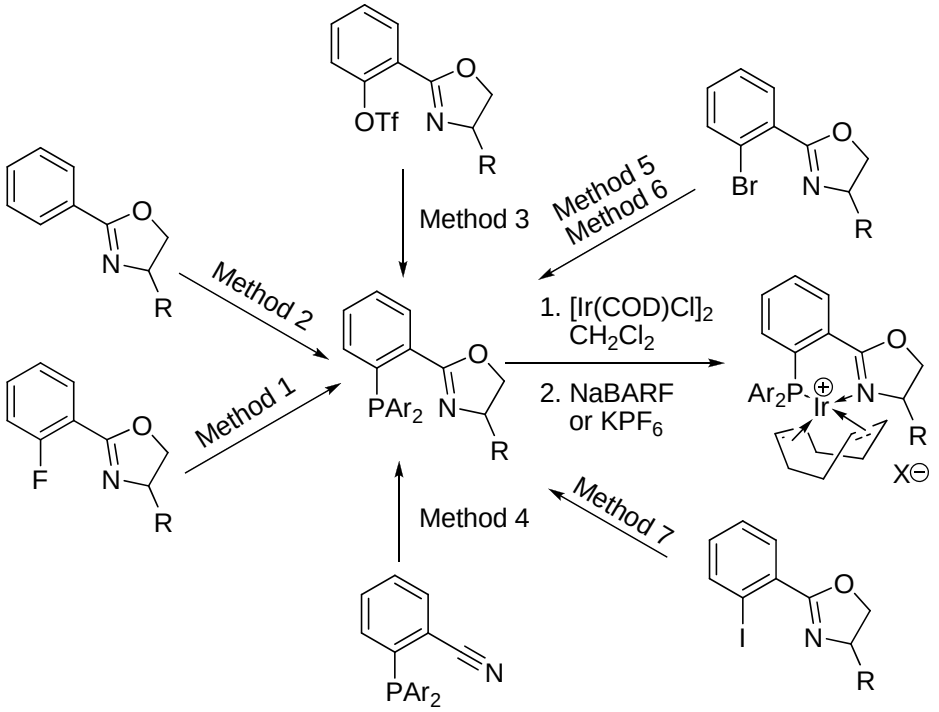
Scheme 111

Hydrogenation, catalyzed by 1 mol-% of [Ir(COD)((S)-iPr-Phox)]BARF in PhMe, but carried out in presence of (R)-N,N-diethyl-1-phenylethanamine (specially purified), resulted in 15%-conversion, and ee of the product was still 12%. Thus, the chirality of base has no influence on stereochemical outcome of the reaction, in other words, ee of the product is controlled by the ligand.

3.4 Nucleophilic hydrogenation: catalyst screening

In order to investigate the nucleophilic reduction, I should synthesize various complexes of iridium. Even with the synthesis of well known **286c** there were some problems, actually not with synthesis of the complex, but with the ligand **316c**.

Current methods of the syntheses of these complexes presume initial ligands' syntheses, their isolation and purification (*via* column chromatography) followed by complexation on iridium (Scheme **112**).

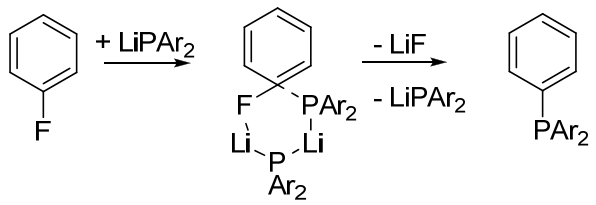


Method 1: Ar_2PLi
Method 2: 1. s-BuLi, TMEDA; 2. Ar_2PCl
Method 3: Ar_2PK
Method 4: NH_2CHRCH_2OH, $ZnCl_2$, then bipy
Method 5: Mg, Ar_2PCl
Method 6: CuI, $MeNHCH_2CH_2NHMe$, Cs_2CO, Ar_2PH
Method 7: Ar_2PH, NEt_3, $Pd(OAc)_2$

Scheme 112

According to the push-pull phosphonylation mechanism[395] (Scheme 113), the method 1[396] requires an excess of phosphine, which prevents further crystallization of the ligand and thus must be separated by column chromatography. Method 1 was reproducible up to chromatography. The ligand **286c** is described as an air-stable compound[397], but in my experiments this was not the case (the chromatography should be performed strictly under nitrogen on deoxygenated sorbent using deoxygenated eluent, otherwise oxide of **286c** was detected by ^{31}P NMR). But the main problem was the irreversible adsorption of ligand on silica, neutral or basic alumina, which remained even when triethylamine was added in eluent.

The irreversible adsorption lowered the yield of ligand to 20-30%. The method 2 gave the purposeful phosphinooxazolines with best GC-yield of 20%, hence was not further explored. According to literature[398], method 3 gives impure ligand, hence chromatogrphy is necessary. Methods 4[399], 5[396], 6[400] and 7[401] also require column chromatography.



Scheme 113

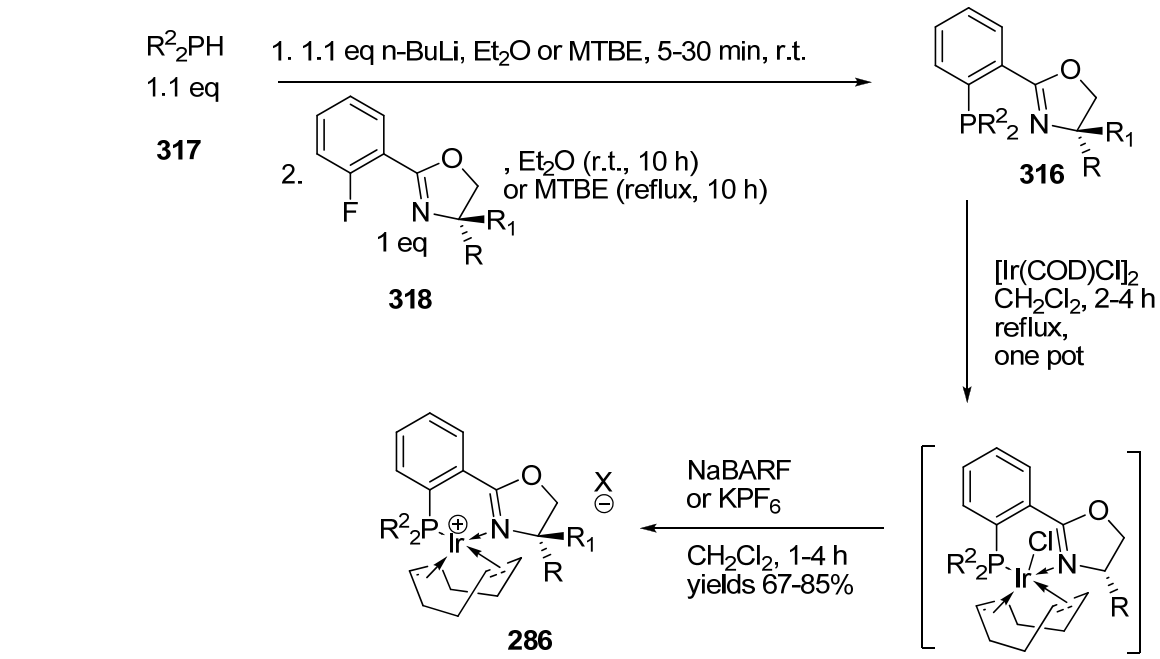
In order to obtain the required complexes I developed a one-pot procedure (Scheme 114). The procedure of ligand synthesis is also notably simplified (comparable with that in[396]). In the experimental section I provide a detailed synthetic procedure. Although an indication on the possibility of impure ligand complexation was made in literature[341], the particular procedure was not described.

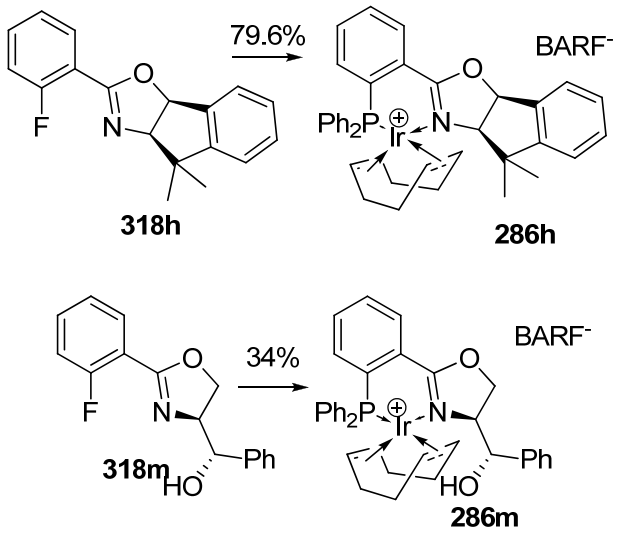
Compounds **286** are insensitive to oxygen and moisture and could be purified by column chromatography (preferably those with BARF as anion) or precipitation by ether (those with PF_6 anion). Complexes are coloured which makes column chromatography extremely simple, because there is no need of fraction collecting.

The identity of synthesized complexes was checked by ^{1}H, ^{13}C and ^{31}P NMR-spectra and ESI/FT-ICR HRMS. Compounds **286c**[341, 402], **286f**[341, 402] **286i**[341] and **286l**[341] are described in literature but the NMR-spectra for **286i** and **286l** are not described. Compounds **286c** and **286f** have NMR-spectra as reported in literature. Spectral information of the other compounds is provided in section 7.4.

N-Butyllithium was used to deprotonate diaryl- or dialkylphosphine. Although according to literature[403], the use of s-BuLi is preferred, it does not result in a better yield of complex **286**. The use of THF is avoided in ligand-preparation (except for **286m**). THF is known to slowly react with lithium diphenylphosphide[404], thus decreasing the yield of desired ligand. Sterically unhindered diphenylphosphine and hindered di-*o*-tolyl-, dixylyl and dicyclohexylphosphine readily enter in phosphonylation reaction, giving the corresponding ligands and Ir-complexes, but hindered phosphines must be deprotonated during 30 min in MTBE, and then refluxed overnight with fluoruoxazoline **318c**. In the case of dicyclohexylphosphine, the neglect of 30 min deprotonation leads to the worse conversion of

318c (60% instead of 90%, observed by GC/MS). Lithium di-*tert*-butylphosphide and lithium phospholan-1-ide failed to enter in this reaction, i.e. ligand formation was not detected.



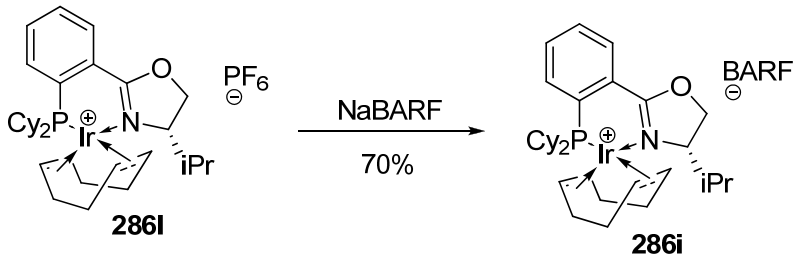


Compd 286, 316-318	R	R^1	R^2	X
a	H	H	Ph	BARF
b	Me, H	racemic	Ph	BARF
c	i-Pr	H	Ph	BARF
d	t-Bu	H	Ph	BARF
e	i-Pr	H	o-Tolyl	BARF
f	t-Bu	H	o-Tolyl	BARF
g	i-Pr	H	2,6-Xylyl	BARF
i	i-Pr	H	Cy	BARF
j	i-Pr	H	Ph	PF_6
k	Me	Me	Ph	BARF
l	i-Pr	H	Cy	PF_6

Scheme 114

Complex **286i** and dicyclohexylphosphine oxide are coeluated by dichloromethane and could not be separated even by hexane-dichloromethane gradient chromatography. The

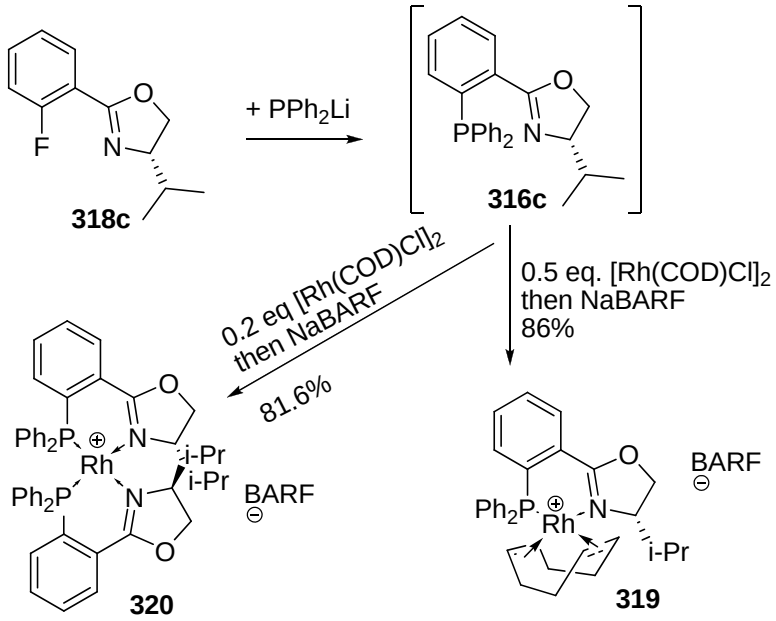
analytically pure complex **286i** was synthesized from **286l** (scheme 115). The latter was purified by precipitation by ether from dichloromethane.



Scheme 115

Complex **286g** was obtained in spectrally impure form. All attempts to purify it by gradient chromatography (hexane-dichloromethane or hexane-chloroform) were in vain. The complex with the same cation, but with PF_6 as counter-ion was also obtained in an impure state, and the above-mentioned strategy with anione-exchange, was not applicable for **286g**. However, the formation of **286g** was proven by its mass-spectrum.

Being successful in the synthesis of Ir-complexes, I checked the possibility of synthesizing the analogous Rh-ones. In case of 1 eq. of ligand for 1 eq. of Rh, complex **319** was synthesized. COD, bound to Rh, is more labile than that bound to Ir, that is why excess of ligand yielded complex **320**.



Scheme 116

Because of the strong trans-effect of the phosphorus atom, the ligands in complex **320** should be cis-arranged. The iminic carbon comes as a triplet of doublets in ^{13}C NMR, and this multiplicity is only possible in case of cis-arrangement (coupling on own phosphorus of ligand, on rhodium and on trans-phosphorus from the other ligand). This coupling is only

visible on a 100 MHz instrument (Varian ^{UNITY}*INOVA* 400), while at 150 MHz it comes as a broad singlet (Bruker Avance DRX600). The signal (after apodization) and the splitting tree are demonstrated in figure 7. The ^{13}C NMR-spectrum of this compound was acquired using special parameters (spectral width 175 - -5 ppm, 256000 points, acquisition time 7.0736 sec, relaxation time 1 sec).

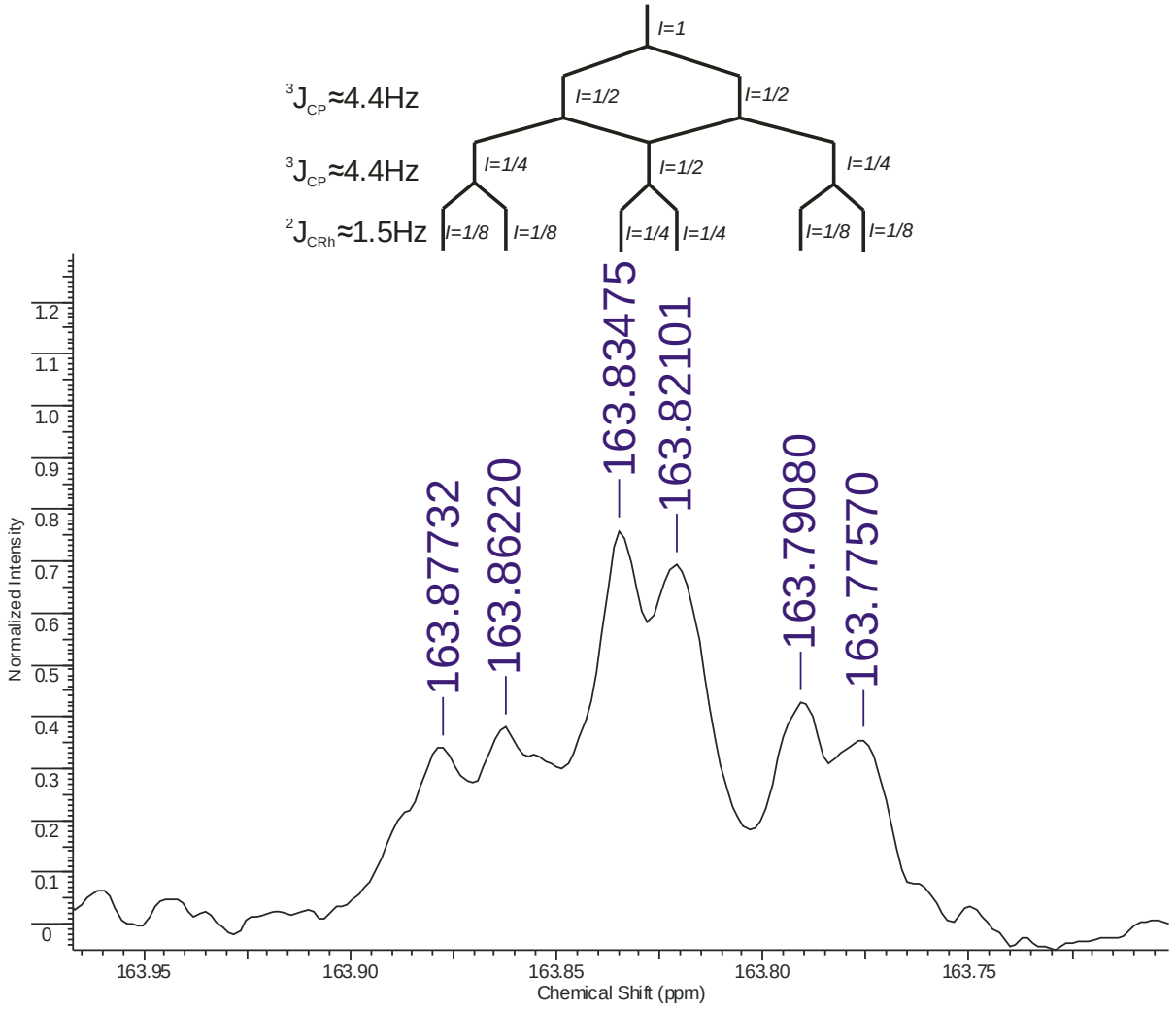
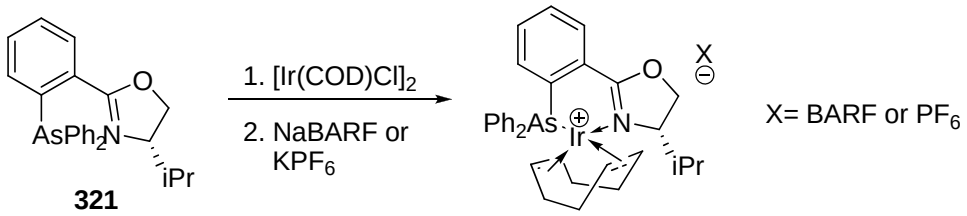


Figure 7

Using this protocol, ligand **321** was synthesized from appropriate oxazoline and diphenylarsine. However, its complexation on iridium leads to a mixture of compounds, and no complex was isolated analytically pure, neither with BARF nor with PF_6 anion. The formation of the desired complex [Ir(COD)(**7**)]BARF (in mixture with other compounds) was proven by mass-spectroscopy. The complex was a weak hydrogenation catalyst of stilbene, that is why its research has been ceased.



321

Scheme 117

The NMR spectra of these complexes are hard to analyze, since too much signals are present. Another complication is that the signals in proton-spectra are not fully resolved (in both aromatic and aliphatic parts). The chirality makes the atoms of phenyl-rings and of COD magnetically nonequivalent which complicates the spectra even more. With help of 2D-techniques (COSY, TOCSY, HSQC, HMBC, ROESY and J-resolved) the assignments could to be done. Because of magnetical nonequivalence, not resolved multiplets (nrm) are inherent for ^{1}H NMR-spectra of chiral complexes. Although the shifts of individual peaks are indistinguishable in 1D-spectra, the precise shifts in ^{1}H NMR could be established from HSQC and HMBC spectra. 2D-spectra were not measured for compounds **318c** and **318f**, because their spectra are in agreement with the ones found in literature.

Complex **286e** has very interesting spectral properties. While the other compounds show a sharp singlet in ^{31}P NMR, **286e** shows two bright singlets at +16.1 and +8.5 ppm in $CDCl_3$. The conformational stability known for tri-*o*-tolylphosphine[405] forced us to examine high-temperature ^{31}P NMR of this compound. At 140º C and higher temperatures the solution of **286e** in 1,2,4-trichlorobenzene shows a sharp singlet at +12.5 ppm (broadening is 26.7 Hz), whereas at cooling this singlet begins to broaden, and at 60º C begins to appear in double. Approximate coalescence temperature in this solvent is 80º C. The ^{1}H NMR-spectrum of this compound shows broad lines, and is not very informative because of broadening. It reacts with DMSO when heating at 140º C, that is why the high-resolved ^{1}H NMR spectrum of this compound being in fast conformational equilibrium cannot be obtained. However, cooling to -40º C gave a sample with sharp peaks in ^{1}H, ^{13}C and ^{31}P NMR. Based on the relative integral intensity of ^{31}P NMR spectra (recorded without proton-decoupling), the relative concentration of conformers at -40º C is 1:0.75 (at +16.1 ppm and +8.5 ppm, resp.) It is impossible to do a full assignment of NMR spectra for this complex, since broad peaks in 1D NMR result in low cross-peaks in HSQC and in HMBC spectra.

Another proof that submitted complexes are prepared are mass-spectra (with isotopic clusters) and the ability of synthesized compounds to perform hydrogenation of stilbene under

100 bar of hydrogen in dichloromethane or toluene. As expected, the hydrogenation of stilbene in toluene was inhibited by DIPEA[338, 341, 342].

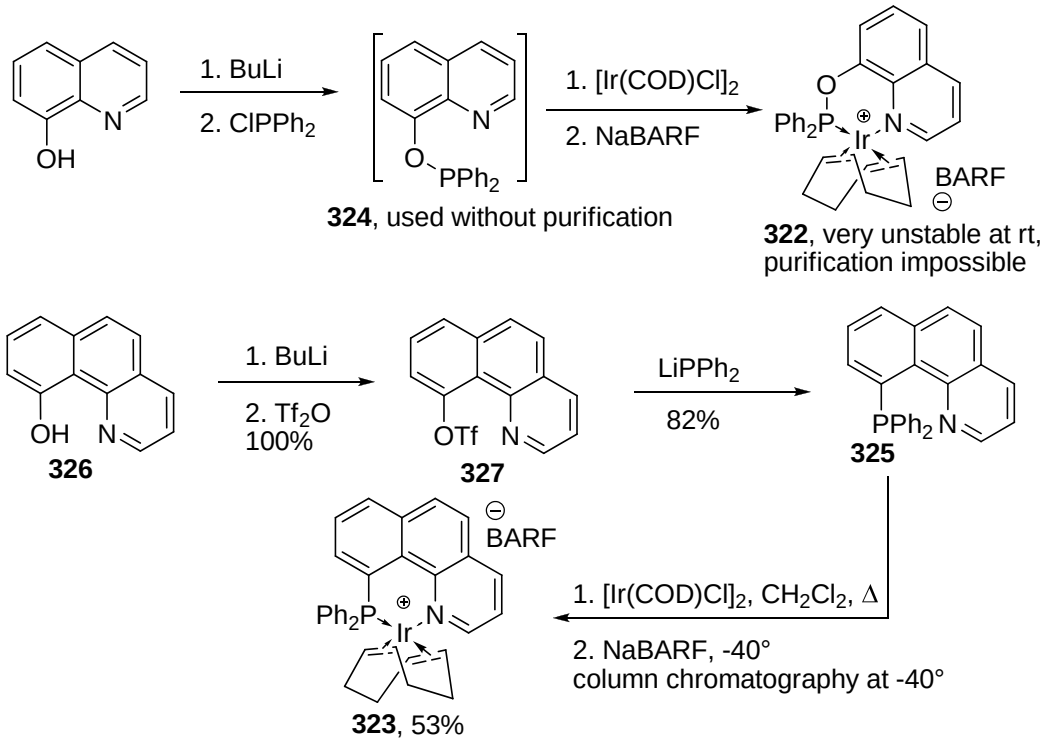
Two additional complexes of type [Ir(COD)(P^N)]BARF having not Phox, but the other ligand were synthesized (**322** and **323**). The complexes **322** and **323** were isolated by column chromatography at r.t. and characterized only be theirs ^{31}P NMR spectra. They could catalyzed electrophlic hydrogenation of stilbene in toluene, and **323** – additionally the nucleophilic hydrogenation of **281**.

The complex **323** was futher synthesized in pure form by performing the anionic exchange and column chromatography at -40ºC. Its solution in CH_2Cl_2 or in $CDCl_3$ is not stable at r.t. (stable only ca. 2 min at r.t.), and the NMR spectra should be measured also at cooling. It is interesting that complex **323** has no plane of symmetry at -40ºC, because its NMR spectra are very complex and show patterns, inherent for chiral complexes of type **286**.

The anionic exchange, forming complex **322**, does not take place at -40º C (no traces of **322** were detected after 24 h stirring with NaBARF at this temperature), hence was not obtained pure.

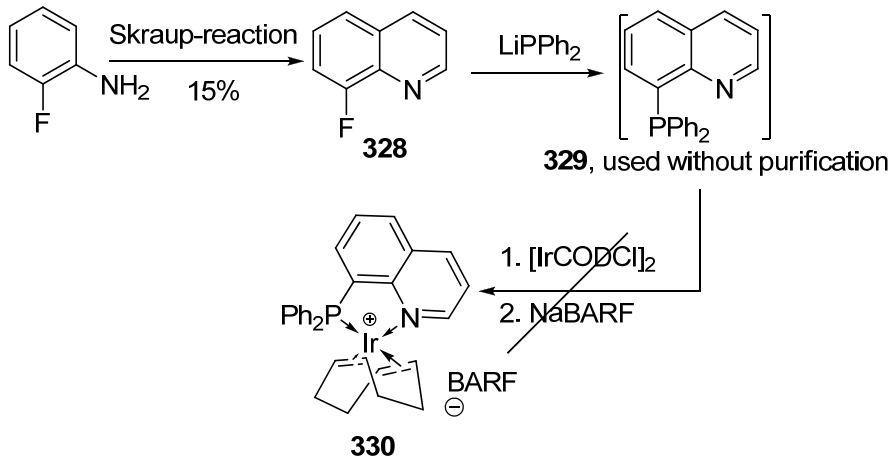
The ligand **324** was not isolated (because of its air-sensitivity) and its formation was confimed by ^{13}P NMR.

Benzo[h]quinolin-10-ol (10-HBQ, **326**) was converted to the triflate **327** with quantitative yield. Compound **327** is very sensitive to water, and cannot be purified by silica gel column chromatography (hydrolized immediately). However, it was purified by fast extraction in system Et_2O/water. Surprisingly, phosphinylation of **327** proceeds without catalyst, and the driving force of the phosphinylation seems to be the insolubility of **325** in ether. It is also insoluble in common organic solvent, even in DMF and in DMSO. It is good soluble in CF_3CO_2D, however it results in formation of different salts, and this solution has shown too much peaks in ^{13}C NMR, while the signals in ^{1}H NMR were very broad. It was characterized by ^{31}P NMR and by HRMS, and through its derivative, namely complex **323**.



Scheme 118

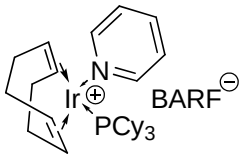
8-Fluoroquinoline **328** was prepared by Skraup reaction with yield of 15%. As usual, phosphine **329** was generated (formation controlled by GC/MS) and subjected to complexation. Unfortunately, the complex **330** was not even detected. Probably, it is inherently not stable (because of 5-membered ring or because of *ortho*-metallation of pyridine-ring, like **322** and **323**).



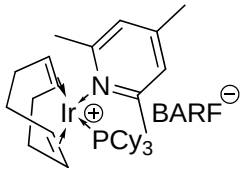
Scheme 119

Having a small library of complexes of type [Ir(COD)(P^N)]BARF, I have synthesized the complexes of type [Ir(COD)(P)(N)]BARF (complexes **331** and **332**), [Ir(COD)(P)(P)]BARF (complex **333**), [Ir(COD)(P^P)]BARF (complexes **334** and **335**), [Ir(COD)(N)(N)]BARF (complex **336**) [Ir(COD)(C)(C)]BARF (complex **337**),

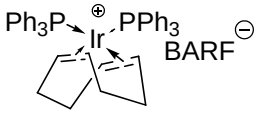
[Ir(COD)(C)(P)]BARF (complex **338**) and [Ir(COD)(C)(N)]BARF (complex **339**). Here and further (C) stands for N-Heterocyclic carbene ligand, (P) – for phosphorus ligand and (N) – for nitrogen ligand.



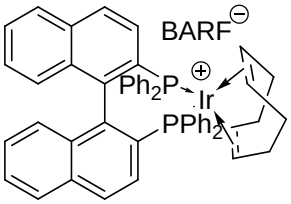
331, [Ir(COD)(PCy_3)(Py)]BARF



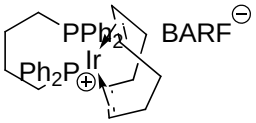
332, [Ir(COD)(PCy_3)(sym-collidine)]BARF



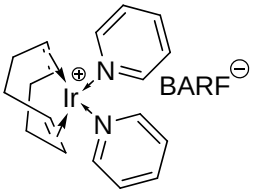
333, [Ir(COD)(PPh_3)$_2$]BARF



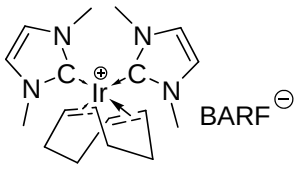
334, [Ir(COD)(rac-BINAP)]BARF



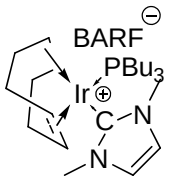
335, [Ir(COD)(DPPB)]BARF



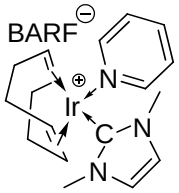
336, [Ir(COD)($Py)_2$]BARF



337, [Ir(COD)($IMe)_2$]BARF



338, [Ir(COD)(IMe)(P(n-$Bu)_3$)]BARF

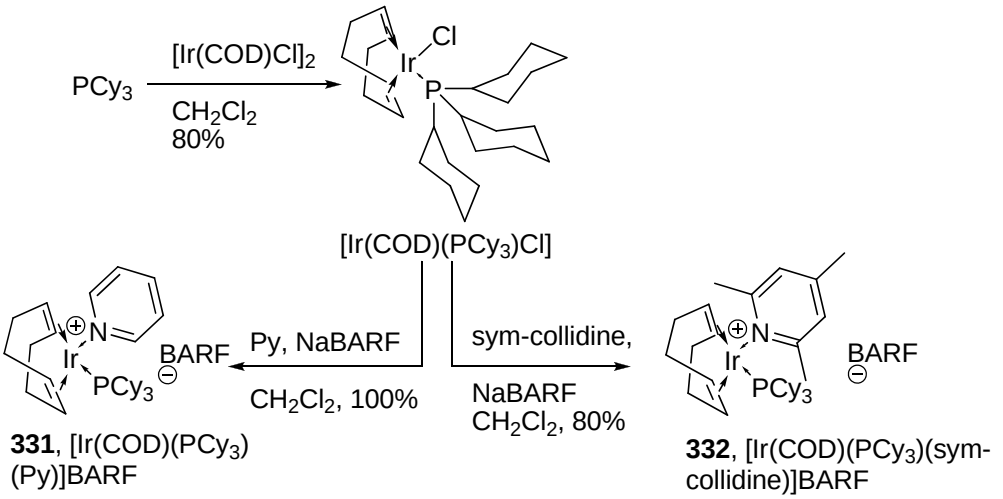


339, [Ir(COD)(IMe)(Py)]BARF

Scheme 120

The complex [Ir(COD)($Py)_2$]BARF **336** is quite unstable at r.t. (stays intact ca 2 days being in crystalline state), and the procedure of its synthesis, found in literature, was irreproducible[347]. After several attempts this complex was obtained in spectrally pure state. It is active in neither nucleophilic, nor electrophilic hydrogenation, because its cation does not add the molecular hydrogen, hence fails to be activated by reductive COD-elimination[343]. In my hands the hydrogenation of 7-methoxyisoflavone in presence of DIPEA resulted in metallic iridium, but the heterogeneous hydrogenation was effectively inhibited by thiophene.

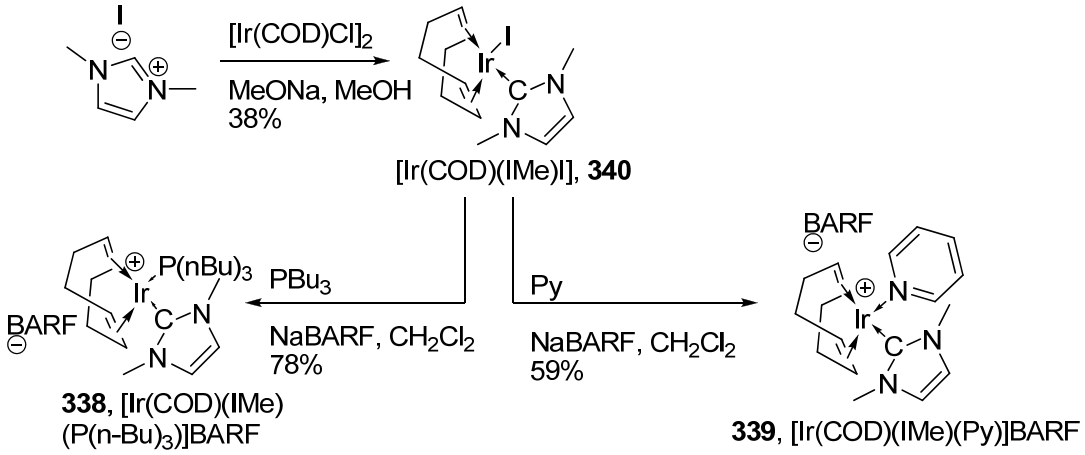
The preparation of complex **331** also was connected with some dificulties. Its preparation, found in literature, was completely irreproducible[347]. After several attempts it was synthesized pure by two-stage procedure (scheme 121). From the same precursor complex **332** was synthesized.



Scheme 121

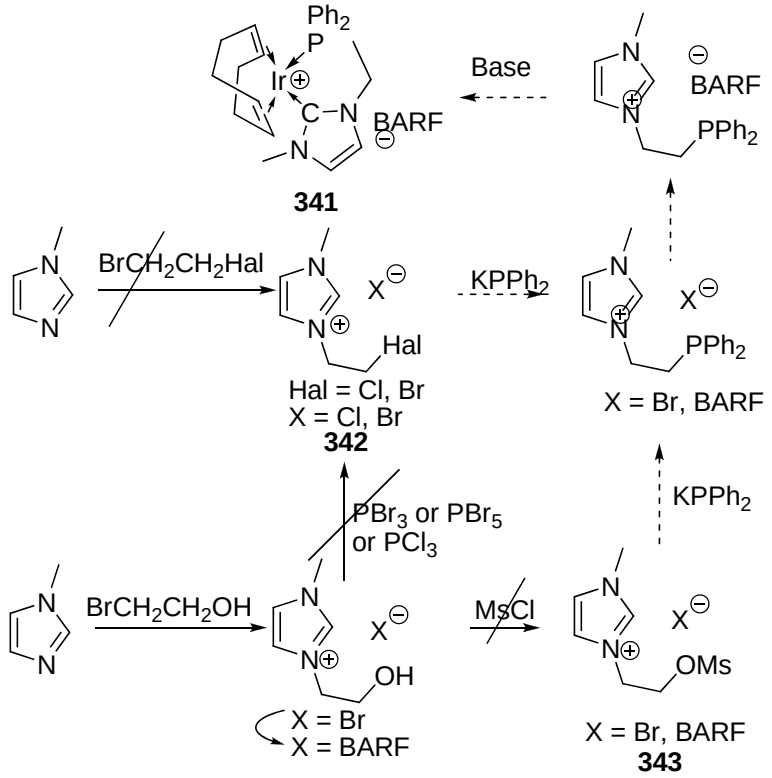
Among the diphosphine complexes of iridium, only the complex [Ir(COD)(PPh_3)$_2$]BARF **333** was stable on storage at r.t. The complex [Ir(COD)(rac-BINAP)]BARF **334** was prepared pure, and it is stable at least 2 weeks at r.t. being in crystalline state, then begins to decompose. The complex [Ir(COD)(DPPB)]BARF **335** cannot be synthesized in pure state at r.t. and begins to decompose immediately after its formation. Only one procedure[406], proviously used for synthesis of [Rh(COD)(DPPB)]BARF, was effective. The other procedures, reported for the cations [Ir(COD)(DPPB)]$^{+}$[363] or [Ir(COD)(DPPP)]$^{+}$[407] were irreproducible in case of BARF as counter-ion. Formation of **335** was proven by HRMS.

The precursor for the complexes **338** and **339** is a complex **340**, which is described in literature, but its purification was found to be unreproducible[347, 408]. However, it was obtained by the reaction, drawn on the scheme 122, and purified by extraction with pentane, while the by-product is insoluble in this solvent. Its yield is only 38%, while the other compound is unidentified orange complex, soluble in $CHCl_3$ and in CH_2Cl_2, but insoluble in pentane. The complexes **338** and **339** were synthesized from **340** by a very simple method, and the complex **339** was found to be unstable on storage.



Scheme 122

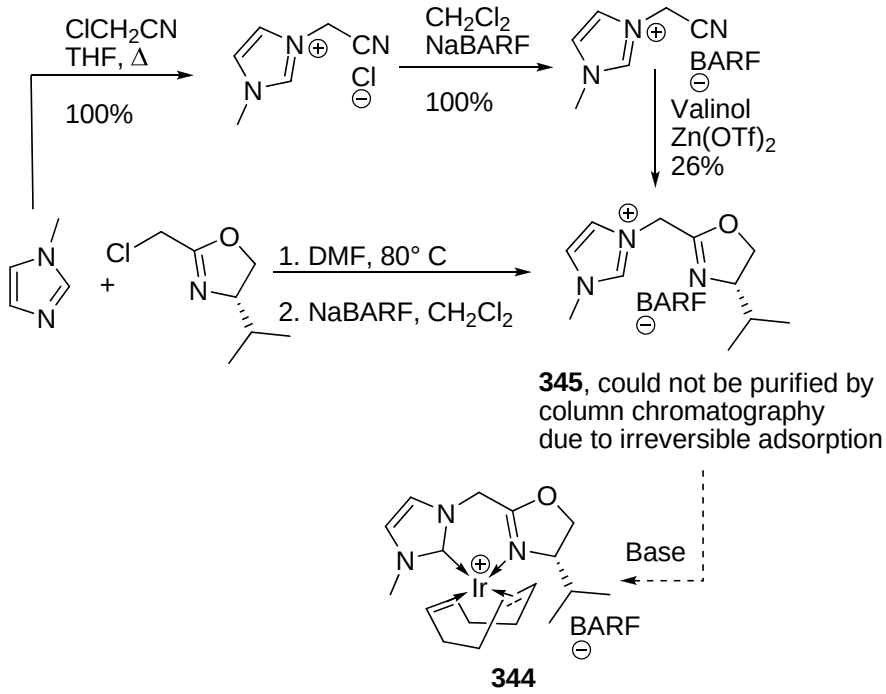
It were interesting to check the complex of type [Ir(COD)(C^P)]BARF in this reaction. I would like to synthesize the complex **341**, but the synthesis of its precursors (the salts **342** and **343**) was not reproduced after several attempts[409].



Scheme 123

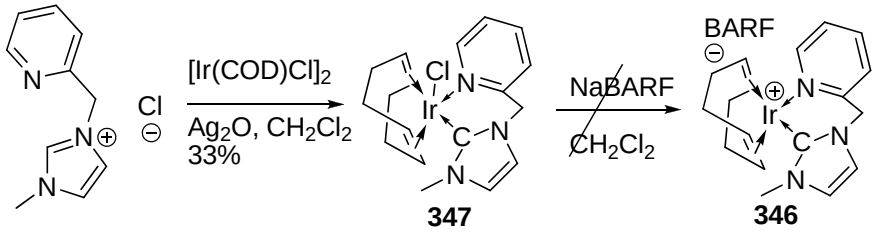
On the other hand, it were interesting to check the complex of type [Ir(COD)(C^N)]BARF in the reaction of nucleophilic hydrogenation. The synthesis of the complex **344** could not be made, since the salt **345** cannot be purified by column chromatography, although this purification procedure is reported for it.[346, 362]. The synthesis of the salt **345**, from 1-methylimidazole and (S)-2-(chloromethyl)-4-isopropyl-4,5-

dihydrooxazole gives the mixture of compounds. They both are irreversibly adsorbed on silica gel, and require prolonged eluation with CH_2Cl_2, which results also in a mixture of compounds. The synthesis from 1-methyl-3-cyanomethylimidazolium tetrakis(3,5-bis(trifluoromethyl)phenyl) borate and valinol gave the wished salt **345** (after prolonged eluation with CH_2Cl_2**)**, but with yield of only 26%. High cost of valinol and of NaBARF makes this synthesis not reasonable. The synthesis of (S)-3-((4-isopropyl-4,5-dihydrooxazol-2-yl)methyl)-1-methyl-1H-imidazol-3-ium chloride also was not reproduced[410].



Scheme 124

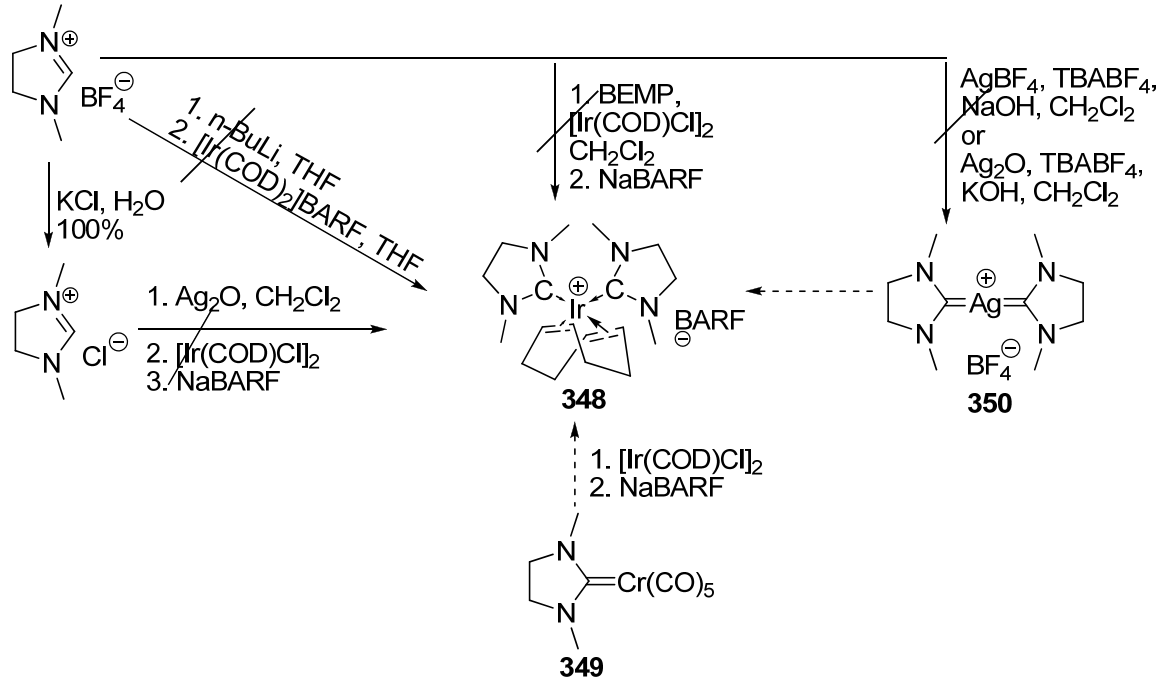
An attempt was made to synthesize another complex with (C^N) ligand, namely **346.** It is found to be inherently unstable at r.t., since the complex **347** was synthesized and characterized spectroscopically, but an anion exchange leads to its destruction (propabily through *ortho*-metallation of pyridine).



Scheme 125

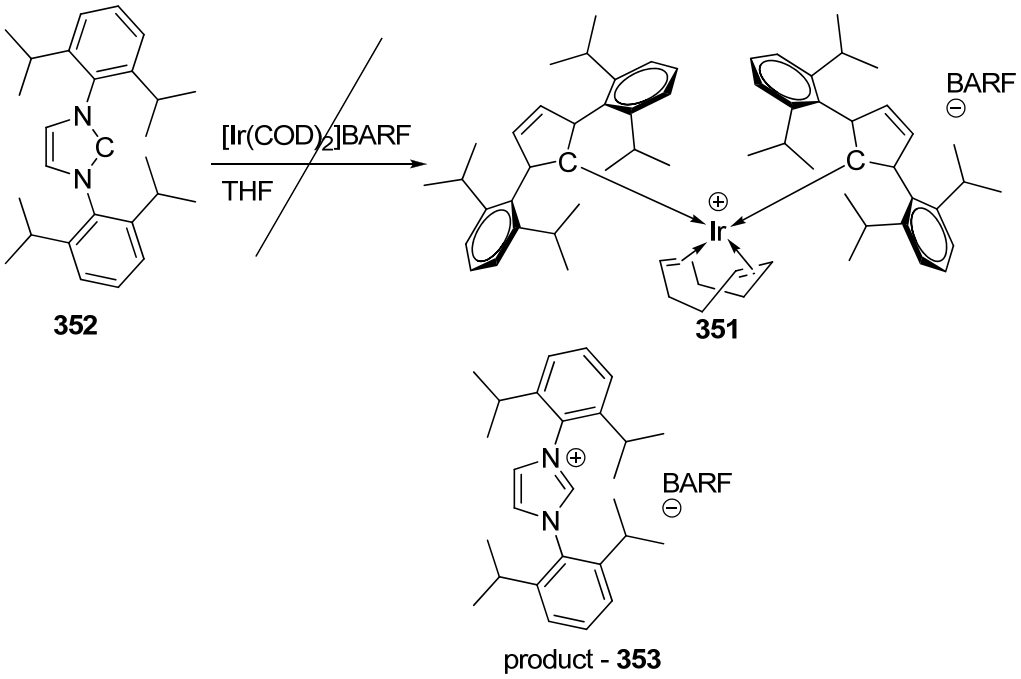
The ability of $[Ir(COD)(IMe)_2]BARF$ **337** to perfrom nucleophilic hydrogenation forced me to synthesize the similar complex with saturated carbene **348**. Unfortunately, all attempts to prepare it failed. Perhaps the transmetallation from chromium could be helpful, but the

complex **349** is hard to sythesize, and this way was not tested. Two attempts to synthesize complex **350**, according to the procedures for analogous unsaturated imidazolenes[411], were in vain.



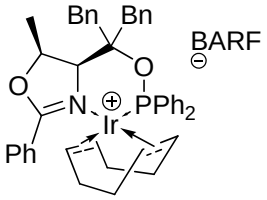
Scheme 126

An attempt was made to synthesize another biscarbene complex, **351**. Commercially available free carbene **352** was subjected to complexation with $[Ir(COD)_2]BARF$. However, the purposeful complex **351** was not obtained, and the synthesis resulted only in imidazoluim salt **353.**



Scheme 127

The commercially available complex **354** was additionally tested in nucleophilic hydrogenation, however was not active.



354

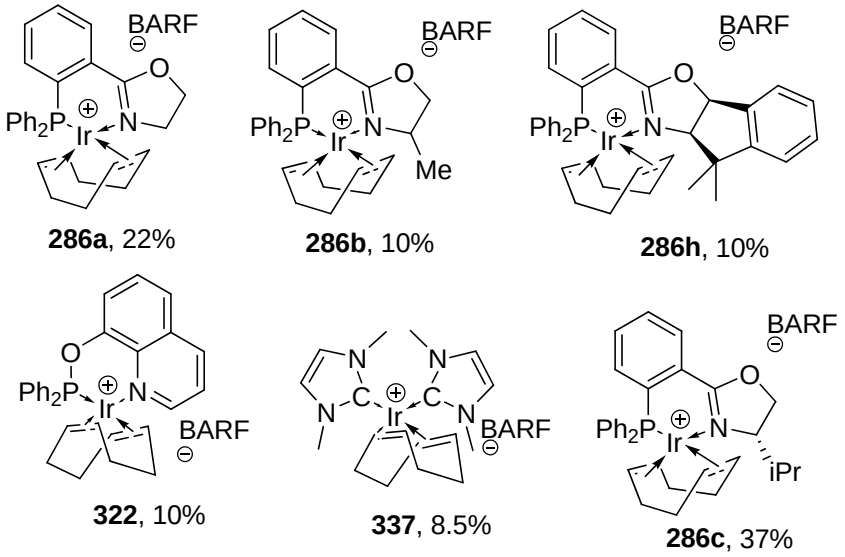
Scheme 128

Among all the synthesized complexes only six have shown the catalytic activity in nucleophilic hydrogenation. Such active complexes are: **286a, 286b, 286c, 286h, 322, 337.** All complexes were tested in conditions, according to the **general procedure G**, using 1 mol-% of the catalyst. All experiments are good reproducible (in teflon vessel and with absolute DIPEA/PhMe). The complex **286h** gave the product with ee of 34%. The complex **286b** was prepared in racemic form, hence the ee was not measured. The other active complexes are not chiral.

Inactivity of most $[Ir(COD)(Phox)]^+$-complexes can be associated with some by-products, which could be present in minimal quantities in [Ir(COD)(iPr-Phox)]BARF **286c**. Such by-products were modelled and checked, if the nucleophilic hydrogenation takes place, but they were inactive (scheme 130). Because not only complexes of phosphinooxazolines, but also biscarbene complex is active, nucleophilic hydrogenation should not be associated

with the existence of some impurities. *Vice versa*, the coordinating compounds (diisopropylamine, water, nitrobenzene in high excess) were found to inhibit the nucleophilic hydrogenation. Interestingly, that coordinating methanol can be used as a solvent for nucleophlilic hydrogenation.

Complexes, active in nucleophilic hydrogenation.
Hydrogenation made according to the **general procedure G**, in presence of 1 mol% of the catalyst.
The test substrate is 7-methoxyisoflavone. Conversion of the substrate is written under the complex.



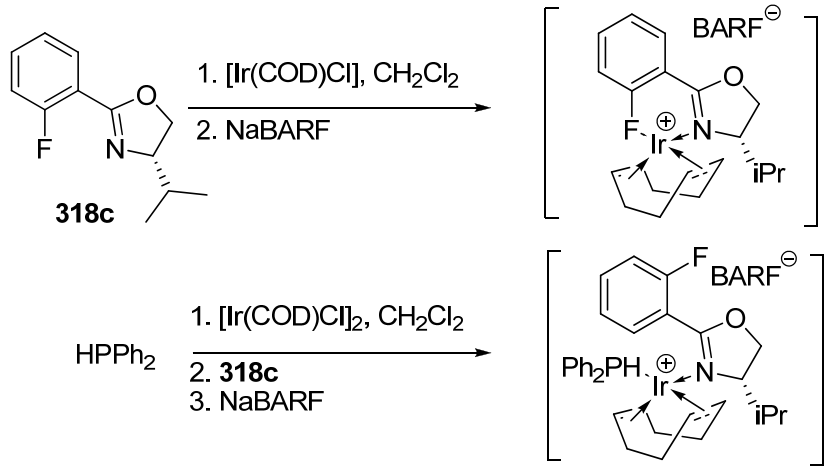
286a, 22% **286b**, 10% **286h**, 10%

322, 10% **337**, 8.5% **286c**, 37%

Scheme 129

The relevance of the negative results was checked by the positive contol. All complexes of iridium were checked by the hydrogenation of stilbene in dichloromethane or in toluene. Except the [Ir(COD)$(Py)_2$]BARF (the reason of its inactivity is described above), only three complexes, [Ir(COD)(rac-BINAP)]BARF, [Ir(COD)(DPPB)]BARF and **320** were ineffective for hydrogenation of stilbene in dichloromethane, but surprisingly [Ir(COD)(rac-BINAP]BARF and [Ir(COD)(DPPB)]BARF effective in toluene. Also they were effective for hydrogenation of benzylideneacetone in dichloromethane (except **320**), thus accomplishing theirs positive control. The hydrogenation of stilbene in toluene was completely inhibited by DIPEA.

Modelling of impurities in [Ir(COD)(iPr-Phox)]BARF
The products were not isolates/purified, since it was not possible by column chromatography
They were checked "as is" in nucleophilic hydrogenation, and were found to be inactive



Scheme 130

3.5 Nucleophilic hydrogenation of various substrates

A set of electron-defficient substrates was checked concerning their activity in nucleophilic hydrogenation, catalyzed by the complex **286c**. In this section only the experimental results, if a certain substance is sensitive to nucleophilic hydrogenation, are reported. For the interpretation, please refer to section 3.6.

At first the hydrogenation of functionalized alkenes (ethyl cinnamate and benzylidene acetone) is reported. The results are presented in Table 20. Hydrogenation is performed according to the **general procedure G** with load of 1 mol-% of catalyst. As one can see, the electrophlic hydrogenation in dichloromethane, and for ethyl cinnamate even in toluene is much more effective than nucleophilic one. On the other hand, here the fact is important, that functionalized alkenes can be hydrogenated in nucleophilic conditions, i.e. in presence of base.

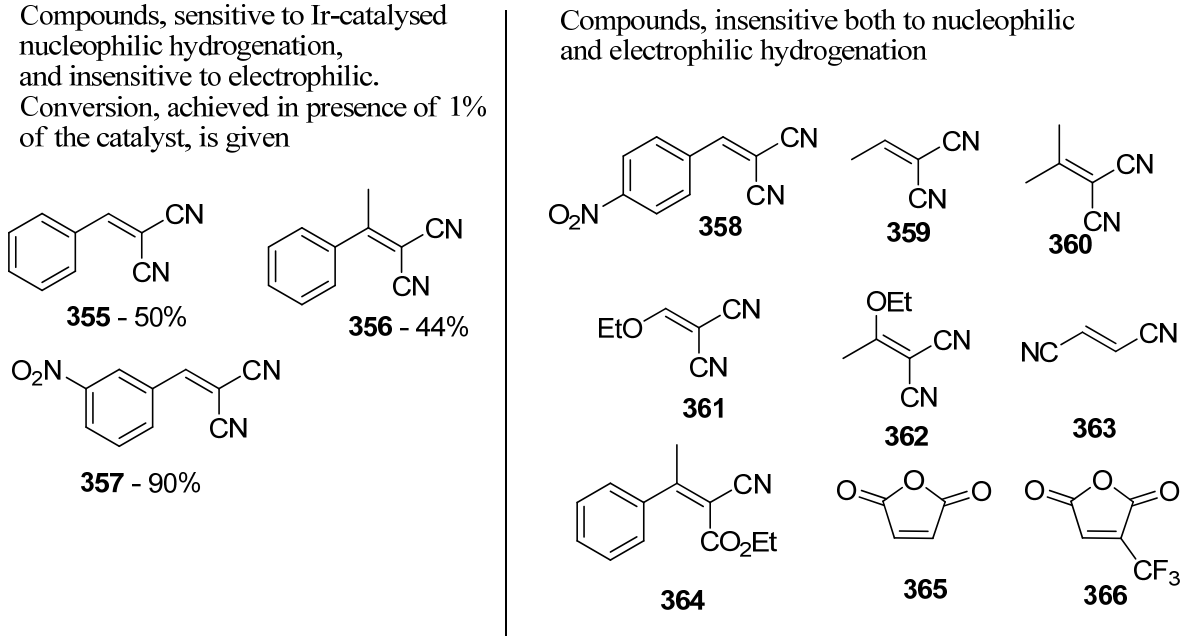
Table 20. Electrophilic and nucleophilic hydrogenation of functionalized alkenes

Substrate	Base	Solvent	Conversion (GC)
Ethyl cinnamate	No base	CH_2Cl_2	100%
Ethyl cinnamate	No base	PhMe	100%
Ethyl cinnamate	DIPEA	PhMe	12%
Benzylidene acetone	No base	CH_2Cl_2	100%
Benzylidene acetone	No base	PhMe	44%
Benzylidene acetone	DIPEA	PhMe	16%

As it was mentioned above, the unfunctionalized electron reach alkene, stilbene, can be hydrogenated only in absence of base in CH_2Cl_2 or in toluene. Addition of base leads to minimal conversion (4% or less).

Sterically unfunctionalized electron defficient alkenes **2-3**, **53**, **281-284, 293, 355-368, 370-379** could not be hydrogenated by the complex **286c** in absence of base in toluene or in CH_2Cl_2. Such compounds can be divided into two large groups: substrates, which are polymerizable or decomposable by DIPEA, and the substrates which are stable in presence of this base. Alkenes, sensitive and insensitive to nucleophilic hydrogenation, can be found in both groups.

The content of the first group (polymerizable and decomposable substrates) is presented in scheme 131. The compounds are electronically very similar, and the essential difference is the rate of base-induced destruction. If such a destruction/polymerization is not too high, the substrate can be hydrogenated in conditions of nucleophilic hydrogenation, otherwise hydrogenation takes no place.



Scheme 131

The outcome of the reaction is strongly dependent on the sequence of reactants' load, i.e. first the substrate and the catalyst should be dissolved in toluene, then base added. The solution must also be diluted. The compounds **358** and **364** were hydrogenated in some experiments, but these hydrogenation experiments are hardly reproducible, hence these substrates are shown as not hydrogenable.

P-benzoquinone was checked in the reaction of nucleophilic hydrogenation. It was reduced in presence of **286c** and DIPEA in toluene and in methanol, but the reduction took place even in absence of catalyst, hence, this reaction does not concern the catalytic nucleophilic hydrogenation.

The hydrogenation of **355**, **356** and **357** can be reproduced pretty good, if the base is added the last and the autoclave is immediately loaded with hydrogen to 100 bar. The hydrogenation, performed according to the **general procedure H**, can yield the corresponding products (Table 21). As one can see, the hydrogenation is selective, only C=C-bond is hydrogenated, while nitro-group or nitril-groups stay intact. The substrate **355** is polymerized quite fast, hence the yield of 2-benzylmalononitrile is only 59%. An interesting observation is that neat **359** polymerizes in presence of DIPEA with explosion.

Table 21. Preparative hydrogenation of 355-357 (load of DIPEA – 500 eq relative to 286c)

Substrate	Product	Yield	Catalyst **286c** load
355	2-benzylmalononitrile	59%	2 mol-%
356	2-(1-phenylethyl)malononitrile	90%	2.4 mol-%
357	2-(3-nitrobenzyl)malononitrile	90%	2 mol-%

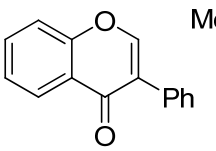
The second group, base-stable substrates, is shown on the scheme 132.

The hydrogenation experiments were performed according to the standard experimental **general procedure G** in presence of 1 mol-% of the catalyst **286c**. The sensitive substrates were further hydrogenated according to the **general preparative procedure H**. The products, yields and catalyst load for such substrates are given in Table 22.

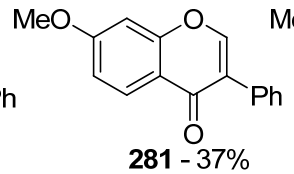
Table 22. Preparative hydrogenation of 1, 281, 3, 367 and 370 (load of DIPEA – 500 eq relative to 286c)

Substrate	Product	Yield	Catalyst **286c** load
1	chroman-4-one	36%	5.3 mol-%
281	7-methoxyisoflavanone	90%	3 mol-%
3	isoflavanone	98%	4.5 mol-%
53	7-methoxychroman-4-one	66%	10 mol-%
367	7-methoxy-2-trifluoromethylisoflavanone (by GC, not isolated)	90%	14 mol-%
370	2-phenylcyclohexanone	90%	10 mol-%

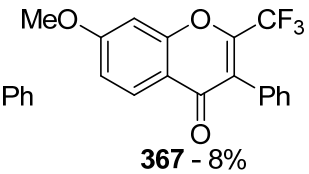
Compounds, sensitive to Ir-catalysed nucleophilic hydrogenation, and insensitive to electrophilic.
Conversion, achieved in presence of 1% of the catalyst, is given below the formula



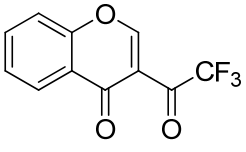
3 - 22%



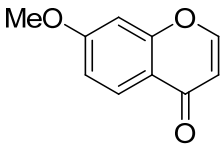
281 - 37%



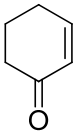
367 - 8%

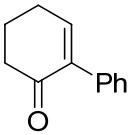


368 - 20%



53 - 10%

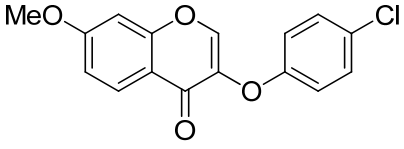




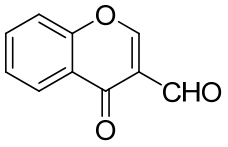
369 - 40.9% (here 34.1% of cyclohexanone, 6.8% of cyclohexanol, according to GC/MS)

370 - 10%

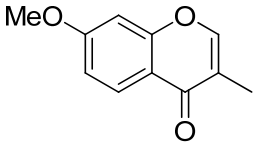
Compounds, insensitive both to nucleophilic and electrophilic hydrogenation.
They show only low conversions in case of nucleophilic hydrogenation.
Conversion, achieved in presence of 1% of the catalyst, is given below the formula (is applicable)



371 - 4%

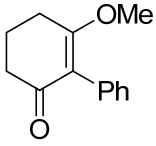


372 - traces of chromanone

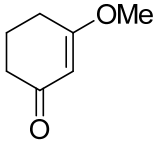


373 - 2%

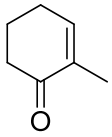
Compounds, insensitive both to nucleophilic and electrophilic hydrogenation



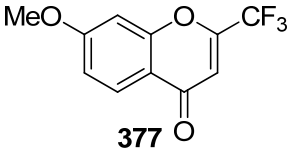
374



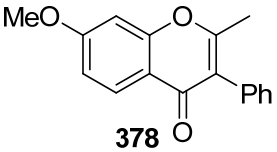
375



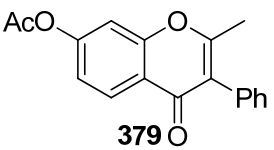
376



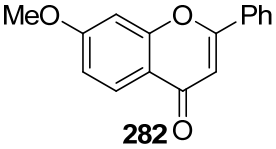
377



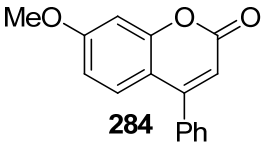
378



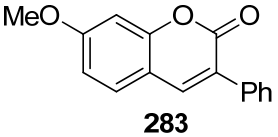
379



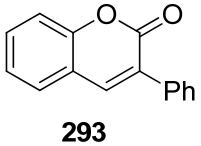
282



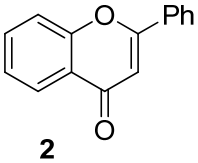
284



283

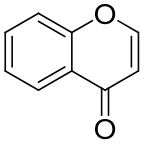


293

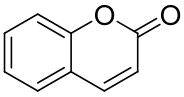


2

Compounds, sensitive both to nucleophilic and electrophilic hydrogenation.
Conversion, achieved in presence of 1% of the catalyst (by nucleophilic hydrogenation), is given



1 - 19%



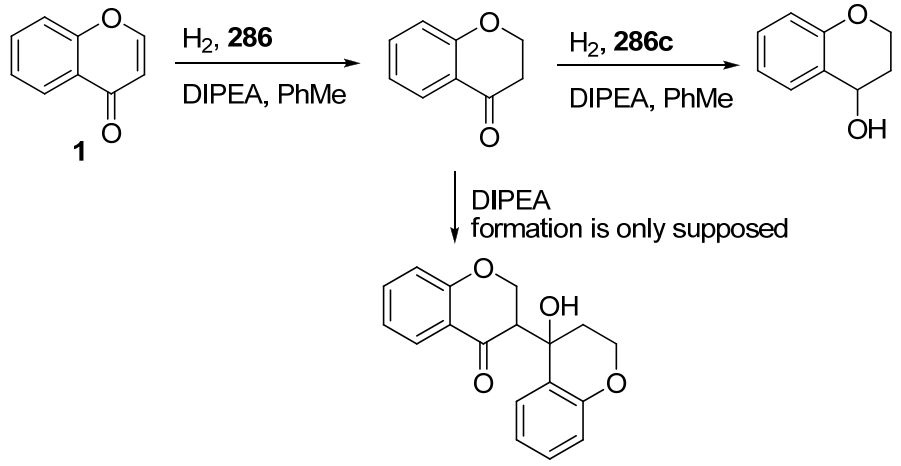
137 - 18%

Scheme 132

Two substances, chromone **1** and coumarin **137** were sensitive both to electrophilic (see section 3.1) and to nucleophilic hydrogenation. The hydrogenation of these compounds in absence of **286c** (both in presence of absence of DIPEA) leaved them intact. If only 1 mol-% of **286c** was used (hydrogenation according to the **general procedure G**), the products of catalytic hydrogenation, detected by GC/MS, were 4- and 2-chromanones, resp. But the

conversion were far from full. The application of a higher catalyst load was not helpful to achieve the full conversions (according the **general procedure H**).

The full conversions were achieved in case of high concentrations (**general procedure L**). The chroman-4-one was obtained in yield of 36% after column chromatography. The low yield of reaction is probabily connected with formation of side-compounds (scheme 133). E.g., the base-induced aldol-reaction is possible. Another side-product, chroman-4-ol, was detected by GC/MS. Here it should be mentioned, that the **general procedure L** seems now to be the best for preparative nucleophilic hydrogenation, although most of preparative experiments were made according to the **general procedure H**.



Scheme 133

Although by use of **general procedure L** the coumarin **137** was fully converted (5 mol-% of **286c**), it gave an inseparable mixture of unidentified compounds (23 mg from 50 mg of coumarin). One of them was chroman-2-one (according to GC/MS and to NMR), which could not be purified.

The substrates **281, 3, 53, 367, 368, 370** were sensitive only to nucleophilic hydrogenation, and were not hydrogenated in absence of base. Electrophilic hydrogenation of 2-cyclohexenone **369**, catalyzed by **268c**, proceeds in toluene with 5% conversion, and takes no place in dichloromethane.

The hydrogenation of 3-trifluoroacetylchromone (pure ketonic form) in presence of 5 mol-% of **286c** and 500 eq of DIPEA (**general procedure H**) afforded a mixture of overreduced compounds (with molecular mass 246). This substance could represent a substrate with sterically functionalized C=C-bond, but is not reducible in absence of DIPEA by the complex **286c**. According to the theoretical investigations of this molecule, oxygen 11 (figure 8) should be attacked by soft electrophiles. For realization of the mechanism of functionalized C=C-bond hydrogenation, the oxygen 13 (figure 8) should be attacked, hence

hydrogenation should proceed according to the mechanism for non-functionalized C=C-bond (see section 3.1). For the method of local softnesses' computation see section 3.6 and 7.6. Experimentally, the hydrogenation, catalyzed by **286c**, gave no product in toluene, and only traces of chromanone in dichloromethane (in electrophilic conditions), hence this substrate is completely not suitable for the mechanism of hydrogenation of functionalized C=C-bond.

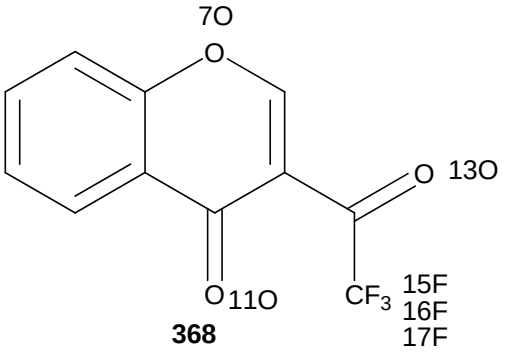
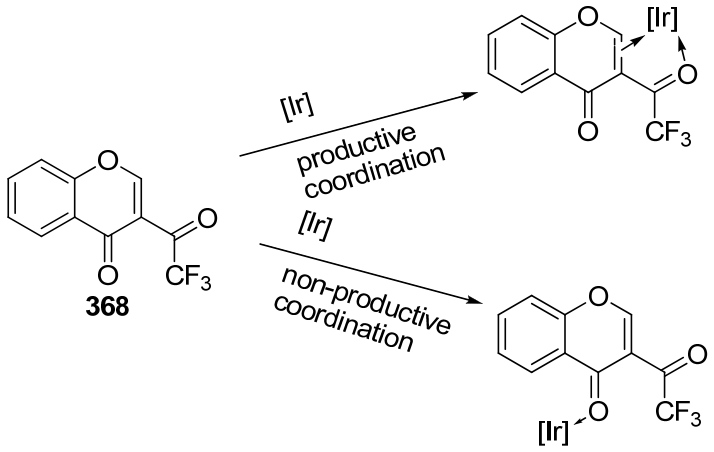
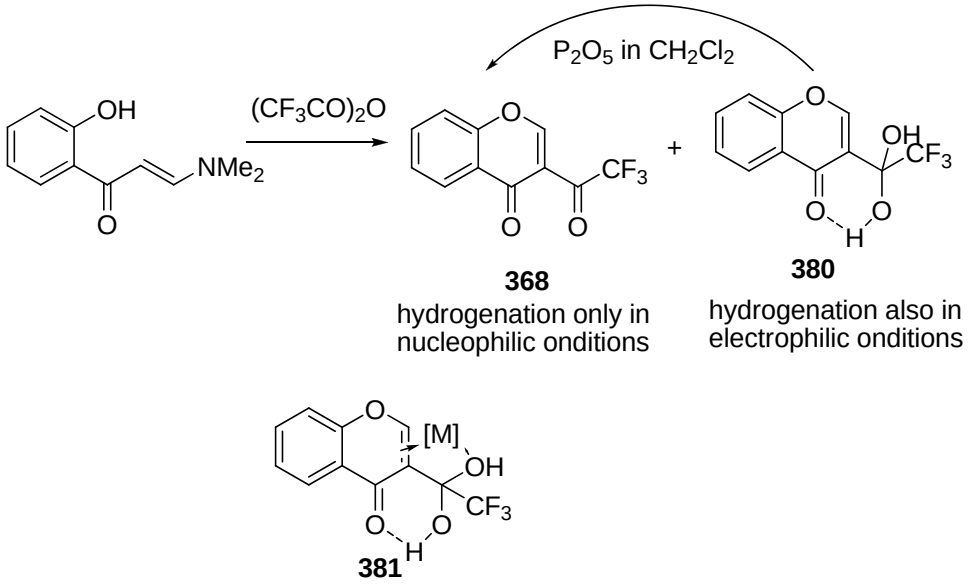


Figure 8



Scheme 134

The above mentioned behaviour of 3-trifluoroacetylchromone is typical only for its ketonic form. It readily reacts with water forming the hydrate **380**[412, 413]. In fact, the synthesis of 3-trifluoromethylchromone[414] gives a mixture of **368** and **380**, but the latter can be converted to **368**. This mixture can be hydrogenated by **286c** in absence of base, hence the hydrate **380** has a functionalized C=C-bond. The participation of OH-group in metal coordination and C=C-bond functionalization is represented by particle **381** (scheme 135).

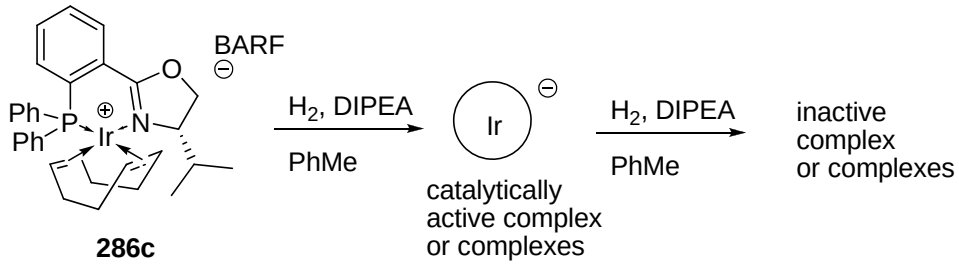


Scheme 135

3.6 Proposed mechanism of nucleophilic hydrogenation

The hydrogenation of the complex **286c** in toluene in presence of DIPEA, with subsequent evaporation of the reaction mixture (all operation were made carefully exluding air, in glovebox if needed) gave a yellow crytalline mass, which was active neither in nucleophilic, nor in electrophilic hydrogenation. Its structure was not determined by NMR-spectra. Its ^{1}H NMR spectrum has not shown signals, resonating in negative-field, hence there are no Ir-H-bonds, or this substance represents a cluster with high molecular-mass, hence the signals were not visible because of high relaxation-time. The main conclusion is, that complex **286c** is inactivated by base, and cannot catalyze the hydrogenation.

As long as the mixture of **286c** with DIPEA do catalyze the nucleophilic hydrogenation, the deactivation of **286c** proceeds *via* formation of some other complex or complexes, which is (are) active in above mentioned hydrogenation (scheme 136). It is speculated, that this complex is anionic, because it should enhance its nucleophilicity, and the protonated base serves as a counter-ion for the presumed anionic complex or complexes. The presumed catalytically active complex will be denoted as $\text{Ir}^{\ominus}$.



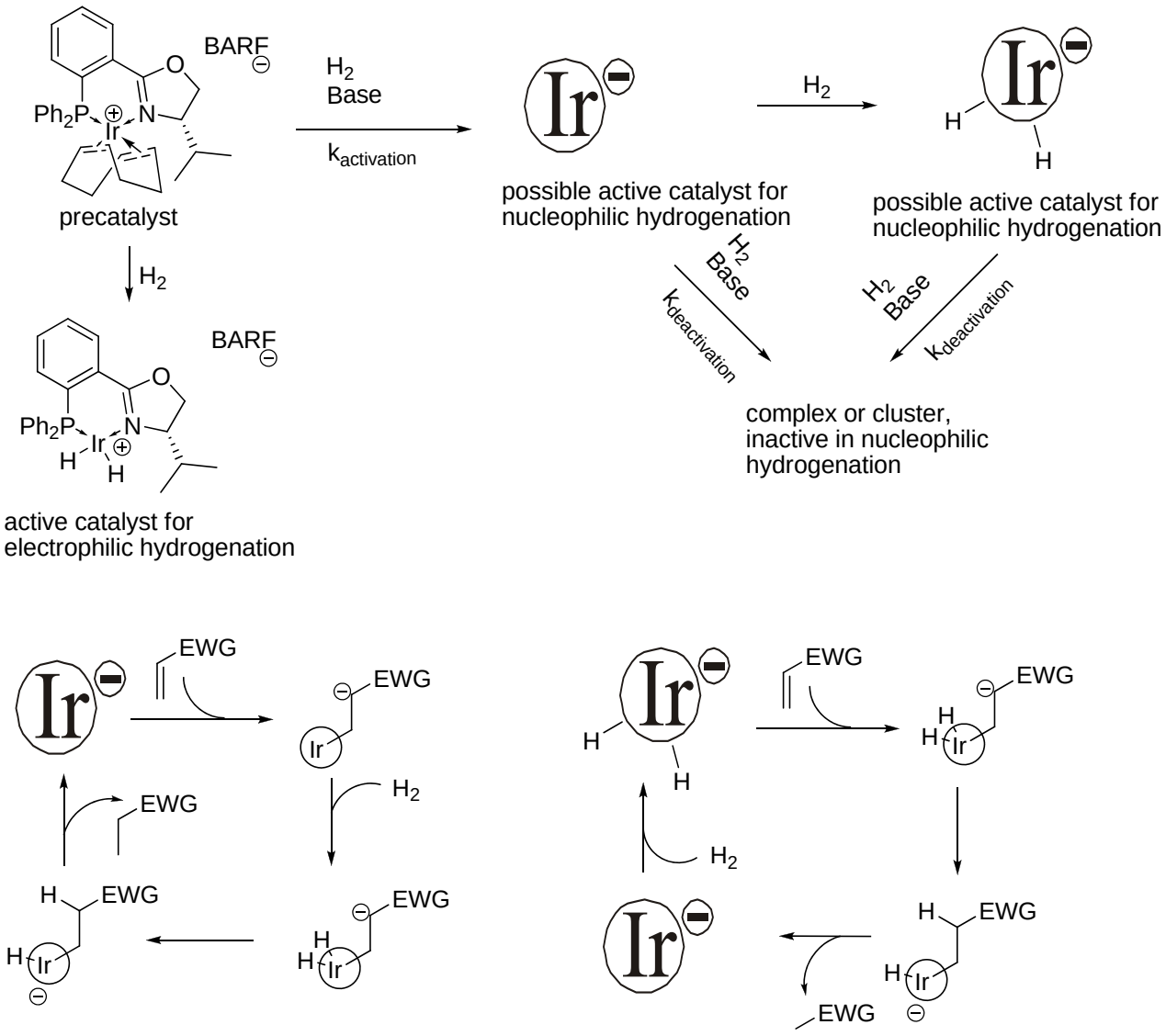
Scheme 136

The activation of the substrate by the organic base should be excluded, since e.g. 7-methoxyisoflavone **281** cannot be deprotonated, and the use of non-nucleophilic bases (e.g. DIPEA) excludes the interaction between substrate and the base with covalent bonds formation. Although the base-induced polarization of the substrate, hence its activation, is possible, the lack of polarisation of the other substrates (e.g. stilbene) should not prevent their hydrogenation by the complex **286c**. Because the latter has no place, first the complex **286c** should be transformed to $\textcircled{Ir}^{\ominus}$, which is inactive in electrophilic hydrogenation, hence does not catalyze the hydrogenation of stilbene.

The mechanisms, involving $\textcircled{Ir}^{\ominus}$, could be speculated to be as on the scheme 137.

For the catalytically active complexes the $k_{activation}$ should be much greater than $k_{deactivation}$. It is also speculated that base-induced deactivation is very fast, and $\textcircled{Ir}^{\ominus}$ should be stabilized by substrate. Although this statement is not proven, it explaines the observed properties of nucleophilic hydrogenation (see below). The failure to perform the nucleophilic hydrogenation with various complexes of type [Ir(COD)(P^N)]BARF can be connected with too low $k_{activation}$ and too high $k_{deactivation}$.

Here it should be mentioned, that nucleophilic $\textcircled{Ir}^{\ominus}$ should also attack the carbonyl-group, since the latter is apt to react with nucleophiles. The admixtures of secondary alcohols were detected (by GC) in some hydrogenation experiments (e.g. in case of 2-cyclohexenone **369**, 7-methoxychromone **53**, chromone **1**, 7-methoxy-2-trifluoromethylchromone **367** and 3-trifluoroacetylchromone **368**).



Scheme 137

The inactivity of some substrates can be caused by their weak electrophilicity. In the table 23 the base-stable substrates are arranged according to their LUMO-energy, which can serve as electrophilicity extent. Additionally, the indexes of electrophilicity ω were computed, according to the following formula[415]:

$$\omega = \frac{(E_{HOMO} + E_{LUMO})^2}{4(E_{LUMO} - E_{HOMO})}$$

where E_{HOMO} and E_{LUMO} are the energies of HOMO and LUMO, resp. The indexes of electrophilicity ω are found not to correlate with substrates' activity in nucleophilic hydrogenation. The quantum-chemical calculations are described in this section below and in section 7.6.

Table 23

Substrate	Activity in nucleophilic hydrogenation	**Basis: 6-31G**			**Basis: 6-31G(d,p)**			**Basis: 6-31++G(d,p)**		
		E_{HOMO}, hartree	E_{LUMO}, hartree	ω, hartree	E_{HOMO}, hartree	E_{LUMO}, hartree	ω, hartree	E_{HOMO}, hartree	E_{LUMO}, hartree	ω, hartree
3-methoxycyclohexenone, **375**	NO	-0.23024	-0.03832	0.003460532	-0.22689	-0.02823	0.003232507	-0.24177	-0.04305	0.004030162
3-methoxy-2-phenylcyclohexenone, **374**	NO	-0.21066	-0.04145	0.002688724	-0.20923	-0.03295	0.002584756	-0.22249	-0.04585	0.003179801
2-methylcyclohexenone, **376**	NO	-0.23829	-0.05159	0.00392212	-0.2358	-0.04416	0.003755071	-0.24882	-0.05909	0.004497007
7-methoxy-2-methylisoflavone, **378**	NO	-0.225	-0.05234	0.003320143	-0.22148	-0.04368	0.003125272	-0.23472	-0.05763	0.003783905
7-methoxy-3-methylchromone, **373**	YES, low converson	-0.23355	-0.05437	0.003713413	-0.22931	-0.04451	0.003463956	-0.24145	-0.0601	0.004122648
7-methoxyisoflavone, **281**	YES	-0.22539	-0.05855	0.00336274	-0.22156	-0.04915	0.003158719	-0.23378	-0.06368	0.003762716
cyclohexenone, **369**	YES	-0.23862	-0.0558	0.003961853	-0.23627	-0.04856	0.00380714	-0.25059	-0.06357	0.004614555
2-phenylcyclohex-2-enone, **370**	YES	-0.23037	-0.05874	0.003586406	-0.2288	-0.05211	0.003485671	-0.23972	-0.06565	0.004058043
7-methoxychromone, **53**	YES	-0.23847	-0.0587	0.003968873	-0.23404	-0.04912	0.002420693	-0.24639	-0.06515	0.00439766
chromone, **1**	YES	-0.24551	-0.06429	0.004348194	-0.2417	-0.05558	0.004112107	-0.25407	-0.07153	0.004838011
isoflavone, **3**	YES	-0.22721	-0.06527	0.003463271	-0.22412	-0.0572	0.003302552	-0.2362	-0.0719	0.003899069
7-methoxyflavone, **282**	NO	-0.23249	-0.0689	0.003714963	-0.22903	-0.06166	0.00353572	-0.24149	-0.07577	0.004170091
7-methoxy-3-(4-chlorophenoxy)chromone, **371**	YES, low conversion	-0.22732	-0.07043	0.003477273	-0.21877	-0.05953	0.00308332	-0.22927	-0.07485	0.003570537
7-methoxyneoflavone, **284**	NO	-0.22639	-0.07076	0.003435459	-0.22101	-0.0632	0.003186788	-0.23314	-0.07637	0.003754502
7-acetyloxy-2-methylisoflavone, **379**	NO	-0.23641	-0.07109	0.00390801	-0.23272	-0.06246	0.003708741	-0.24617	-0.07668	0.004416576
7-methoxy-3-phenylcoumarin, **283**	NO	-0.21641	-0.07266	0.00300299	-0.21174	-0.06539	0.002809958	-0.2234	-0.0779	0.003302184
flavone, **2**	NO	-0.23593	-0.07302	0.003887444	-0.23354	-0.06625	0.003758757	-0.24565	-0.08049	0.004391906
coumarin, **137**	YES	-0.24395	-0.0766	0.004298899	-0.23894	-0.06945	0.004029811	-0.25125	-0.0835	0.004699414
3-phenylcoumarin, **293**	NO	-0.22725	-0.07842	0.003476451	-0.22349	-0.07239	0.003307011	-0.23525	-0.0851	0.003852253
7-methoxy-2-trifluoromethylisoflavone, **367**	YES	-0.24152	-0.0819	0.004174083	-0.23376	-0.06478	0.003765133	-0.24869	-0.08095	0.004556763
7-methoxy-2-trifuoromethylchromone, **377**	NO	-0.25084	-0.08492	0.004676239	-0.24229	-0.06587	0.004188325	-0.25625	-0.08374	0.004985246
3-formylchromone, **372**	YES, low conversion	-0.25219	-0.08596	0.00475191	-0.24651	-0.07504	0.00443226	-0.26094	-0.09067	0.005262603
3-trifluoroacetylchromone, **368**	YES	-0.27177	-0.10765	0.00590666	-0.26181	-0.0879	0.005317171	-0.27656	-0.10363	0.006249017
(S)-carvone, **385**	see text	-0.2355	-0.04801	0.003767514	-0.2358	-0.04585	0.003767028	-0.24857	-0.06106	0.00449418

The inactivity of first three substrates, namely **374-376**, can be explained by theirs low E_{LUMO}, hence low electrophilicity (but not the index of electrophilicity ω).

The low conversion of 7-methoxy-2-trifluoromethylisoflavone **367**, compared with that of 7-methoxyisoflavone **281**, and lower-lying LUMO of **367**, compared to that of **281**, makes to think that trifluoromethyl-group causes a sterical hindrance to nucleophilic Ir-complex $\textcircled{Ir}^{\ominus}$. The sterical hindrance can also explane the inactivity of compounds **282, 284, 2, 377-379.**

Another explanation could be an attack on the "wrong" atom, not the atom of C=C-bond. In order to test this assumption, the local sofnesses on atoms against nucleophilic (as well as electrophilic) attack were computed. Here it was made a speculation, that $\textcircled{Ir}^{\ominus}$ should be a soft nucleophile (and not hard).

The method of softnesses' computation[415, 416] uses condensed Fukui funktions f_k^- and f_k^+, where *k* represents atom-number. In this case numbering of atoms has nothing to do with numbering, according to UIPAC-rules, but is simply a number in Z-Matrix of molecule or its representation in Cartesian coordinates. The function f_k^- represents the case of electrophilic attack on nucleophilic molecule, while f_k^+ represents the case of nucleophilic attack on electrophilic molecule. In other words, f_k^- is assosiated with molecule, attacked by *external* electrophile, while f_k^+ is assosiated with that, attacked by *external* nucleophile. Fukui funktions can be approximated from the atomic net charges (q_k) of neutral molecule (*N*), its cation-readical (*N-1*) and anion-radical (*N+1*). These functions have the following view:

$$f_k^- = q_k(N) - q_k(N-1)$$
$$f_k^+ = q_k(N+1) - q_k(N)$$

Here, e. g. the expression $q_k(N)$ means the net charge of atom *k* in the neutral molecule (*N*). The vertical transition (i.e. without change in molecule geometry) are considered to proceed in case of (*N+1*) or (*N-1*), compared to *N*.

From the Fukui function the local softness can be calculated as:

$$s_k = f_k \cdot S$$

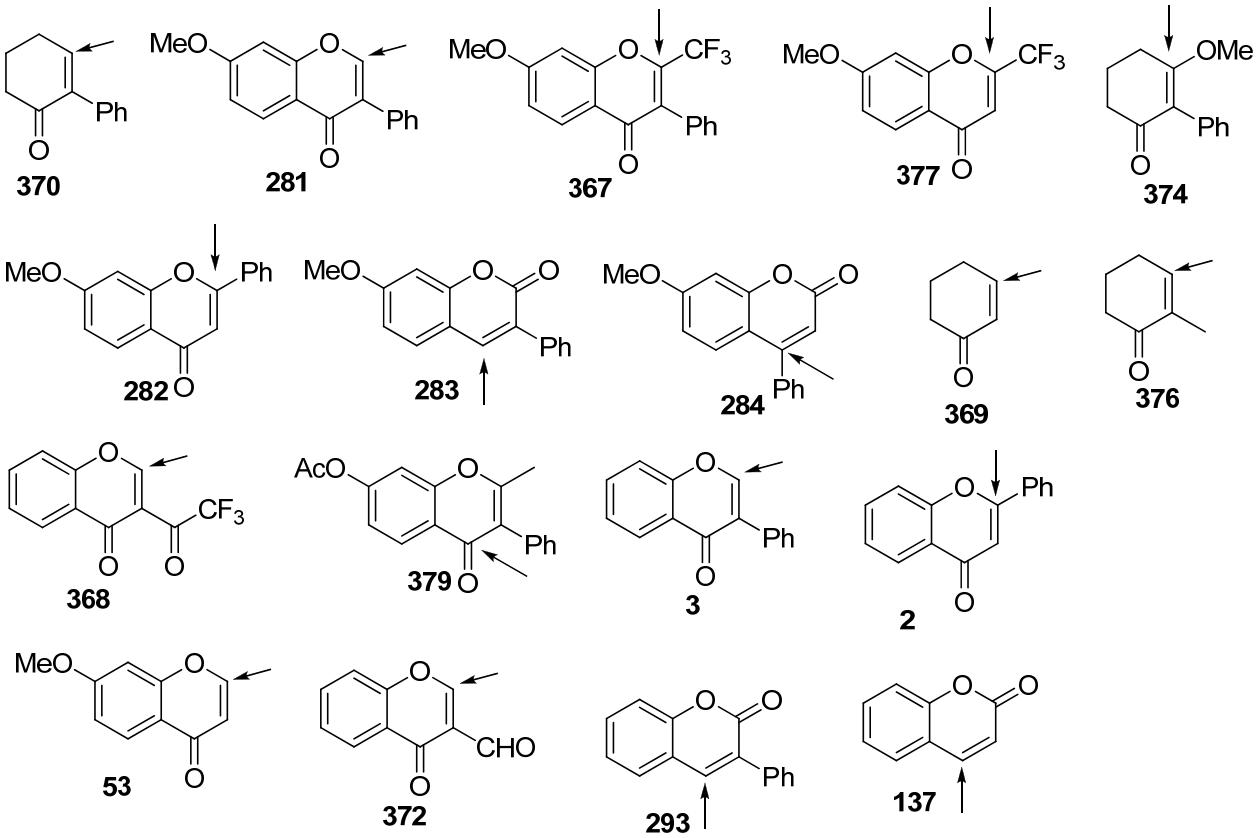
Global softness *S* is defined through the global hardness η simply as $2S \cdot \eta = 1$, hence $S = 1/2\eta$. The global hardness η is defined through ionization potential *I* and electron affinity *A*, which, according to Koopman's frontier orbital theorem are $-E_{HOMO}$ and $-E_{LUMO}$, respectively:

$$\eta = \frac{I - A}{2} = \frac{-E_{HOMO} + E_{LUMO}}{2}$$

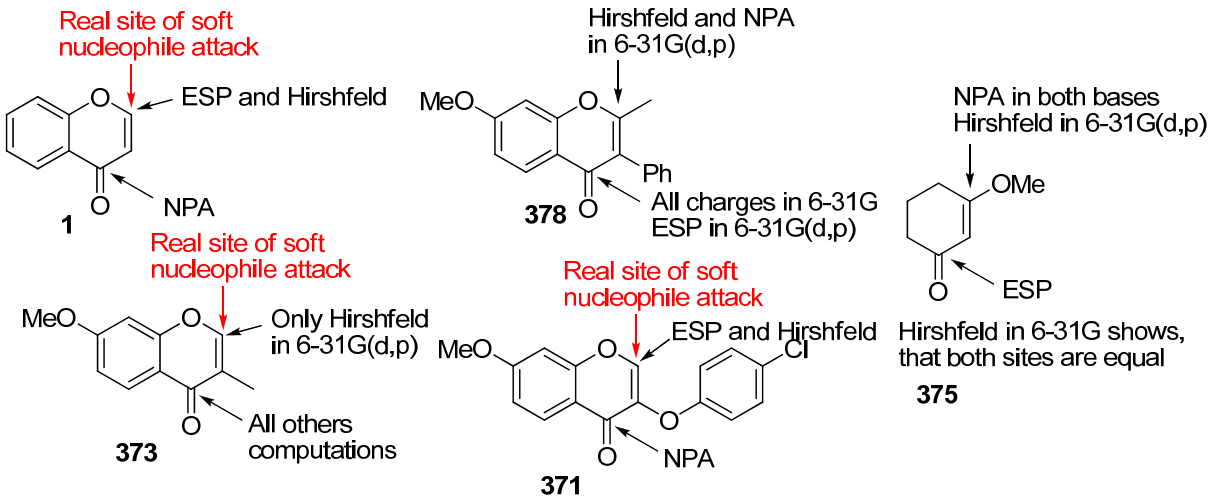
The needed information, actually orbital energies and net charges, are obtained from quantum-chemical computations. More detailed the computation of local softnesses is described in[415, 416] (see also references therein). Here the substances were computed with the B3LYP functional[417] and the 6-31G, 6-31G(d,p) and 6-31G++(d,p) basis sets. Following net charges were computed for every substance: ESP, Mulliken, Hirshfeld and NPA.

The local softnesses, computed in B3LYP/6-31G++(d,p), were found completely irrelevant, and often showed the values larger than +1 or lower than -1. The local softnesses, computed using Mulliken charges, were also found to be irrelevant (in all bases). Therefore, the indexes of local softnesses are only reported (see section 7.6) for B3LYP/6-31G and B3LYP/6-31G(d,p) using ESP, Hirschfeld and NPA (coming from NBO analysis) charges. The local softnesses only on the atoms with the same atomic number are comparable (e.g. only on carbons or only on oxygens). The local softnesses computed for carbon and oxygen (or nitrogen) for the same molecule could not be compared (this is a restriction of a method).

The sites of nucleophilic attack (by soft nucleophiles) for the educts are shown on the scheme 138 (undoubted cases). and on the scheme 139 (doubtful cases).



Scheme 138. The sites of attack by soft nucleophiles, undoubted cases

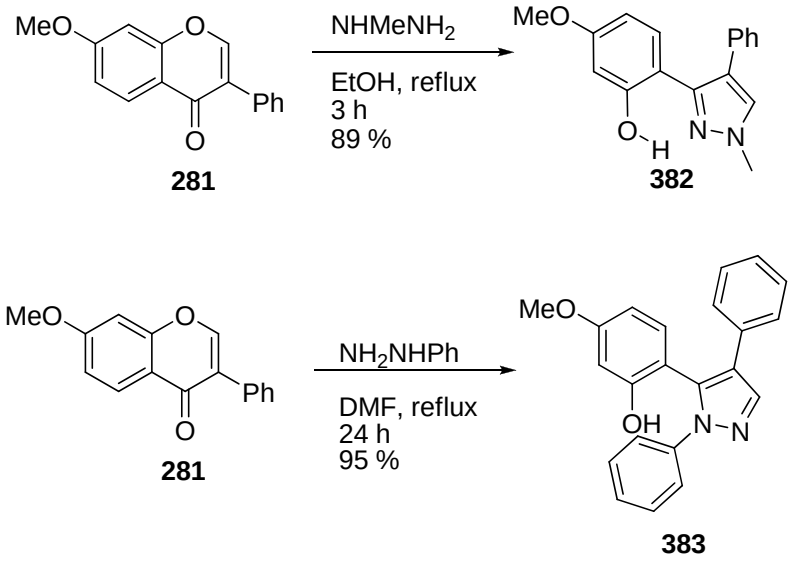


Scheme 139. The sites of attack by soft nucleophiles, doubtful cases

From the computations it is not clear, what atom of compounds **1**, **371**, **373**, **375** and **378** is favored to react with soft nucleophiles. Because the substance **375** has a too high-lying LUMO, it's softness was not further examined.

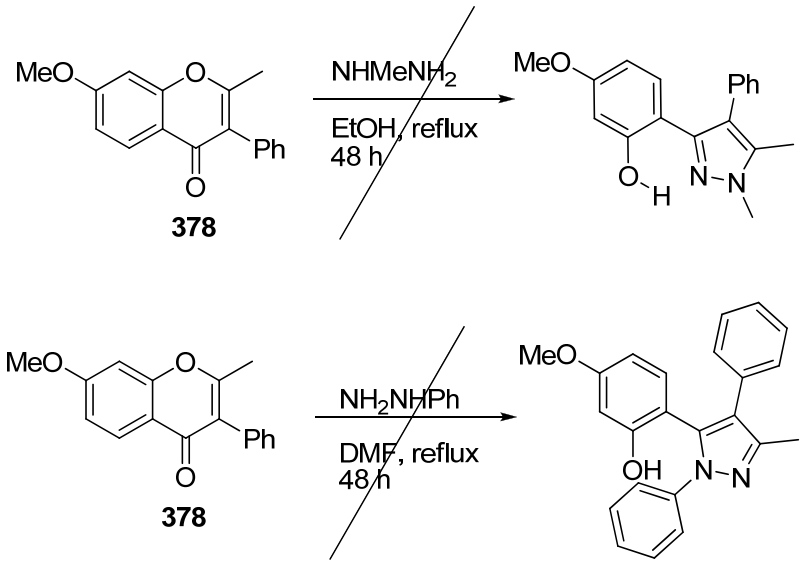
The soft atom of compound **369** is known[415], and it corresponds to the theoretically determined one. The soft atom of coumarins is also known, from the reactions with hydrazines, $NaHSO_3$, etc[418]. The latter attack soft 4-C of coumarins (which is also predicted by computations).

The computation predicts that 2-C of **281** is attacked by soft nucleophiles. It was confirmed by the reactions of **281** with phenylhydrazine and with methylhydrazine. These unsymmetrical hydrazines have a soft nucleophilic site (NH_2 for phenylhydrazine, NHMe for methylhydrazine) and a hard one (NHPh for phenylhydrazine, NH_2 for methylhydrazine). The reactions were regiospecific and gave as products compounds **382** and **383**, hence the soft atom of **281** was predicted correctly. It should be noted, that **281** does react neither with PhSH, nor with PhSNa. The reaction with PhSH was used for verification of softnesses computations of cyclohexenones[415].



Scheme 140

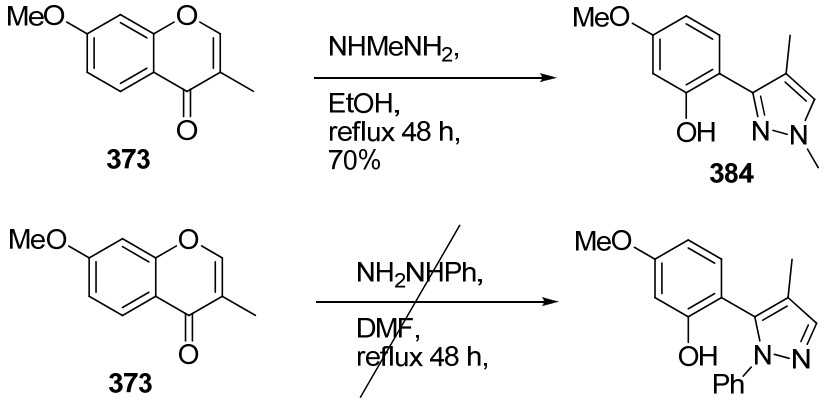
The substance **378** has reacted neither with phenylhydrazine nor with methylhydrazine after 48 h of refluxing (in DMF and in EtOH, respectively) and was isolated unchanged. Although its soft atom was not determined, it was shown that it does not react even with such a strong nucleophile as methylhydrazine. This explaines the lack of hydrogenation in nucleophilic conditions. Any additional research on **379** was not performed, and properties of **378** are extrapolated on it.



Scheme 141

The substance **373** reacted only with methylhydrazine, yielding regiospecifically **384**. With phenylhydrazine no reaction took place. Hence, 2-C of **373** is disposed to react with soft nucleophiles. This atom was predicted to be a target of soft nucleophiles only using the Hirshfeld charges with 6-31G(d,p) basis set. All other computations have predicted 4-C

(carbonyl) atom to be a target, which is wrong. **373** Was hydrogenated in nucleophilic conditions with very bad conversion, which is probabily caused by its high-lying LUMO.



Scheme 142

6-Methylchromone is known to be attacked by methylhydrazine[419] and by phenylhydrazine [420] on 2-C. Polish scientists have shown, that methylhydrazine[421] and phenylhydrazine[420] attack 2-C of 2-methylchromone, hence 2-C is disposed to react with soft electrophiles. Also 2-C was shown to be disposed to react with methylhydrazine for 5-benzyloxy-2-methylchromone and 5-benzyloxyflavone[422]. Chromone, as well as 2-methyl- and 3-methylchromone, is attacked by thiosemicarbazide on 2-C, but methyl-groups deactivate this attack[423]. Resembling regularity is observed by nucleophilic hydrogenation: chromone **1** and 7-methoxychormone **53** are attacked by nucleophile and can be hydrogenated, while 7-methoxy-3-methylchromone **373** shows only 2% conversion in hydrogenation reaction (in presence of 1 mol-% of **286c**).

Phenoxychromone **371** is hydrogenated with conversion of *ca* 4% (according to NMR spectra of reaction mixture). The 4-C of **371** resonates at 172.2 ppm, while that of the product at 187.52 ppm (figure 9). This displacement is characteristic for carbonyl group, conjugated with benzene-ring, hence the 2-C should be attacked by nucleophilic Ir-complex.

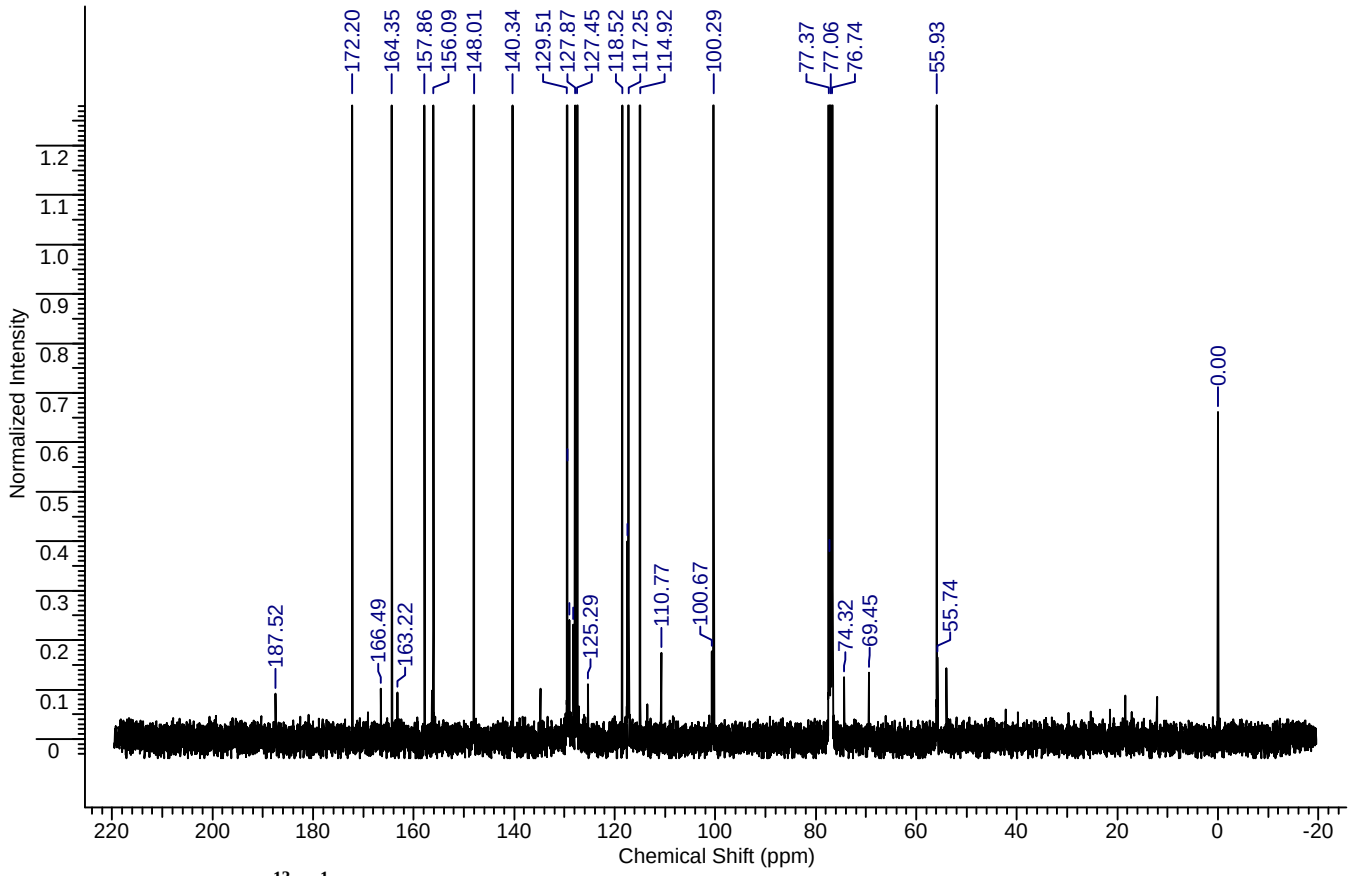


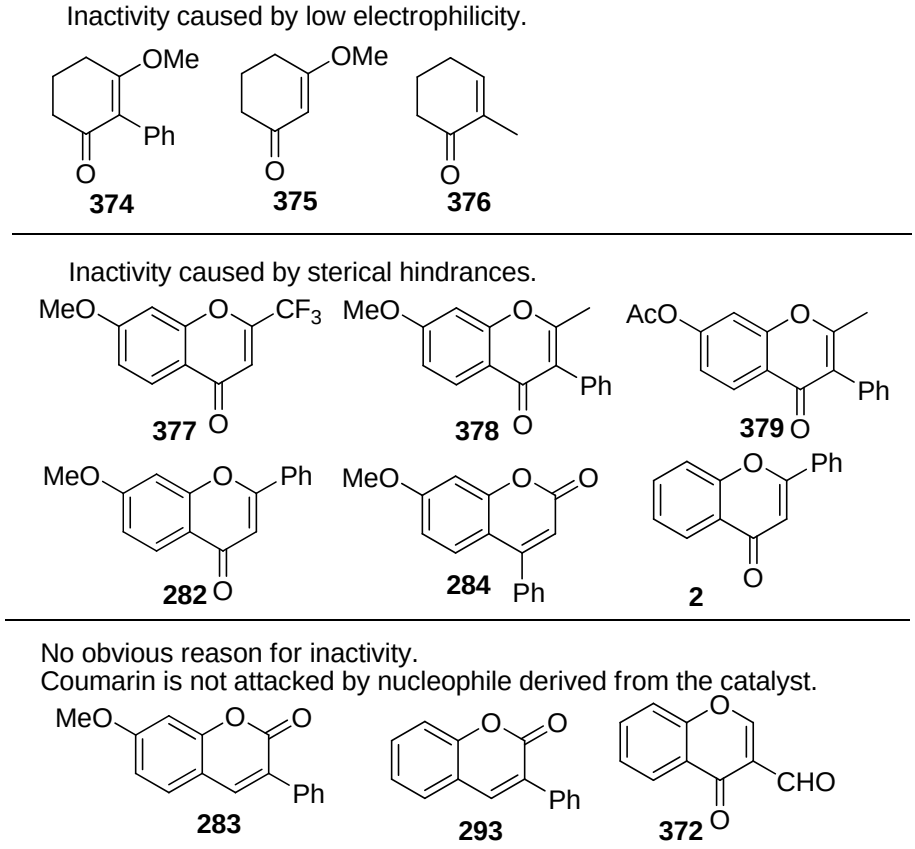
Figure 9. $^{13}C\{^{1}H\}$ NMR of reaction mixture, after nucleophilic hydrogenation of 371.

The very bad activity of 3-formylchromone is difficult to explaine. According to the computations, it should be hydrogenated in nucleophilic conditions, but in fact only traces of chromanone were detected. It is possible, that decarbonylation takes place[424], which inactivates the catalyst.

An interesting case represent two coumarins **283** and **293**. According to the computations, they both should be hydrogenated in nucleophilic conditions. In reality, both could be hydrogenated neither in electrophilic nor in nucelophilic conditions. 50 Mg of coumarin **293** were tried to be hydrogenated in nucleophilic conditions using 10 mol-% of **286c** (according to the **general procedure L**). Chromatographical purification of the reaction mixture afforded 50 mg of the substance, consisting of 98% of **293** and 2% of 3-phenylchroman-2-one. In the other experiment a mixture of equimolar quantities of **281** and **293** was subjected to nucleophilic hydrogenation in presence of 1 mol-% of **286c** (according to the **general procedure L**). The GC/MS analysis has shown, that **281** was reduced to the corresponding 7-methoxychroman-4-one, while **293** stayed intact. This implyies that coumarin does not inhibit the nucleophilic hydrogenation, is not decomposed by the complex **286c** or by $\textcircled{Ir}^{\ominus}$, but is simply not attacked by nucleophilic $\textcircled{Ir}^{\ominus}$ or attacked very inefficient (as

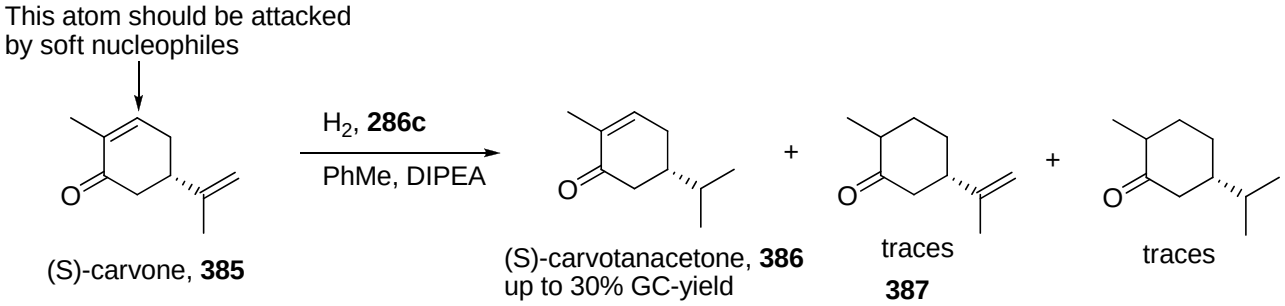
in case of 10 mol-% of the catalyst). The parallel reaction of catalyst's deactivation makes the slow hydrogenation of coumarin impossible.

On the scheme 143 the inactive substrates are put together with the apparent reasons of theirs inactivity.



Scheme 143

The assumption about the mechanism is not perfect, and one fact cannot be explained within this assumption. (S)-Carvone **385**, subjected to hydrogenation in presence of 1 mol-% of **286c** (**general procedure G** or **L**) resulted in formation of unexpected (S)-carvotanacetone **386** (proven by ^{13}C NMR), and only traces of expected **387** were detected by GC/MS. Conversion of **385** was up ot 30%. The same carvotanacetone was detected after hydrogenation by **286c** in electrophilic conditions (**general procedure D**). E_{LUMO} of **385** of carvone is low enough, to be attacked by supposed $\textcircled{Ir}^{\ominus}$. The indicated atom (scheme 144) should be attacked by soft nucleophiles. However, the carvotanacetone **386** is the product of hydrogenation. The equimolar mixture of 7-methoxyisoflavone **281** and stilbene is hydrogenated, in nucleophilic conditions (**general procedure G**), as expected, to a mixture of **281**, 7-methoxychroman-4-one and stilbene, i.e. the hydrogenation of stilbene does not take place.

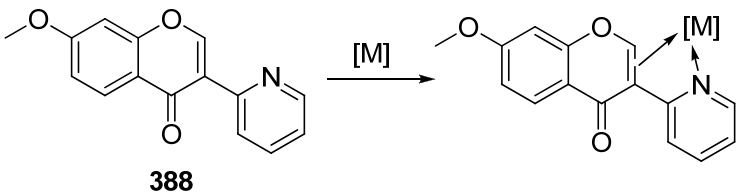


Scheme 144

As a summary of this section, it is speculated, that cationic complex [Ir(COD)(iPr-Phox)]BARF **286c** forms under action of hydrogen and organic non-coordinating base another complex $\ominus$Ir. Everything, which is attacked by this nucleophilic particle $\ominus$Ir, is hydrogenated. Normally, $\ominus$Ir attacks the soft electrophilic sites of the substrates. Nucleophilicity of $\ominus$Ir is comparable with that of hydrazines. The rate of nucleophilic hydrogenation is low, and parallel reaction of catalyst deactivation can make actually hydrogenation not observable. The case of nucleophilic hydrogenation of carvone does not agree with the above mentioned scheme, hence the mechanism of electrophilic hydrogenation needs further examination and investigantion.

3.7 Hydrogenation of 7-methoxy-3-(pyridin-2-yl)chromone

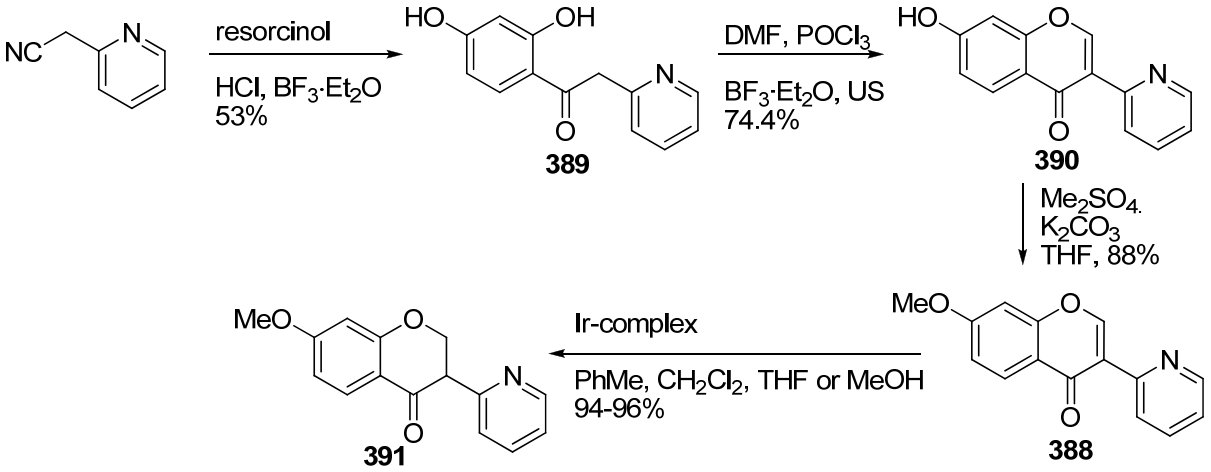
7-Methoxy-3-(pyridin-2-yl)chromone **388** represents a substrate with a very electron-deficient C=C-bond, since the pyridine-ring is electron aceptor. But this C=C-bond is functionalized because of the nitrogen-atom of the heterocycle (Scheme 145). Because of its unique electronic and sterical properties, there was interest in checking the homogeneous hydrogenation of this compound.



388

Scheme 145

The synthesis of **388** is presented on the scheme 146. **389** was synthesized from the pyridylacetonitrile and resorcinol according to the Houben-Hoesch reaction, then Wilsmeyer-formylation yielded **390**, which was carefully methylated (in order to avoid methylation of nitrogen) to give **388**.



Scheme 146

As well as for 7-methoxyisoflavone **281**, the catalysts [Rh(COD)(BINAP)]OTf, [Rh(COD)(BINAP)Cl], [Rh((S)-iPr-Phox)$_2$]BARF **320**, [Rh(PPh$_3$)$_3$Cl], [Ru(PPh$_3$)$_3$Cl$_2$] (with or without base-activation), [Ru(S-BINAP)(p-cymene)Cl]Cl (with or without base-activation), [Ru(R-BINAP)(OAc)$_2$] (with or without acid-activation) and NH_2Et_2[Ru(BINAP)Cl(μ-Cl)$_3$Ru(BINAP)Cl] (with or without base-activation) were ineffective, and left **388** intact (hydrogenation according the methods for model 7-methoxyisoflavone **281**).

The complexes of iridium were effective in hydrogenation of **388**, in both electrophilic and nucleophilic conditions.

Homogeneous hydrogenation (electrophilic conditions, **general procedure D**) in presence of 1 mol-% of catalyst cleanly gave **391** in PhMe, CH_2Cl_2, $CHCl_3$, THF or MeOH at r.t. Prolongued hydrogenation (overnight) resulted in traces of overreduced compounds, if the solvent was other than THF. In THF, no overreduction was observed even after overnight hydrogenation. In all solvents no overreduction was observed in case of hydrogenation for 1 h. The performed reactions are given in table 24. In case of full conversion, if overreduced compounds were not detected, column chromatography (Et_2O, silica gel) afforded pure **391** with yields of 94-96%. Thiophene does not inhibit the hydrogenation of **388**, hence this is homogeneous catalytic process.

Here it should be mentioned that the hydrogenation of **388** could not be traced using GC/MS, since **391** readily enlolizes (see later) at high temperature in injector, and the enol-form does not fly through the column.

Table 24. Homogeneous hydrogenation (electrophilic conditions) of 388

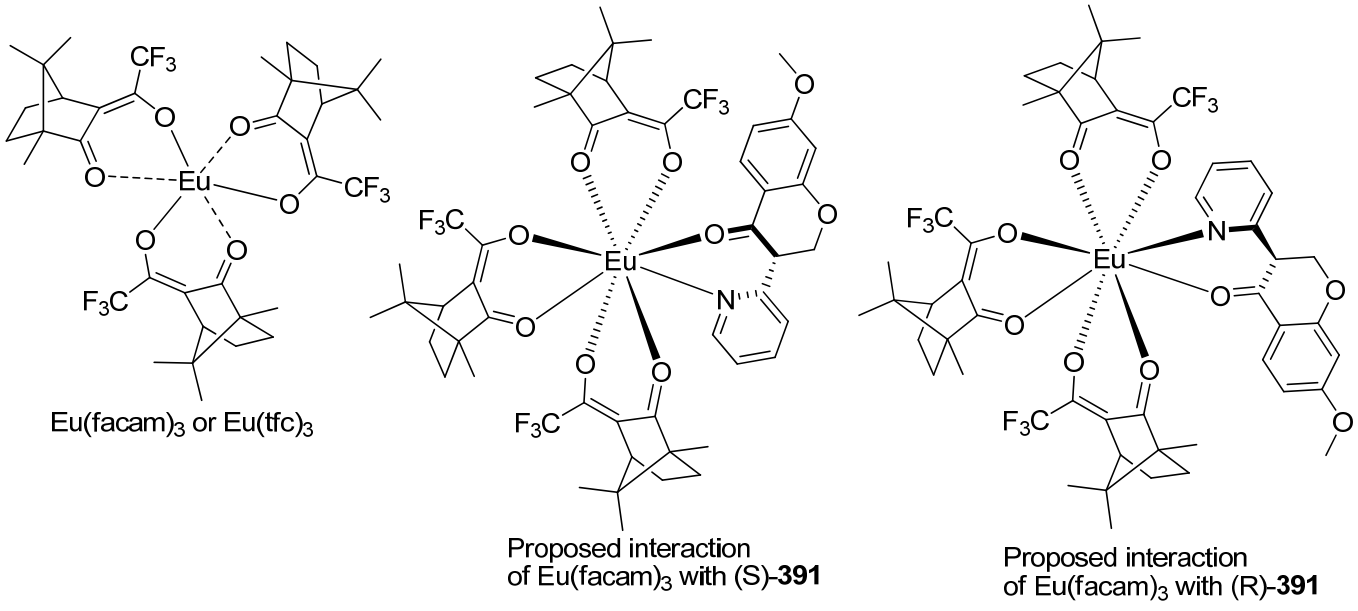
Catalyst	Solvent	NMR conversion, %
286c	THF, CH_2Cl_2, PhMe, MeOH	100

286h	THF	100
286d	THF	100
286e	THF	100
286i	THF	100
286g	THF	100
[Ir(COD)(rac-BINAP)]BARF	THF, PhMe, CH_2Cl_2	100
[Ir(COD)(R-BINAP)]BARF	$CHCl_3$	100
$[Ir(COD)(PPh_3)_2]$BARF	$CHCl_3$ + 1 drop thiophene	100
$[Ir(COD)(PCy_3)(Py)]PF_6$	CH_2Cl_2	100
$[Ir(COD)(PPh_3)_2]PF_6$	CH_2Cl_2	41
[Rh(COD)((S)-iPr-Phox)]BARF, **319**	THF	7

As one can see, the complex of rhodium even with BARF counter-ion was very inefficient in hydrogenation of **388**, while the other above mentioned complexes of rhodium have shown no conversion of **388** into **391**.

Enantiomers of **391** were not resolved (to baseline) using analytical chiral HPLC. Following eluents were tested: ethanol-hexane mixtures, chloroform-hexane mixtures, chloroform-ethanol-hexane mixtures. The reason of fail of enantiomer-resolution is enolization even in unpolar solvents (see below).

However, the use of chiral lantanoid shift reagent (LSR), Tris[3-(trifluoromethylhydroxymethylene)-D-camphorato]europium(III) ($Eu(facam)_3$ or $Eu(tfc)_3$ as alternate abbreviations)[425], resulted in splitting in ^{1}H NMR spectra of resonance frequencies of two enantiomers. The formula of $Eu(facam)_3$ and proposed coordination of **391** are shown in scheme 147. Here I speculate, that 8-coordinated Eu forms a quadratic antiprism, by analogy to the known complex of 8-coordinated europium[426].



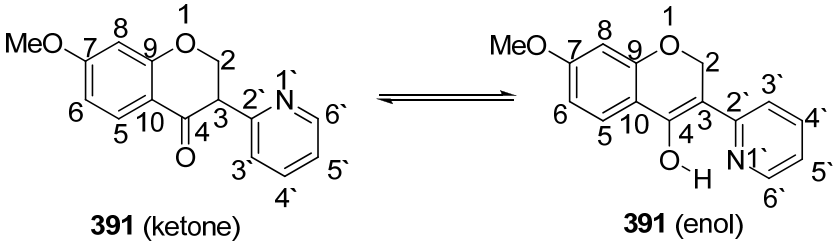
Scheme 147

Under action of Eu(facam)$_3$ the signals in ^{1}H NMR of racemic **391** began to appear in double. The changes of chemical shifts (titration with LSR) are shown in table 25 and in figure 10. Here it should be mentioned that chromanone **391** is coordinated to europium in its ketonic form (evident from titration with LSR). For the determination of ee the most useful is the splitting of methyl-group: the signals are always sharp and resolved to baseline, if the quantity of Eu(facam)$_3$ is 10-100 mol-%, relative to **391**. Numeration of atoms of **391** see in scheme 148.

Table 25. Lantanoid shift of ^{1}H NMR signals of 391

	C(Eu(facam)$_3$)/C(chromanone 391)										
Resonating proton	**0**	**0.1**	**0.2**	**0.29**	**0.4**	**0.49**	**0.59**	**0.7**	**0.81**	**0.91**	**1**
Me	3.84	3.88	3.94	3.98	4.03	4.05	4.08	4.12	4.12	4.14	4.15
Me	3.84	3.89	3.97	4.02	4.08	4.11	4.15	4.19	4.2	4.22	4.25
3-CH	4.12	5.20	5.55	5.76	6.06	6.19	6.34	broadening to baseline			
2-CH$_2$-alpha	4.75	4.99	5.30	5.51	5.79	5.93	6.06	6.10	6.11	6.13	6.28
2-CH$_2$-alpha	4.75	4.99	5.30	5.51	5.79	5.93	6.06	6.26	6.31	6.39	6.49
2-CH$_2$-beta	4.97	5.20	5.50	5.76	6.10	6.29	6.48	6.57	6.6	6.70	6.8
2-CH$_2$-beta	4.97	5.20	5.65	5.91	6.25	6.41	6.60	6.77	6.82	6.89	6.97
8-CH	6.44	6.54	6.75	6.81	6.88	6.92	6.96	7.02	7.03	7.05	7.09
8-CH	6.44	6.54	6.75	6.87	7.03	7.10	7.18	7.29	7.31	7.36	7.44
6-CH	6.61	6.63	6.69	6.73	6.77	6.80	6.83	6.86	6.87	6.89	6.91
6-CH	6.61	6.65	6.76	6.79	6.92	6.98	7.05	7.18	7.18	7.20	7.13
5`-CH	7.21	7.21	7.21	7.20	7.19	7.18	7.17	7.16	7.16	7.16	7.14
5`-CH	7.21	7.28	7.36	7.41	7.47	7.50	7.54	7.59	7.60	7.62	7.66
3`-CH	7.27	7.50	7.96	8.09	8.37	8.51	8.66	8.88	8.92	9.00	9.11
3`-CH	7.27	7.50	7.96	8.09	8.42	8.57	8.73	8.97	8.98	9.00	9.11
4`-CH	7.66	7.77	7.91	8.01	8.14	8.20	8.26	8.35	8.37	8.41	8.45
4`-CH	7.66	7.77	7.98	8.09	8.24	8.32	8.40	8.51	8.53	8.58	8.65
5-CH	7.91	7.97	8.11	8.21	8.32	8.39	8.44	8.53	8.55	8.60	8.69
5-CH	7.91	8.03	8.29	8.46	8.66	8.76	8.87	9.02	9.05	9.11	9.23
6`-CH	8.59	8.72	8.79	8.82	8.88	8.90	8.93	8.97	8.98	9.00	9.11
6`-CH	8.59	8.44	7.87	7.75	7.43	broadening to baseline					

NMR spectra with lantanoid shift of **391**, obtained in presence of chiral catalyst, has shown that the product is racemic. It is not surprisingly, since the chromanone **391** is disposed towards the enolization, which destroys its chiral centrum (scheme 148). The enolization is spontaneous, does not require some additives (e.g. bases or acids), and proceeds readily at r.t.



391 (ketone) **391** (enol)

Scheme 148

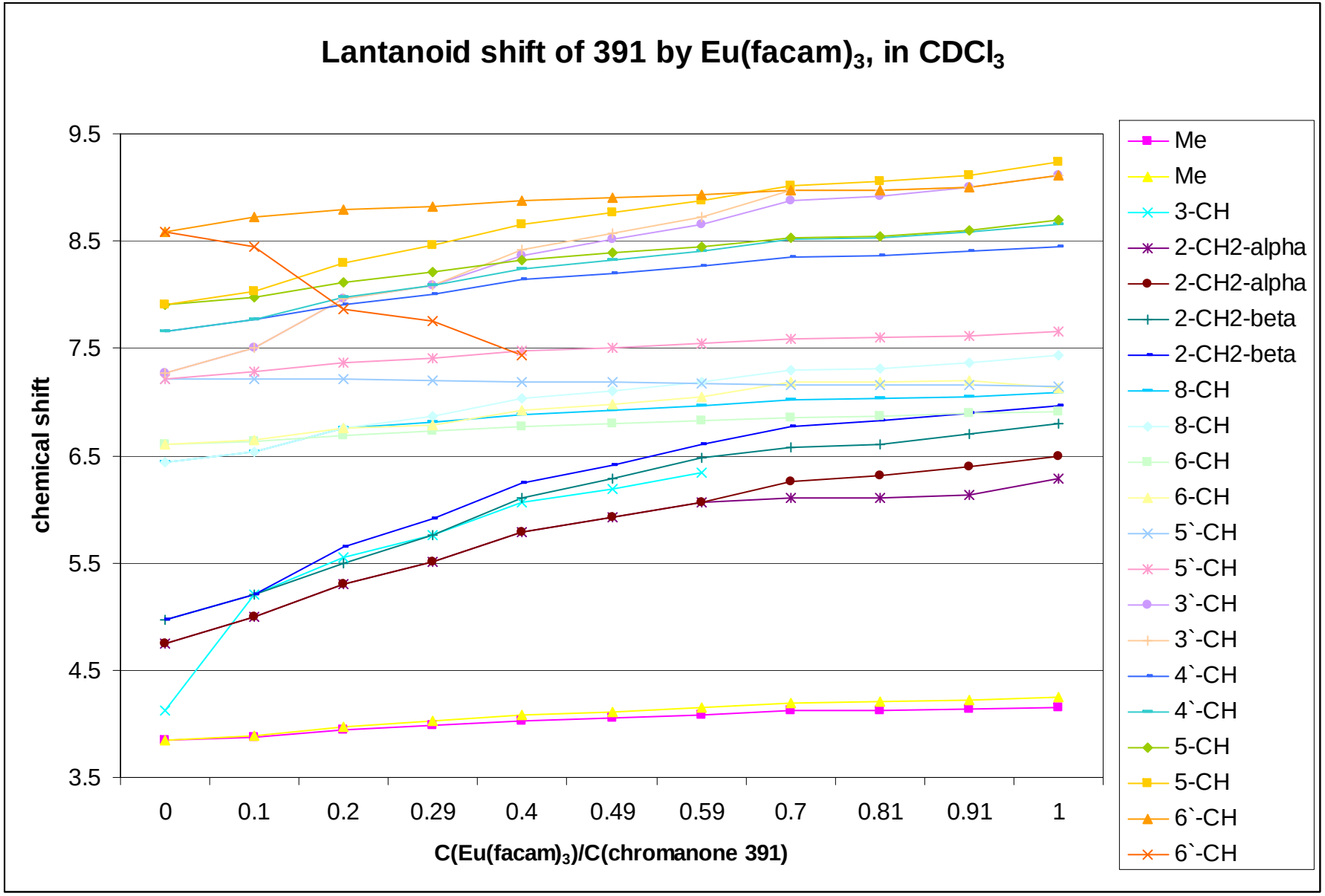

Lantanoid shift of 391 by Eu(facam)3, in CDCl3
chemical shift
9.5
8.5
7.5
6.5
5.5
4.5
3.5
0
0.1
0.2
0.29
0.4
0.49
0.59
0.7
0.81
0.91
1
C(Eu(facam)3)/C(chromanone 391)
Me
Me
3-CH
2-CH2-alpha
2-CH2-alpha
2-CH2-beta
2-CH2-beta
8-CH
8-CH
6-CH
6-CH
5`-CH
5`-CH
3`-CH
3`-CH
4`-CH
4`-CH
5-CH
5-CH
6`-CH
6`-CH

Figure 10

The NMR spectra of **391**, recorded in C_6D_6, $CDCl_3$ or in THF-D_8 always showed the presence of enol. The ratio ketone/enol was found to be 1:0.04 in $CDCl_3$, 1:0.2 in THF-D_8 and 1:0.13 in C_6D_6. Another indirect proof of enolization is the yellow colour of pure **391** (even in crystalline state). The parent **388** is colourless. On the other hand, there is no reason to expect that **391** should be coloured (e.g. 7-methoxyisoflavanone is colourless). The C=C-bond, appeared in enol, conjugates electron-donor methoxychromone with electron-aceptor pyridine, hence this structure can be coloured.

The impossibility of preparation of enantiomerically pure **391**, at least at r.t., is not a drawback of this compound. FDA requires either preparation of enantiomerically pure drugs, or a proof that racemisation readily occurs. The last demand was implemented with help of NMR-spectroscopy. Additionally, with help of LSR, it was proven, that enantioselective synthesis is still impossible even in chloroform, where the relative quantity of enol is minimal.

Hydrogenation of **388** in nucleophilic conditions, according to **general procedure G** in presence of 1 mol-% of **286c** showed 90%-conversion (NMR) of **388** into **391**. The use of 1.5 mol-% of the catalyst (**general procedure L**) afforded pure **391** with yield of 99% (after column chromatography on silica gel, eluation by Et_2O).

The energies of the frontier orbitals with the nucleophilicity indexes (ω) of **388** are presented in table 26. The energies of LUMO are low enough to ensure effective attack by $Ir^{\ominus}$. According to the computations of local softnesses the nucleophiles should undoubtedly attack 2-C (wished atom) of chromone **388**.

Table 26. Frontier orbital energies and nucleophilicity indexes of 388

Basis: 6-31G			**Basis: 6-31G(d,p)**			**Basis: 6-31++G(d,p)**		
E_{HOMO}, hartree	E_{LUMO}, hartree	ω, hartree	E_{HOMO}, hartree	E_{LUMO}, hartree	ω, hartree	E_{HOMO}, hartree	E_{LUMO}, hartree	ω, hartree
-0.22933	-0.06044	0.00354528	-0.22417	-0.05208	0.00328322	-0.23563	-0.06664	0.00386003

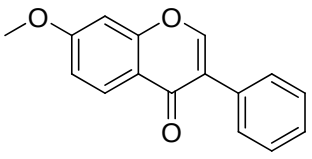
As a summary, functionalized electron-deficient alkene **388** can be effectively homogeneously hydrogenated with high chemoselectivity to give the corresponding chroman-4-one **391**. For the hydrogenation various solvents and Ir-complexes are suitable. The complexes of choice are commercially avaliable Crabtree complex $[Ir(COD)(PCy_3)(Py)]PF_6$ or $[Ir(COD)(PPh_3)_2]$BARF, which can be synthesized from inexpensive ligand. However, the complex $[Ir(COD)(PPh_3)_2]PF_6$ is not recommended because 1 mol-% of this catalyst has shown insufficient conversion. The enolization of 7-methoxy-3-(2-pyridyl)chroman-4-one **391** excludes its formation in enantiomerically pure state in high- or low-polar solvents.

4 SUMMARY

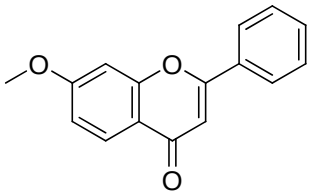
Flavonoids are known as biologically active compounds. To the class of flavonoids belong chromones, coumarins and their derivatives. Flavanones, isoflavanones and neoflavanones also represent the flavonoids. Natural Flavanones, isoflavanones and neoflavanones, as well as the other chroman-2-ones and chroman-4-ones, have a wide spectrum of biological activity. Hence, the synthesis of new chromanones has both theoretical and practical significance.

Flavanones, isoflavanones, neoflavanones and 3-arylchroman-2-ones (the latter are isosteric to isoflavanones) have a chiral centrum and are sensitive to racemization (except the neoflavanones). Enantioselective homogeneous hydrogenation, which proceeds in very mild conditions, could be a method of enantioselective synthesis of such compounds, *via* hydrogenation of chromones and coumarins.

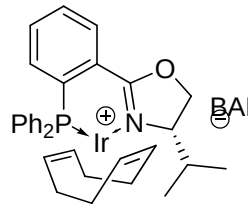
Four model compounds **281-284** were found to be not hydrogenated under pressure of hydrogen 100 bar in presence of common catalysts, which are effective in homogeneous hydrogenation: $[Rh(PPh_3)_3Cl]$, [Rh(rac-BINAP)(COD)Cl] (generated *in situ*), [Rh(COD)(rac-BINAP)]OTf , [Ir(COD)(rac-BINAP)Cl] (generated *in situ*), [Ir(COD)(rac-BINAP)]BARF, [Ir(COD)(iPr-Phox)]BARF **286c**, $[Ru(PPh_3)_3Cl_2]$, [Ru(S-BINAP)(p-cymene)Cl]Cl, [Ru(R-BINAP)$(OAc)_2$], NH_2Et_2[Ru(BINAP)Cl(μ-Cl)$_3$Ru(BINAP)Cl] and [Ru(p-cymene)(Tsen)Cl]Cl (**278**, generated *in situ*, transfer hydrogenation by NEt_3-HCO_2H).



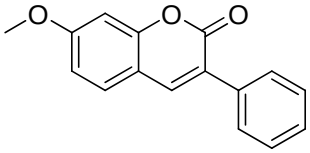
7-methoxyisoflavone , **281**



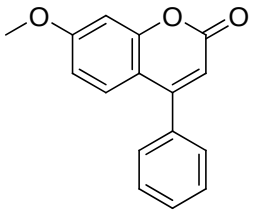
7-methoxyflavone, **282**



[Ir(COD)((S)-iPr-Phox)]BARF, **286c**



7-methoxy-3-phenylcoumarin, **283**

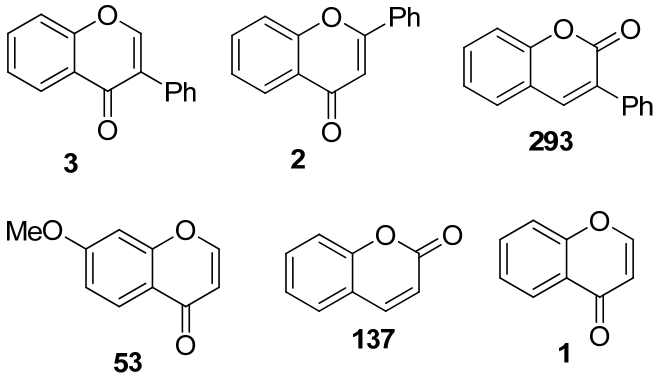


7-methoxyneoflavone, **284**

Scheme 149

It was shown, that both sterical and electronic properties of flavonoids are responsible for a lack of homogeneous hydrogenation. The C=C-bond of flavonoids is conjugated with carbonyl-group, but has a fixed *s-trans*-conformation. The precoordination of the metal on the

carbonyl-groups is not helpful for hydrogenation of C=C-bond. The homogeneous hydrogenation of chromone **1** and coumarin **137** was observed in presence of [Rh(COD)(rac-BINAP)]OTf and [Ir(COD)(iPr-Phox)]BARF in THF, while isoflavone **3**, flavone **2,** 3-phenylcoumarin **293** and 7-methoxychromone **53** were not hydrogenated in the same conditions. This implies that side phenyl-groups of **2-3** and **293** produce the sterical hindrances for the catalytically active particle, which should attack the C=C-bond. On the other hand, the lack of hydrogenation of **53** implies the inhibitory activity of 7-methoxy-group on the homogeneous hydrogenation. In the latter case the most probable site for attack by electrophilic catalyst is 8-C of chromone ring, while hydrogenation needs the 3-C or 4-C to be attacked.



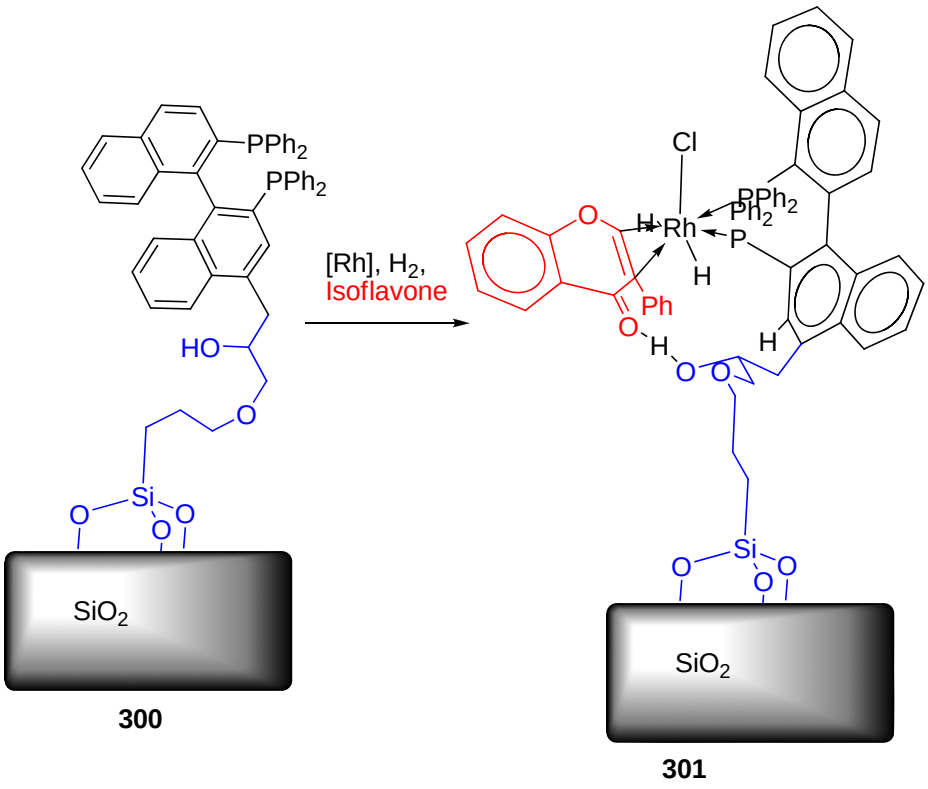
Scheme 150

An attempt to prepare a heterogenized catalyst with a special linker, which could facilitate the coordination of the metal on C=C-bond *via* the formation of hydrogen-bond (scheme 151), was not successful.

Surprisingly, 7-methoxyisoflavone **281** was hydrogenation in toluene in presence of complex **286c** and triethylamine. According to the literature, this hydrogenation should be inhibited by organic base, although it was activated. After base and solvent screening it was established, that not coordinating (hence not nucleophilic) DIPEA is the best base, suitable for this hydrogenation, while appropriate solvents are toluene or methanol. Later the reactions were performed in toluene.

Stilbene is effectively hydrogenated in presence of complex **286c** under pressure of hydrogen (100 bar) in various solvents, but its hydrogenation is inhibited by DIPEA. Stilbene represents an electron rich alkene, disposed to react with electrophiles, while **281** represents an electron deficient alkene, disposed to react with nucleophiles. From this the following names were constructed: “nucleophilic hydrogenation” if the attacking complex is nucleophilic and hydrogenates electron deficient alkenes, and “electrophilic hydrogenation” if

the attacking complex is electrophilic and hydrogenates electron rich alkenes. Similarly, "nucleophilic conditions" presume hydrogenation by Ir-complex in presence of base in toluene, while "electrophilic conditions" – in absence of base in dichloromethane or in toluene.

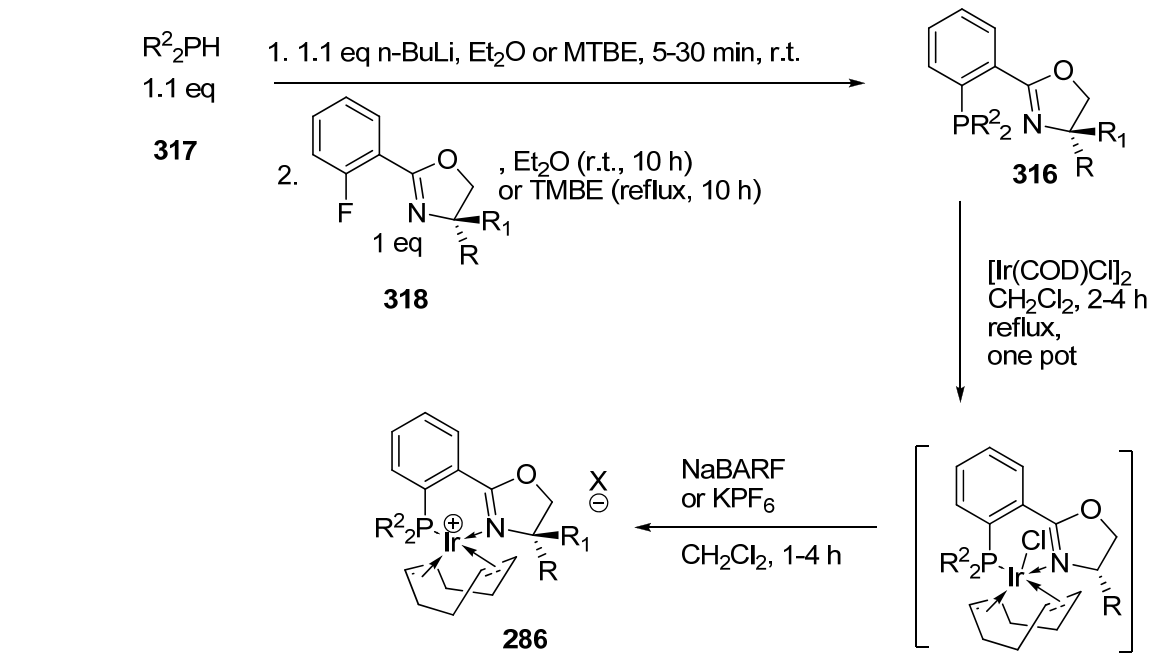


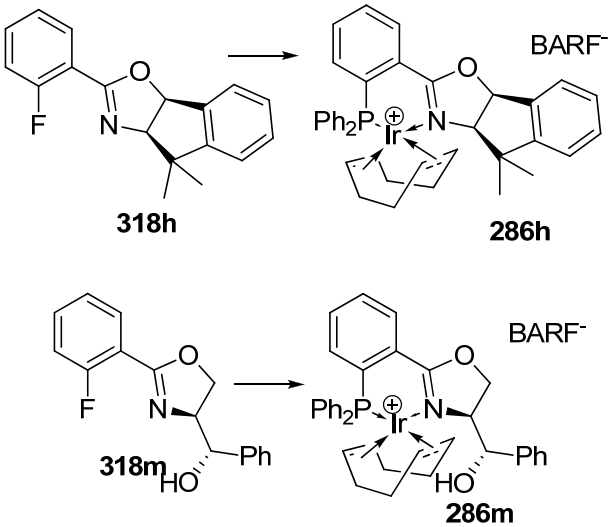
Scheme 151

The quality of DIPEA was found to be significant for successful reaction, because DIPEA should be used in 300-600 fold excess relative to the catalyst, and small contamination with coordinating base (supposed diisopropylamine) is deleterious for the reaction. It was established, that DIPEA is effectively purified by distillation over crystalline ninhydrine, then twice over crystalline LiH. Thereafter DIPEA should be stored in nitrogen filled glovebox or in tightly closed container, in dark.

The complexes of type [Ir(COD)(Phox)]X, where X is BARF of PF_6, Phox is phosphinooxazoline, are usefull precatalysts for homogeneous asymmetric hydrogenation (if Phox is chiral). Current methods of synthesis of such complexes imply a reaction of pure phosphinooxazoline with $[Ir(COD)Cl]_2$ with subsequent anione exchange. In my hands the isolation of pure iPr-Phox **316c** was not possible because of air-sensivity and irreversible adsorption on silica gel and on Alox. However, the way to the complexes **286** was designed, which does not need the isolation of such ligands (scheme 152). The crude ligands were subjected to complexation with $[Ir(COD)Cl]_2$, then anione-exchange proceeded, and the

complexes **286** were purified by column chromatography (with BARF counter-ion) or by precipitation (with PF_6 counter-ion). Two complexes of rhodium were synthesized using this protocol, namely [Rh(COD)(iPr-Phox)]BARF and [Rh(iPr-Phox)$_2$]BARF, where (iPr-Phox) denotes ligand **316c**.





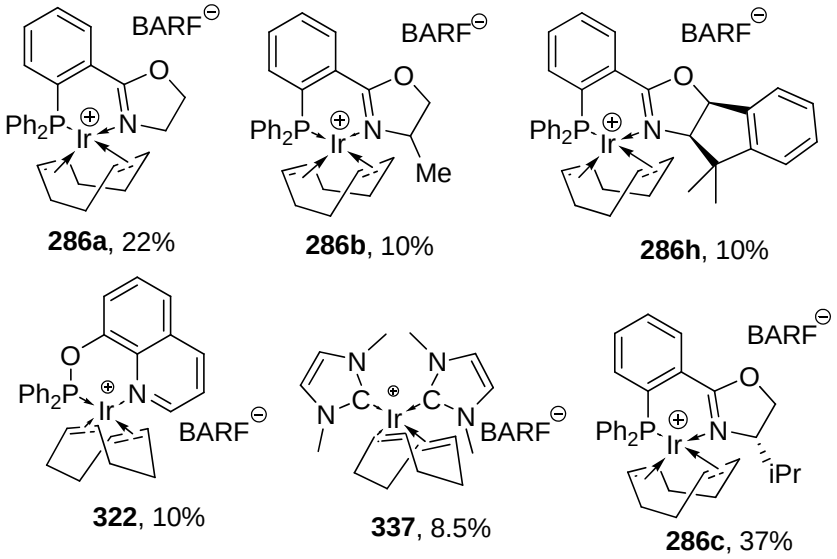
Compd 286, 316-318	R	R^1	R^2	X
a	H	H	Ph	BARF
b	Me, H	racemic	Ph	BARF
c	i-Pr	H	Ph	BARF
d	t-Bu	H	Ph	BARF
e	i-Pr	H	o-Tolyl	BARF
f	t-Bu	H	o-Tolyl	BARF
g	i-Pr	H	2,6-Xylyl	BARF
i	i-Pr	H	Cy	BARF
j	i-Pr	H	Ph	PF_6
k	Me	Me	Ph	BARF
l	i-Pr	H	Cy	PF_6

Scheme 152

In order to define the catalaphor, significant for nucleophilic hydrogenation, more complexes of iridium were synthesized or purshased.

The catalytically active complexes are shown on the scheme 153. The complex **286c** was the most active in nucleophilic hydrogenation of **281**, hence further investigations were performed with it. 7-Methoxyisoflavone **281** was reduced in presence of **286c** with ee 12%. The complex **286h** gave ee 34%, but too bad conversion. The addition of chiral base (R)-N,N-diethyl-1-phenylethylamine instead of DIPEA does not change the ee of the reaction, hence the chiral induction is connected only with ligand.

Complexes, active in nucleophilic hydrogenation.
Hydrogenation made according to the **general procedure G**, in presence of 1 mol% of the catalyst.
The test substrate is 7-methoxyisoflavone. Conversion of the substrate is written under the complex.



286a, 22% **286b**, 10% **286h**, 10%

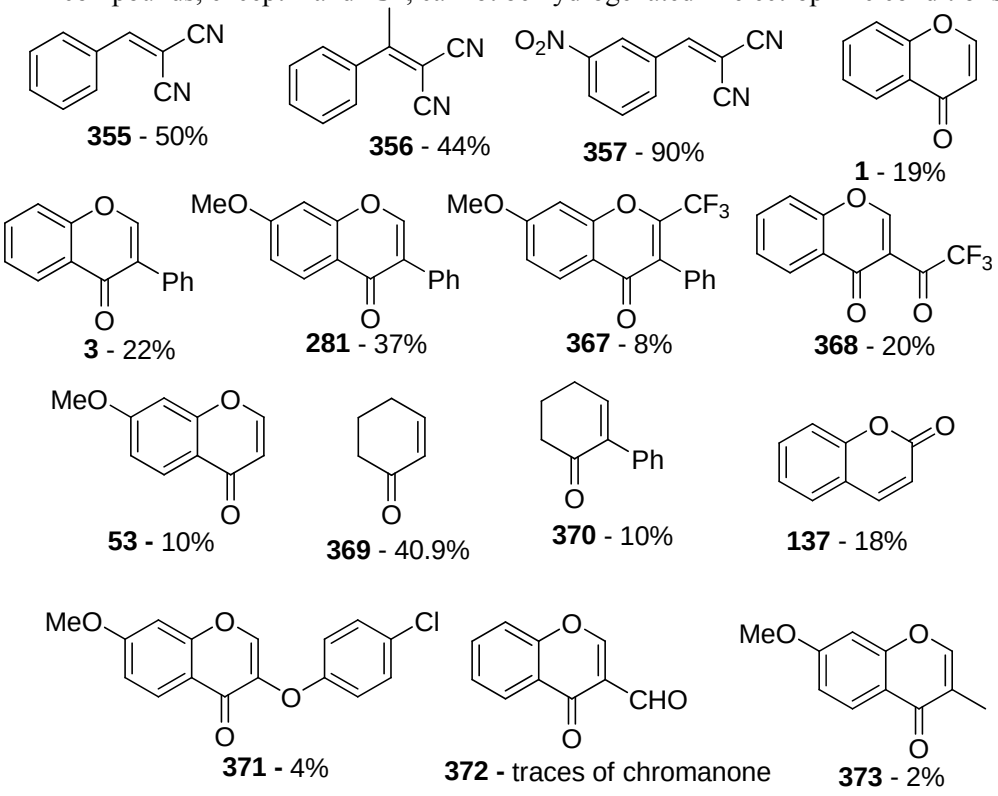
322, 10% **337**, 8.5% **286c**, 37%

Scheme 153

The complex **286c** is shown to catalyze homogeneous hydrogenation of various electron deficient alkenes, however a large part of activated alkenes was not hydrogenated. The active substrates are shown on the scheme 154. The application of higher load of catalyst resulted in full conversion of the substrates and sometimes in overreduction (reduction of carbonyl group). The reduced products were isolated with yields of 36-98% by column chromatography.

An attempt was made to find a correlation between activity of a certain substrate with its properties. The substrates with high-lying LUMO were inactive. The reactivity of the substrates, which have low-lying LUMO, in conditions of nucleophilic hydrogenation depends on the remaining functional groups in the molecule. Sterical hindrances near the atom, which is attacked by nucleophile, also can prevent the hydrogenation. It seems, that everything, attacked by the catalytically active nucleophilic complex, is reduced. Sometimes the conversion of the substrate was only 2% (in presence of 1 mol-% of the catalyst **286c**). I associate this with the parallel reaction of catalyst deactivation by base.

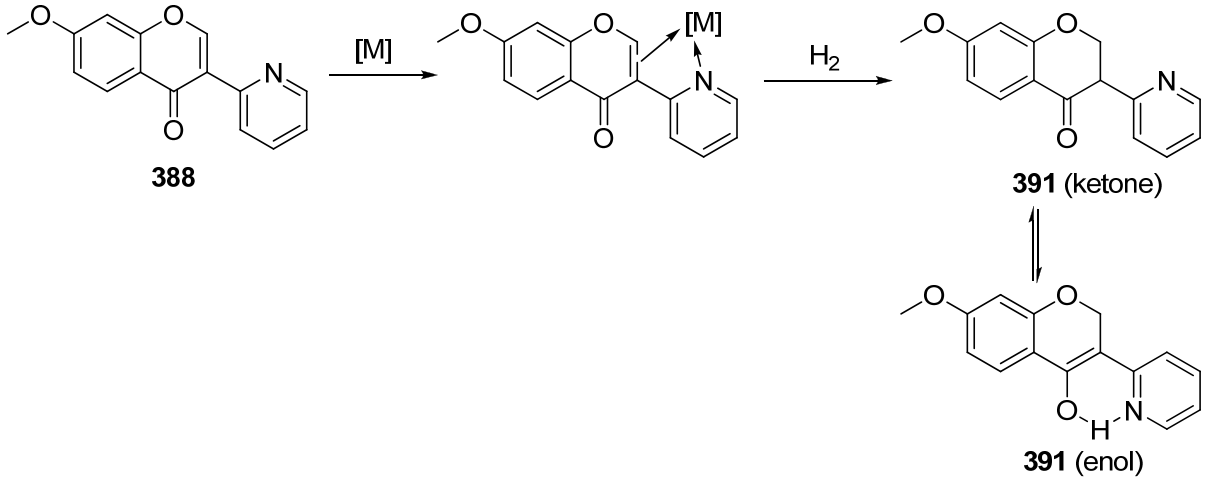
Conversions, achieved in presence of 1 mol-% of the catalyst **286c**, are given.
All compounds, except **1** and **137**, cannot be hydrogenated in electrophilic conditions.



Scheme 154

7-Methoxy-3-(pyridin-2-yl)chromone **388** is an electron deficient alkene with a functionalized C=C-bond (scheme 155). It was homogeneously hydrogenated by various complexes of iridium under both electrophilic and nucleophilic conditions (isolated yields of **391** up to 99%). Complexes of rhodium were not effective for homogeneous hydrogenation of **388**.

Substance **391** is quite easy enolizable because of the formation of a new hydrogen-bond (scheme 155). The enolization takes place even in low-polar solvents and in solid state. Enolization makes the synthesis of enantiomerically pure **391** impossible.



Scheme 155

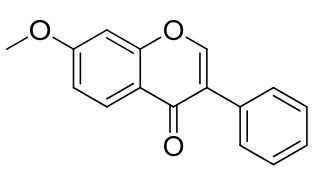
It is shown and proven, that the flavonoids represent a unique class of alkenes, for which the homogeneous hydrogenation is not known till now (except for some functionalized representatives). It is proven, that assigned task could not be resolved *via* traditional (electrophilic) homogeneous hydrogenation. However, a new reaction was discovered, namely nucleophilic hydrogenation. At the current state the nucleophilic hydrogenation by Ir-complexes is only of academical significance. An investigation of the mechanism is needed for its practical usage. Homogeneous hydrogenation of 7-methoxy-3-(pyridin-2-yl)chromone is very effective both in its electrophilic and in nucleophilic versions, and affords the corresponding chroman-4-one in almost quantitative yield.

5 ZUSAMMENFASSUNG

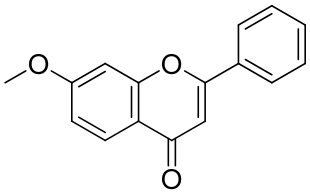
Flavonoide sind als Wirkstoffe bekannt. Zu der Klasse der Flavonoide gehören die Chromone, Coumarine und deren Derivate. Ebenso sind die Flavanone, Isoflavanone und Neoflavanone Vertreter der Flavonoide. Natürliche Flavanone, Isoflavanone und Neoflavanone weisen wie die Chroman-2-one und Chroman-4-one ein breites Spektrum an biologischer Aktivität auf. Demzufolge hat die Synthese der neuen Chromanone sowohl theoretische als auch praktische Bedeutung.

Flavanone, Isoflavanone, Neoflavanone und 3-Arylchroman-2-one (die letzteren sind isosterisch zu den Isoflavanonen) haben einen chiralen Zentrum und sind empfindlich gegen Racemisierung (ausgenommen Neoflavanone). Die Enantioselektive homogene Hydrierung, die unter sehr milden Bedingungen abläuft, könnte eine Methode für die enantioselektive Synthese solcher Verbindungen sein.

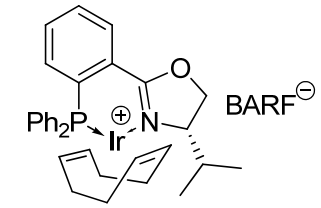
Bei vier Modellverbindungen **281**-**284** wurde festgestellt, dass die Hydrierung mit Wasserstoff unter Druck (100 bar) in Gegenwart der üblichen Katalysatoren, die für homogene Hydrierung effektiv sind, nicht funktioniert: $[Rh(PPh_3)_3Cl]$, [Rh(rac-BINAP)(COD)Cl] (generiert *in situ*), [Rh(COD)(rac-BINAP)]OTf , [Ir(COD)(rac-BINAP)Cl] (generiert *in situ*), [Ir(COD)(rac-BINAP)]BARF, [Ir(COD)(iPr-Phox)]BARF **286c**, $[Ru(PPh_3)_3Cl_2]$, [Ru(S-BINAP)(p-cymene)Cl]Cl, $[Ru(R\text{-}BINAP)(OAc)_2]$, $NH_2Et_2[Ru(BINAP)Cl(\mu\text{-}Cl)_3Ru(BINAP)Cl]$ und [Ru(p-cymene)(Tsen)Cl]Cl (**278**, generiert *in situ*, Transfer-Hydrierung mit NEt_3-HCO_2H).



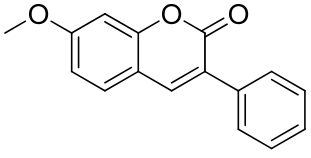
7-Methoxyisoflavon, **281**



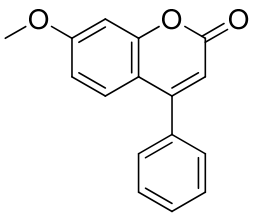
7-Methoxyflavon, **282**



[Ir(COD)((S)-iPr-Phox)]BARF, **286c**



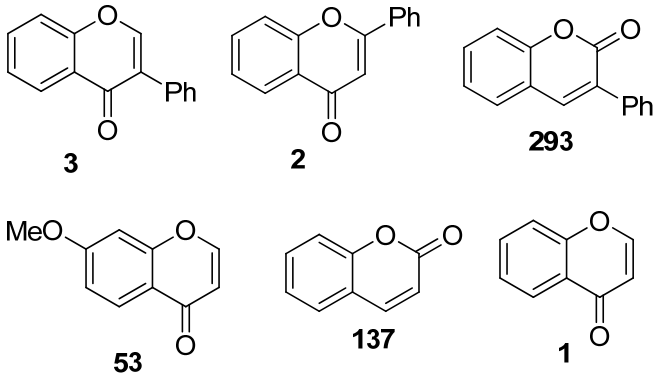
7-Methoxy-3-phenylcoumarin, **283**



7-Methoxyneoflavon, **284**

Schema 149

Es wurde festgestellt, dass sowohl sterische als auch elektronische Eigenschaften der Flavonoide für das Scheitern der homogenen Hydrierung verantwortlich sind. Die C=C-Bindung der Flavonoide ist wie in funktionalisierten Alkenen mit einer Carbonylgruppe konjugiert, hat aber eine *s-trans*-fixierte Konformation. Die Präkoordination des Metals an die Carbonylgruppe ist für die Hydrierung der C=C-Bindung nicht nützlich. Die homogene Hydrierung des Chromons **1** und des Coumarins **137** wurde in Gegenwart von [Rh(COD)(rac-BINAP)]OTf und [Ir(COD)(iPr-Phox)]BARF in THF beobachtet, wohingegen Isoflavon **3**, Flavon **2**, 3-Phenylcoumarin **293** und 7-Methoxychromon **53** unter denselben Bedingungen nicht hydriert wurden. Hieraus folgt, dass die Phenylringe in den Verbindungen **2-3** und **293** eine sterische Hinderungen für die katalytisch aktive Partikeln darstellen, die die C=C-Bindung angreifen sollten. Andererseits folgt aus der Abwesenheit der Hydrierung von **53**, dass die 7-Methoxygruppe eine hemmende Wirkung auf die homogene Hydrierung hat. In letzteren Fall ist der wahrscheinlichste Ort des Angriffs der elektrophilen Katalysatoren das 8-C des Chromonrings. Für eine erfolgreiche Hydrierung muss jedoch das 3-C oder 4-C angegriffen werden.

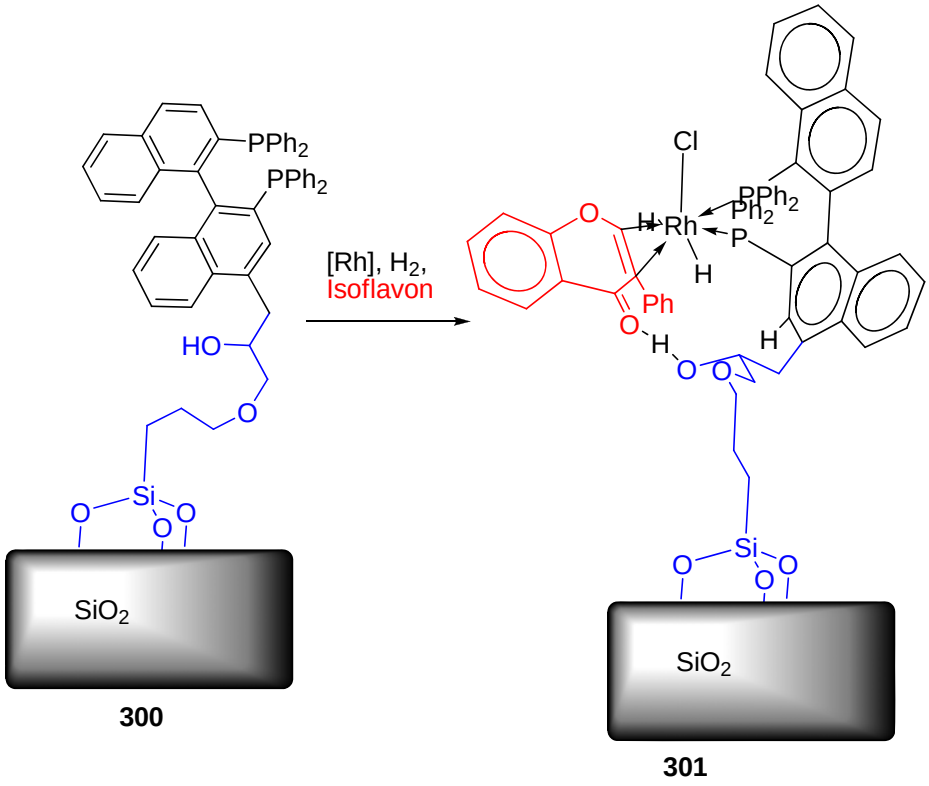


Schema 150

Der Versuch einen heterogenisierten Katalysator mit einem speziellen Linker darzustellen, der über die Bildung einer Wasserstoffbrückenbindung (Schema 151) die Koordinierung des Metals auf die C=C-Bindung erleichtern könnte, war nicht erfolgreich.

Überraschenderweise wurde 7-Methoxyisoflavon **281** in Toluol in Gegenwart von Komplex **286c** und Triethylamin hydriert. Entsprechend der Literatur, sollte diese Hydrierung durch eine organische Base gehemmt werden, wurde jedoch aktiviert. Nach einem Base- und Lösungsmittel-Screening wurde festgestellt, dass die nicht koordinierende (demzufolge also nicht nucleophile) Base DIPEA am besten für diese Hydrierung geeignet ist. Geeignete Lösungsmittel sind dabei Toluol und Methanol. Später wurden die Reaktionen in Toluol durchgeführt.

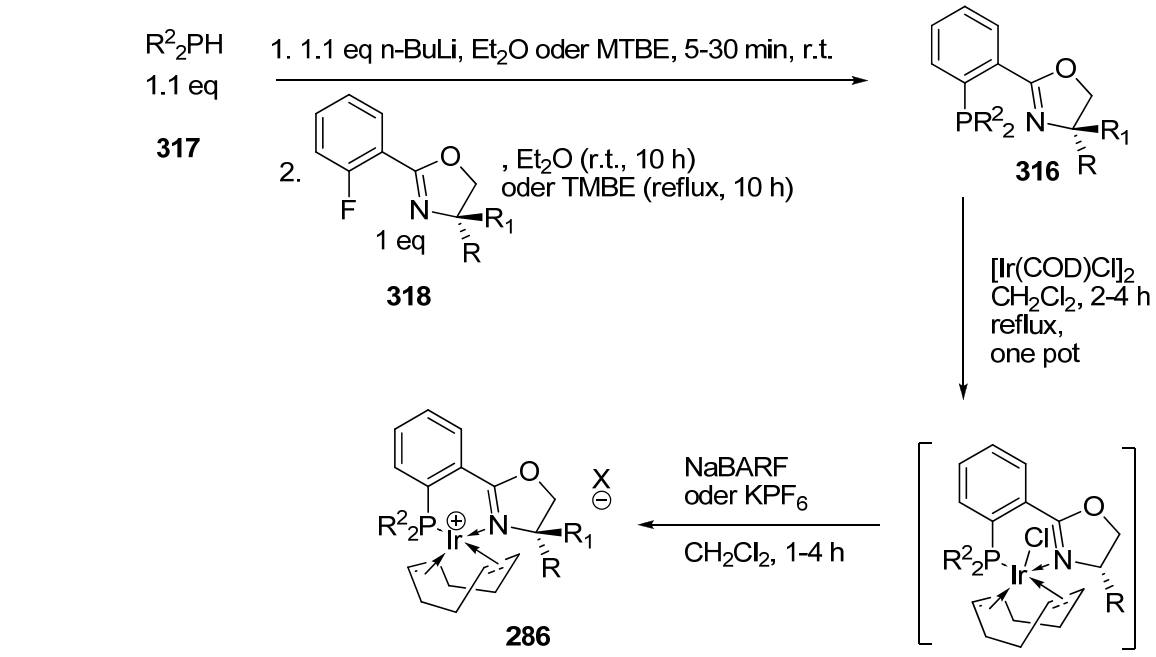
Stilben wird effektiv in Gegenwart von Komplex **286c** unter Wasserstoffdruck (100 bar) in verschieden Lösungsmittel hydriert. Mit DIPEA ist die Hydrierung jedoch gehemmt. Stilben ist ein elektronreiches Alken, das prinzipiell mit Elektrophilen reagiert, während **281** ein elektronenarmes Alken darstellt, das eher mit Nucleophilen reagiert. Hieraus wurde der Begriff „Nucleophilhydrierung“ gebildet, was bedeutet, dass der angreifende Komplex nucleophil ist und elektronarme Alkene hydriert. Mit „Elektrophilhydrierung“ ist gemeint, dass der angreifende Komplex elektrophil ist und ein elektronreiches Alken hydriert. Dementsprechend ist unter „nucleophilen Bedingungen“ die Hydrierung von Ir-Komplexen in Gegenwart von Base in Toluol zu verstehen, und unter „elektrophilen Bedingungen“ – die Abwesenheit von Base im Dichloromethan oder im Toluol.

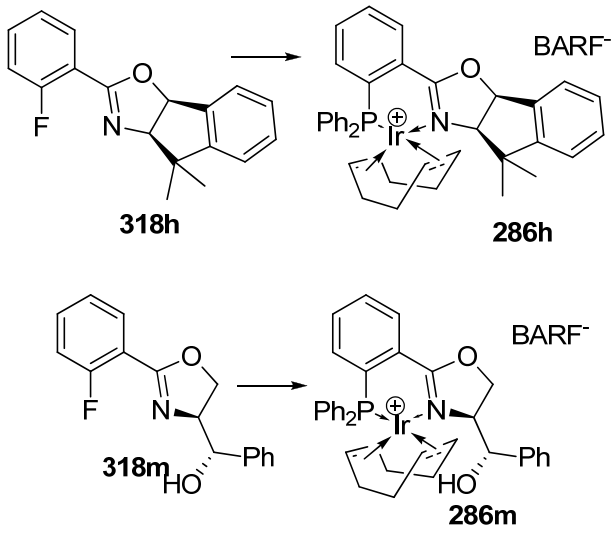


300 **301**

Schema 151

Die Qualität des DIPEA ist für die erfolgreiche Reaktion von großer Wichtigkeit, da DIPEA im 300-600-fachen Überschuss bezüglich des Katalysators verwendet wird, und kleine Kontaminationen mit koordinierender Base (vermutlich Diisopropylamin) schädlich für die Reaktion sind. DIPEA kann effektiv durch Destillation über kristallinem Ninhydrin und anschließende zweifacher Destillation über kristallinem LiH gereinigt werden. Die Lagerung sollte unter Stickstoff erfolgen (z.B. in einer Glovebox oder in dicht verkorkten Behältern im Dunkeln).





Compd 286, 316-318	R	R^1	R^2	X
a	H	H	Ph	BARF
b	Me, H	rac.	Ph	BARF
c	i-Pr	H	Ph	BARF
d	t-Bu	H	Ph	BARF
e	i-Pr	H	o-Tolyl	BARF
f	t-Bu	H	o-Tolyl	BARF
g	i-Pr	H	2,6-Xylyl	BARF
i	i-Pr	H	Cy	BARF
j	i-Pr	H	Ph	PF_6
k	Me	Me	Ph	BARF
l	i-Pr	H	Cy	PF_6

Schema 152

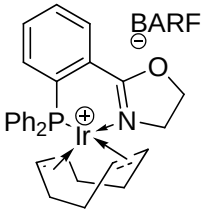
Die Komplexe vom Typ [Ir(COD)(Phox)]X (mit X = BARF oder PF_6, Phox = Phosphinooxazolin), sind nützliche Präkatalysatoren für die homogene asymmetrische Hydrierung, wenn das Phosphinooxazolin chiral ist. Literaturbekannte Methoden der Synthese dieser Komplexe beschreiben die Reaktion von reinem Phosphinooxazolin mit $[Ir(COD)Cl]_2$ mit anschließendem Anionaustausch. Die Isolation des reinen iPr-Phox **316c** gelang wegen der Lüftempfindlichkeit und wegen der irreversibeln Adsorption auf Kieselgel

und auf Alox nicht. Es wurde jedoch ein Weg für Komplexe **286** gefunden, der ohne die Isolierung dieser Liganden (Schema 152) auskommt. Die ungereinigten Liganden wurden mit $[Ir(COD)Cl]_2$ umgesetzt, ein Anionaustausch durchgeführt, und der Komplexe **286** durch Säulenchromatographie (mit BARF als Gegenion) oder durch Umkristallisieren (mit PF_6 als Gegenion) gereinigt. Die beiden Rhodiumkomplexe [Rh(COD)(iPr-Phox)]BARF und $[Rh(iPr\text{-}Phox)_2]$BARF (mit iPr-Phox als Ligand **316c**) wurden auf diese Weise synthetisiert.

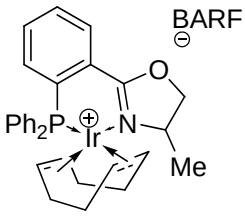
Um ein Catalaphor, das wichtig für Nucleophilhydrierung ist, zu bestimmen, wurden mehr Ir-Komplexe synthetisiert oder gekauft.

Katalytisch aktive Komplexe sind in Schema 153 gezeigt. Der Komplex **286c** war der aktivste bei der Nucleophilhydrierung von **281**. Demzufolge wurden die nächsten Untersuchungen damit gemacht. 7-Methoxyisoflavon **281** wurde in Gegenwart von **286c** mit einem ee von 12% reduziert. Der Komplex **286h** ergab einen ee von 34% bei schlechter Umsetzung des Substrats. Die Zugabe von chiraler Base (R)-N,N-diethyl-1-phenylethylamine statt DIPEA ändert den ee der Reaktion nicht. Demnach lässt sich die chirale Induktion nur auf den Ligand zurückführen.

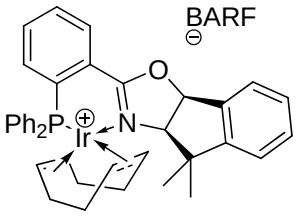
Komplexe, active in Nucleophilhydrierung. Hydrierung wird gemäß der **allgemeinen Prozedur G** in Gegenwart von 1 mol-% von Katalysator gemach. Das Testsubstrat war 7-Methoxyisoflavon **281.** Konversion des Substrates wird unter dem Komplex geschrieben.



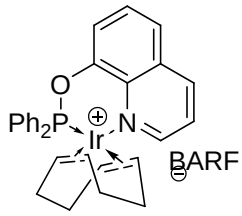
286a, 22%



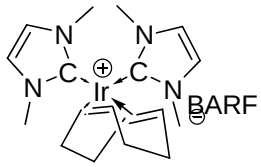
286b, 10%



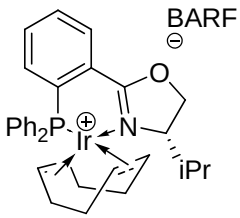
286h, 10%



322, 10%



337, 8.5%



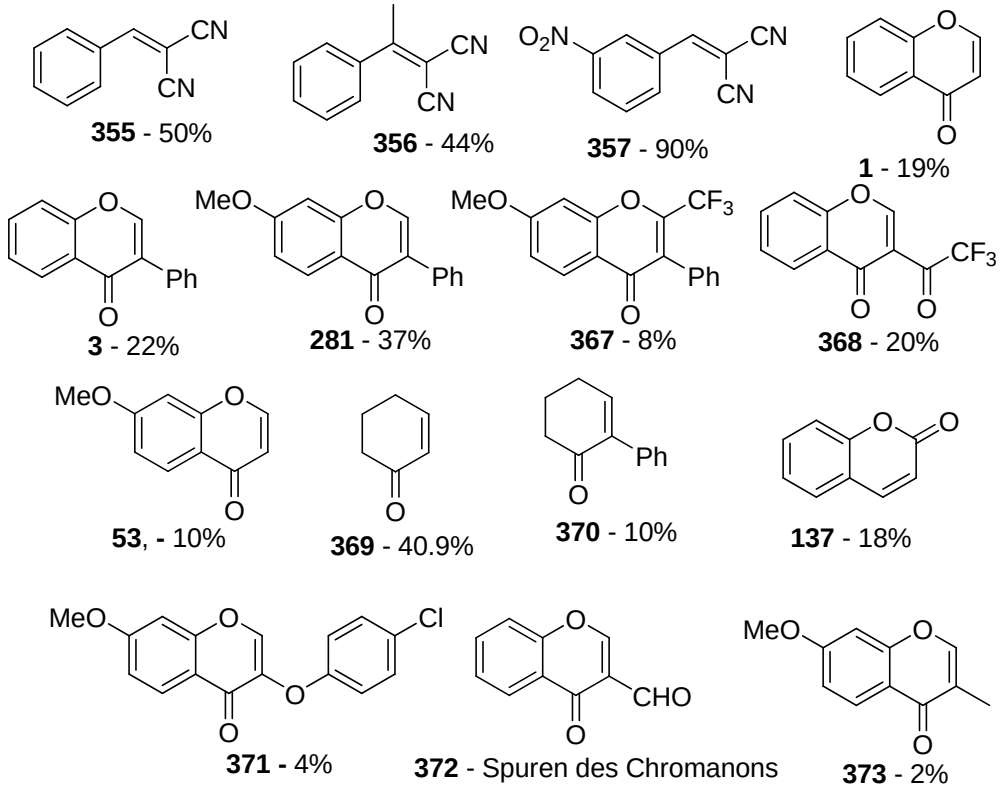
286c, 37%

Schema 153

Der Komplex **286c** katalysiert die homogene Hydrierung verschiedener elektronenarmer Alkene, einen großen Teil der aktivierten Alkene dagegen nicht. Die aktiven Substrate sind in Schema 154 gezeigt. Höhere Einsätze an Katalysator resultierten in der kompletten Konversion der Substrate und führten manchmal zu Überreduktion (Reduktion der

Carbonylgruppe). Die reduzierten Produkte wurden mit Ausbeuten von 36-98% durch Säulenchromatographie isoliert.

Die Konversionen, erhaltene in Gegenwart von 1 mol-% des Katalzsators **286c**, werden gegeben
Alle verbindungen, außer **1** und **137**, werden in elektrophilen Bedingungen nicht Hydrogeniert

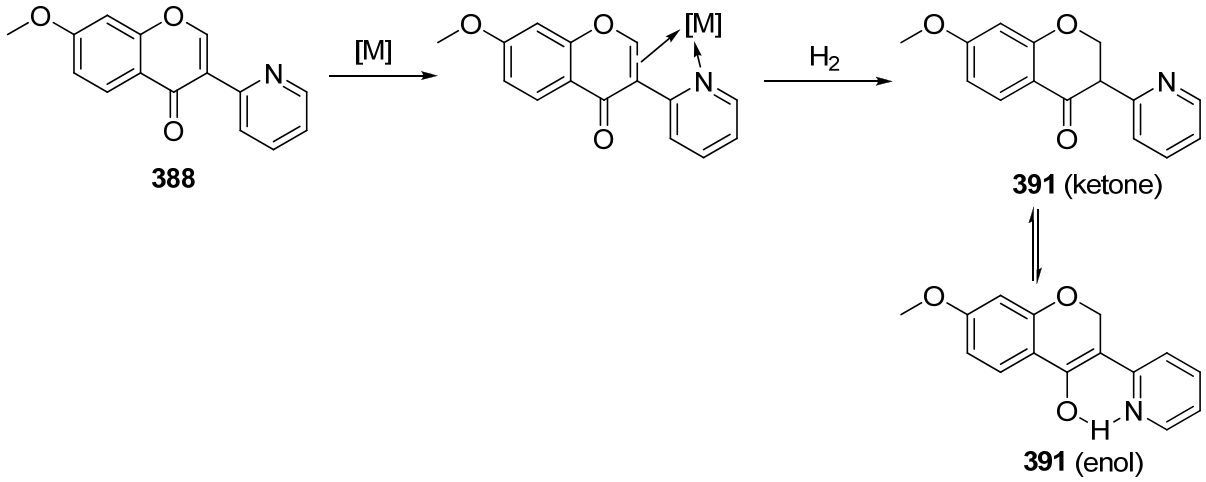


Schema 154

Es wurden Versuche durchgeführt, eine Korrelation zwischen der Aktivität eines bestimmten Substrats und seinen elektronischen und strukturellen Eigenschaften zu finden. Die Substrate mit hoch liegendem LUMO waren nicht aktiv. Bei den Substraten mit tief liegendem LUMO hängt die Reaktivität unter den Bedingungen der Nucleophilhydrierung von den restlichen funktionellen Gruppen im Molekül ab. Eine sterische Hinderung neben dem Atom, das vom Nucleophil angegriffen wird, behindert die Hydrogenierung. Es sieht so aus, dass alles das, was vom katalytisch aktiven Komplex angegriffen wird, auch reduziert wird. Manchmal betrug die Konversion nur 2% (in Gegenwart von 1 mol-% an Katalysator **286c**). Das hängt warscheilich von der parallelen Reaktion der Katalysatordeaktivierung durch die Base ab.

7-Methoxy-3-(pyridin-2-yl)chromon **388** ist ein elektronenarmes Alken mit funktionalisierter C=C-Bindung (Schema 155). Es wurde homogen mit verschiedenen Iridiumkomplexen sowohl unter elektrophilen als auch nukleophilen Bedingungen hydriert wobei die Ausbeuten vom **391** bis 99% erzielt wurden. Die Rhodiumkomplexe waren in der homogene Hydrierung von **388** nicht effektiv.

Der Substanz **391** ist durch die Bildung einer neuen Wasserstoffbindung sehr leicht enolizierbar (Schema 155). Die Enolisierung läuft auch in einem weniger polaren Lösungsmittel und in festem Zustand ab. Die Enolisierung macht die Synthese enantiomerreiner Verbindung **391** unmöglich.



Schema 155

Die Flavonoide stellen wie oben gezeigt eine einzigartige Klasse der Alkene dar, für die die homogene Hydrogenierung bis jetzt nicht bekannt war (außer bei einzelnen funktionalisierten Vertretern). Es wurde gezeigt, dass die gestellte Aufgabe über die traditionelle (elektrophile) homogene Hydrierung nicht gelöst werden kann. Es wurde jedoch eine neue Reaktion gefunden, die Nucleophilhydrierung. Nach dem jetzigen Stand der Entwicklung hat die Nucleophilhydrierung mit Ir-Komplexen nur akademische Bedeutung. Die Bestimmung des Mechanismus ist für praktische Nützung sehr wichtig. Die Homogenhydrierung von 7-Methoxy-3-(pyridin-2-yl)chromon ist sehr effektiv sowohl bei elektrophiler als auch in nukleophiler Durchführung, und liefert das entsprechende Chroman-4-on mit fast quantitativer Ausbeute.

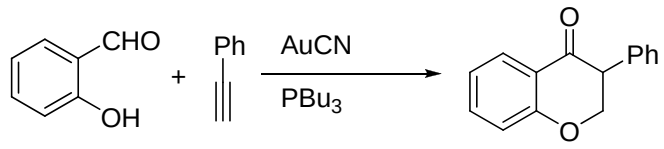
6 OUTLOOK

Concerning the Ir-catalyzed nucleophilic hydrogenation, a headway can be achieved only if the mechanism is determined and the calalytically active complex is synthesized. If the latter does not need the base activation (or needs only one equivalent of the base), the problem of base-induced deactivation of valuable Ir-complex will be solved, thus allowing to enhance conversions, use less of the catalyst, and synthesize much more active complexes.

According to preliminary research of Dr. Jérémie Pelletier and Dr. Jonathan Iggo (University of Liverpool), the transformations of **286c** in conditions of nucleophilic hydrogenation could be traced with help of NMR under high pressure of hydrogen. This research is kindly acknowledged.

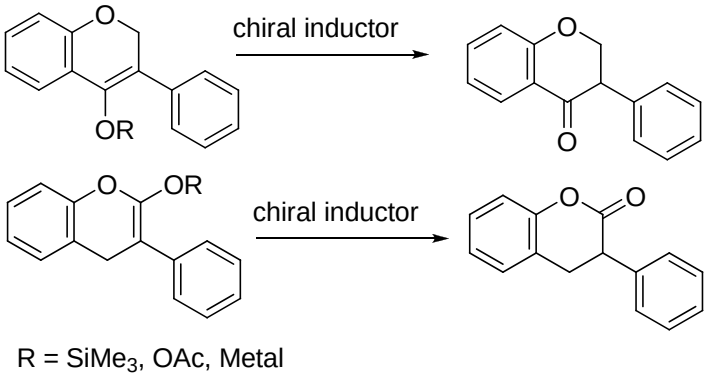
Concerning the enantioselective synthesis of flavonoids, the Ir-catalyzed nucleophilic hydrogenation has sense only if the mechanism is established and more active catalysts are synthesized.

Otherwise for synthesis of chiral isoflavanones the gold-catalyzed annulation of salicylaldehydes with aryl acetylenes can be used[427]. Although the achiral version is known now, the application of chiral ligands makes to expect some ee. Unfortunately, this reaction is very dependent on the phosphine-ligand, and the selection of active chiral phosphine can be very complicated.



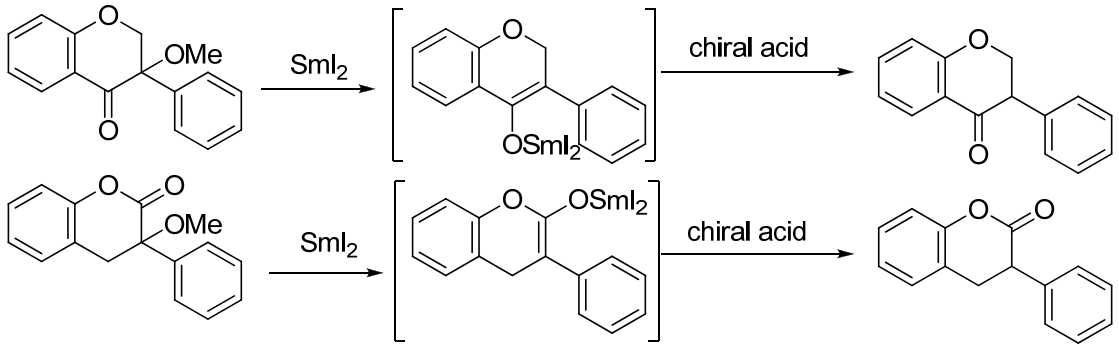
Scheme 156

Another possibility to synthesize chiral isoflavones and 3-arylcoumarins could be a reaction of enol protonation (scheme 157)[295, 428]:



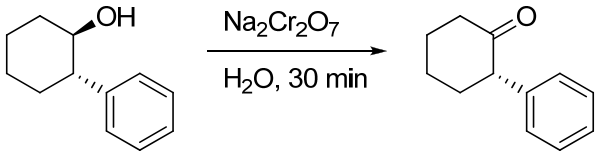
Scheme 157

Interesting reaction is the protonation of enols, derived from SmI_2 and 2-methoxy-2-aryl-cyclohexanones (scheme 158)[429]. It can be also applicable for flavonoids:



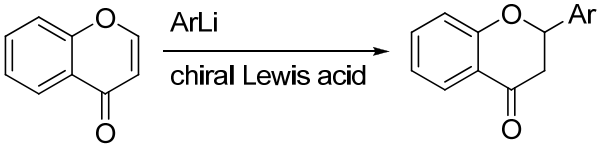
Scheme 158

Although the isoflavones are very racemization-sensitive, the careful oxidation of chiral isoflavonol could be a method of synthesis of enantiomerically pure isoflavanones (example on 2-phenylcyclohexanol, scheme 159[430]):



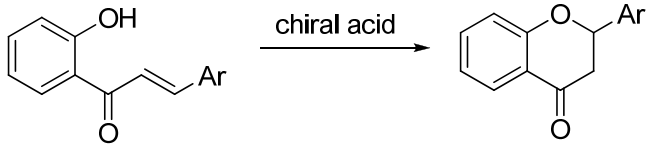
Scheme 159

Chromones are known to react with organometallics in presence of Lewis acids[431], and an application of a chiral Lews acid could be a method of flavanones' synthesis (scheme 160).



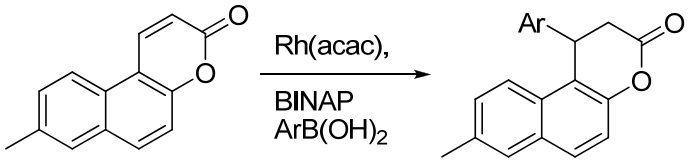
Scheme 160

Another method of synthesis of chirally pure flavanones could be a careful cyclization of chalcones by chiral acids:



Scheme 161

A rhodium-catalyzed enetioselective Heck-reaction was applied for enantioselective synthesis of neoflavanones[432].



Scheme 162

As it was mentioned in section 1.2.5, the neoflavones enter to homogeneous metallocomplex-catalyzed hydrogenation[191, 192, 298, 299] after activation by bases. One chromone was enantioselectively reduced by Ipc_2BH[158] (section 1.1.6).

Concerning the immobilization techniques, the grafting *via* organometallics could be a new versatile method for synthesis of grafted silica gels. Such methods is already known[433], but the grafting was performed without linker. The absence of linker is very undesirable in case of ligand grafting, because the catalytically active complex stays too close to the supporter, and cannot effectively react with the substrates. The problem, how to prepare halogen-free organometallics at -78º C should be solved, since at r.t. the organolithium compound decomposes the C-P-bond, hence the phosphorus-ligand is destroyed.

3-Heteroarylchromones should represent apropriate substrates for Ir-catalyzed homogeneous hydrogenation, if heteroatom makes the C=C-bond sterically functionalized. Various 3-heteroarylchromones should be hydrogenated, and the biological activity of obtained chroman-4-ones should be tested. It were also interesting to check the hydrogenation of 2-heteroarylchromones, since 2-heteroarylchroman-4-ones are also potentially biologically active compounds.

7 EXPERIMENTAL SECTION

All operations with air- and moisture-sensitive compounds were carried out in nitrogen or in argon atmosphere (for nitrogen-sensitive compounds) using the Schlenk-and-syringe techniques, or in MBRAUN Labmaster 130 glovebox (filled with nitrogen). Nitrogen or argon line was equipped with safety valve that allowed the maximal overpressure 100 mbar. The safety valve allowed to work under pressure of nitrogen in quasi-corked apparature.

The reactions under high pressure were performed in stainless-steel autoclaves from Carl-Roth (50 ml) or Berghof (250 ml) in teflon-vessels.

The sovents were absolutized by distillation in nitrogen atmosphere over the corresponding compounds: toluene, NEt_3, MeOH, pyridine: metallic Na; benzene, THF, Et_2O, MTBE, hexane, pentane: Na/K (1/3) alloy; CH_2Cl_2, $CHCl_3$, PhCl, PhBr: CaH_2. DMF was stored over P_2O_5 for 6 month and distilled in vacuum. Deoxygenated solvents were prepared from the usual solvent (p.a. or HPLC grade) by bubbling of nitrogen for 30 min. DIPEA was distilled in vacuum over ninhydrin, then twice over LiH.

If otherwise not stated, the other chemicals were purshased from Acros, Sigma-Aldrich, Fluka, Merck KGaA, ABCR, AlfaAesar, Strem, Carl-Roth and used “as is”, but the solvents of technical grade were distilled before using. A part of reagents was taken from the collections of chemicals of AG Groth.

Reactions under ulrasound sonication were performed using standard ultrasonic bath (Elma Transsonic T 460/H, 35 kHz), eqiupped with heater.

Column chromatography was performed on MN Kieselgel 60 M (silica gel, 40-63 μm 230-400 mesh ASTM, Macherey-Nagel, Düren, Germany) or on neutral or basic alumina from Fluka (0.05-0.15 mm, Brokmann activity I).

TLC was performed on polymeric plates Polygram Sil G/UV_{254} (0.2 mm of silica gel, Macherey-Nagel, Düren, Germany), or on aluminium plates from Merck (silica gel 60 or neutral alumina, F254). The spots were observed under UV-lamp or visualized by phosphor-molybdene acid pentahydrate (5% solution in EtOH).

Analytical HPLC was performed on Merck RP-18 column (250x4.1 mm) using gradient or isocratic eluation by acetonitrile-water mixture (UV detection at 254 nm).

Analytical chiral HPLC was performed on Daicel Chiralpack IA column (250x4.1 mm, amylose tris (3,5-dimethylphenylcarbamate) immobilized on 5μm silica-gel).

Analytical GC/MS was performed on HP GC/MS 5890/5972 instrument (EI, 70 eV) equipped with Phenomenex Zebron ZB-5 column (30m x 0.25mm x 0.25μm). Helium was used as carrier gas.

HRMS ESI/FT-ICR were recorded on Bruker APEX II FT/ICR instrument with 7 Tesla magnet in positive polarisation, by Rheinhold Weber. HRMS ESI/TOF were recorded on Bruker Daltonics microTOF II, using sodium formate as internal standard, in positive polarisation, by Sascha Keller.

Rotation angles were measured on the Perkin-Elmer 241 polarimeter with 5 sec integration time.

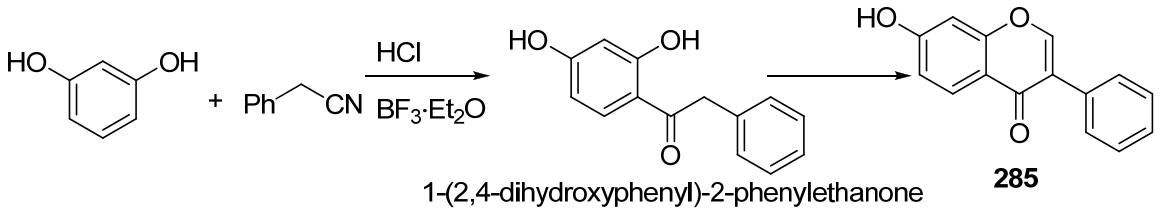
NMR spectra were recorded on Bruker Avance DRX600 (600 MHz), Jeol JNM-LA 400 (400 MHz), Varian ^{UNITY}*INOVA* 400 (400 MHz) or Bruker Avance 400 (400 MHz). Reference standards are: tetramethylsilane (internal) for ^{1}H, ^{31}C and for ^{29}Si NMR, 85% aqueous H_3PO_4 (external) for ^{31}P NMR, $Et_2O{\cdot}BF_3$ (external) for ^{11}B NMR, $CFCl_3$ (internal) for ^{19}F NMR. Spin-spin coupling constants (J) are given in Hertz. Folowing abbreviations are used for multiplicity: s – singlet, d – doublet, t – triplet, q – quartet, sep – septet, dd - doublet of doublets, dt - doublet of triplets, m – multiplet, nrm – not resolved multiplet.

7.1 Attempts to hydrogenate model flavonoids

Dry K_2CO_3 was prepared from the commercially available K_2CO_3 by heating it at 500º C (heatgun) in deep vacuum during one hour, cooling and storing in a tightly closed containder, or similarly by heating at 200º C (oil bath) for 10 h in deep vacuum. Complex [Ru(R-BINAP)$(OAc)_2$] was synthesized from [Ru(benzene)$Cl]_2$ and R-BINAP according to the known procedure[364]. The complex [Ru(benzene)$Cl]_2$ was synthesized from $RuCl_3{\cdot}3H_2O$ and cyclohexa-1,4-diene (Acros) according to the known procedure[434]. NaBARF is synthesized according to the published procedure[435] from 3,5-bis(trifluoromethyl)benzene (Fluorochem) and $NaBF_4$ (from Fluka, dried in vacuum of oil pump at 250º C overnight). 3-Phenylcoumarin **293**[436] and isoflavone **3**[437] synthesized according to the known procedures. [Rh$(PPh_3)_3$Cl], coumarin, (+)-Diisopropyl L-tartrate, ethyleneglycol (Fluka), [Ru$(PPh_3)_3Cl_2$] (Lancaster), [Rh(COD)$Cl]_2$, flavone (Acros), [Rh$(COD)_2$]OTf, chromone (Aldrich) are commercially available. [Ir(COD)$Cl]_2$ was purshased from Chempur, Acros, ABCR or obtained as a gift from Umicore. 7-Hydroxy-3-phenylcoumarin and 7-hydroxy-4-phenylcoumarin obtained from Garazd Ya. L, Garazd M. M and from Moskvina V. as gifts,

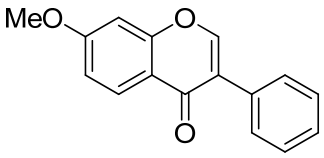
racemic or enantiomerically pure BINAP and $RuCl_3 \cdot 3H_2O$ obtained from MCAT as gifts. All gifts are kindly aknowleged.

7-Hydroxyisoflavone 285



1-(2,4-dihydroxyphenyl)-2-phenylethanone synthesized with help of Frasyniuk M. from resorcinol and phenylacetonitrile in $BF_3 \cdot Et_2O$ by bubbling of dry HCl, according to the published procedure for Houben-Hoesch reaction[370, 438]. The crude 1-(2,4-dihydroxyphenyl)-2-phenylethanone was converted to 7-hydroxyisoflavone **285** according to the published procedure for Wilsmeyer reaction[370, 438].

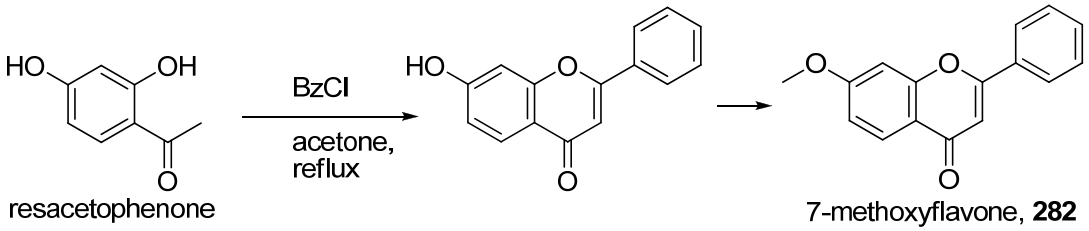
General procedure A for methylation of model flavonoids (example on **285**)



281

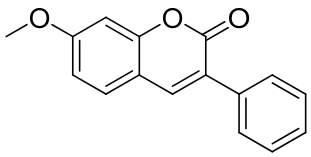
In nitrogen atmosphere 5 g (0.021 mol) of 7-hydroxyisoflavone **285** and 26.1 g (0.189 mol) of dry K_2CO_3 were suspended in 100 ml of dry acetone. 6 Ml (0.063 mol) of dimethylsulfate were added *via syringe* and the mixture was stirred for 4 hours (TLC controlled). After completion the mixture was poured in 1L of water and stirred 2 hours. The precipitated product was filtrated and washed by water. Yield of **281** is quantitative. The refluxing in acetone or in DMF is not recommended, since the reaction needs 36 h to complete (in DMF) and the yield is understated. Spectral properties of 7-methoxyisoflavone are in accordance with the published[439].

7-Methoxyflavone 282



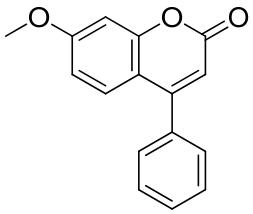
7-Hydroxyflavone synthesized according to the published procedure[440]. Methylated according to the **general procedure A.** Spectral properties of 7-methoxyflavone are in accordance with the published[441].

7-Methoxy-3-phenylcoumarin 283



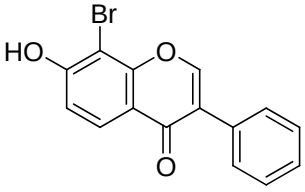
Synthesized form the corresponding 7-hydroxy-3-phenylcoumarin according to the **general procedure A**. Spectral properties are in accordance with the published[442].

7-Methoxyneoflavone 284



Synthesized form the corresponding 7-hydroxyneoflavone according to the **general procedure A**. Spectral properties are in accordance with the published[443].

8-Bromo-7-hydroxyisoflavone 288



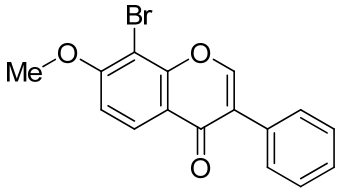
Synthesized according to the known procedure[368] with yield of 81%. ^{1}H NMR corresponds to the published[444], but the assignment of the NMR-spectra was not earlier performed.

^{1}H NMR (DMSO, 400 MHz): δ = 7.13 (d, J 9.0, 1H, 6-H), 7.36-7.48 (m, 3H, 3`-H and 4`-H), 7.85 (m, 2H, 2`-H), 7.99 (d, J 9.0, 5-H), 8.55 (s, 1H, 2-H), 11.69 (s, 1H, OH)

^{13}C NMR (DMSO, 100 MHz): δ = 96.68 (8-C), 114.59 (6-CH), 117.58 (10-C), 123.63 (3-C), 125.84 (5-CH), 127.90 (4`-CH), 128.13 (3`-CH), 128.96 (2`-CH), 131.66 (1`-C), 154.06 (2C, 2-CH and 9-C), 159.72 (7-C), 174.19 (4-C).

HRMS ESI/FT-ICR, observed (calculated): [M+H^{+}] 316.9829, 318.9810 (316.9813, 318.9793); [M+Na^{+}] 338.9627, 340.9619 (338.9633, 340.9612).

8-Bromo-7-methoxyisoflavone 289



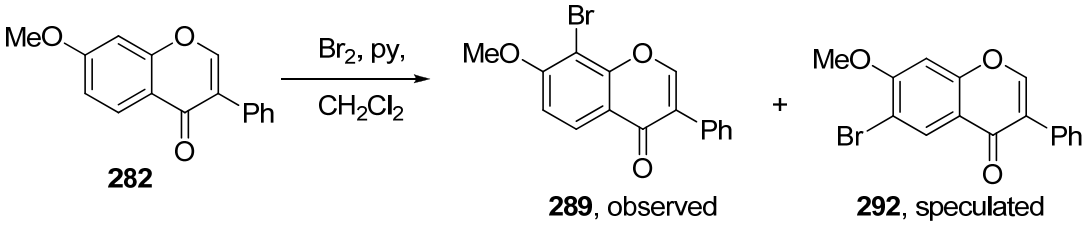
Synthesized form the corresponding 8-bromo-7-hydroxyisoflavone according to the **general procedure A** with yield of 95%.

^{1}H NMR (DMSO, 400 MHz): δ = 4.01 (s, 3H, Me), 7.03 (d, J 9.0, 6-H), 7.36-7.48 (m, 3H, 3`-H and 4`-H), 7.56 (m, 2H, 2`-H), 8.04 (s, 1H, 2-H), 8.23 (d, J 9.0, 5-H)

^{13}C NMR (DMSO, 100 MHz): δ = 56.92 (Me), 99.32 (8-C), 109.51 (6-CH), 119.42 (10-C), 125.03 (3-C), 126.73 (5-CH), 128.31 (4`-CH), 128.50 (3`-CH), 128.93 (2`-CH), 131.42 (1`-C), 152.94 (2-C), 154.08 (9-C), 160.30 (7-C), 175.32 (4-C).

HRMS ESI/FT-ICR, observed (calculated): [M+H^{+}] 330.9971, 332.9950 (330.9970, 332.9949).

Bromination of 7-methoxyisoflavone



276 Mg (1.1 mmol) of 7-methoxyisoflavone were dissolved in 20 ml of absolute dichloromethane. 3.6 ml (44 mmol) of dry pyridine were added, and the mixture was cooled to 0º C. 2.3 Ml (44 mmol) of bromine were added, the flask was sealed and the mixture was stirred overnight in dark. In *ca* 11 h the solution was carefully poured in aqueous $NaHSO_3$, extracted with dichloromethane (5x50 ml), dried by Na_2SO_4, filtrated and evaporated. The ^{1}H

NMR of the crystalline rest revealed the presence of the starting material (13.5 %), unidentified compound (tentatively 6-bromo-7-methoxyisoflavone, 16.6 %) and 8-bromo-7-methoxyisoflavone (69.9%). The presence of 7-methoxyisoflavone and of 8-bromo-7-methoxyisoflavone is confirmed by comparison with ^{1}H NMR-spectra of the pure compounds. The mass-spectrum (ESI) of this rest showed only the peaks of starting 7-methoxyisoflavone (253, [M+H^{+}]) and of monobrominated 7-methoxyisoflavone (331 and 333, [M+H^{+}]). Unidentified compound and 8-bromo-7-methoxyisoflavone are coeluated during HPLC on reverse-phase and were not separated.

Unidentified compound is tentatively **292**, since two characteristic singlets in ^{1}H NMR spectrum (at 6.81 and 8.38 ppm) could be observed. 2-H of this substance goes together with 2-H of **289** at 8.00 ppm. In ^{13}C NMR spectrum three characteristic signals of 2-CH carbons can be observed: at 152.94 (belongs to **289**), at 152.63 and at 152.69 ppm. One of them belongs to educt, the other – to **289**. If the third compound were 2-brominated, only two signals were observed in region 151-153 ppm. The NMR spectra of the mixture are presented on the figures 11-14.

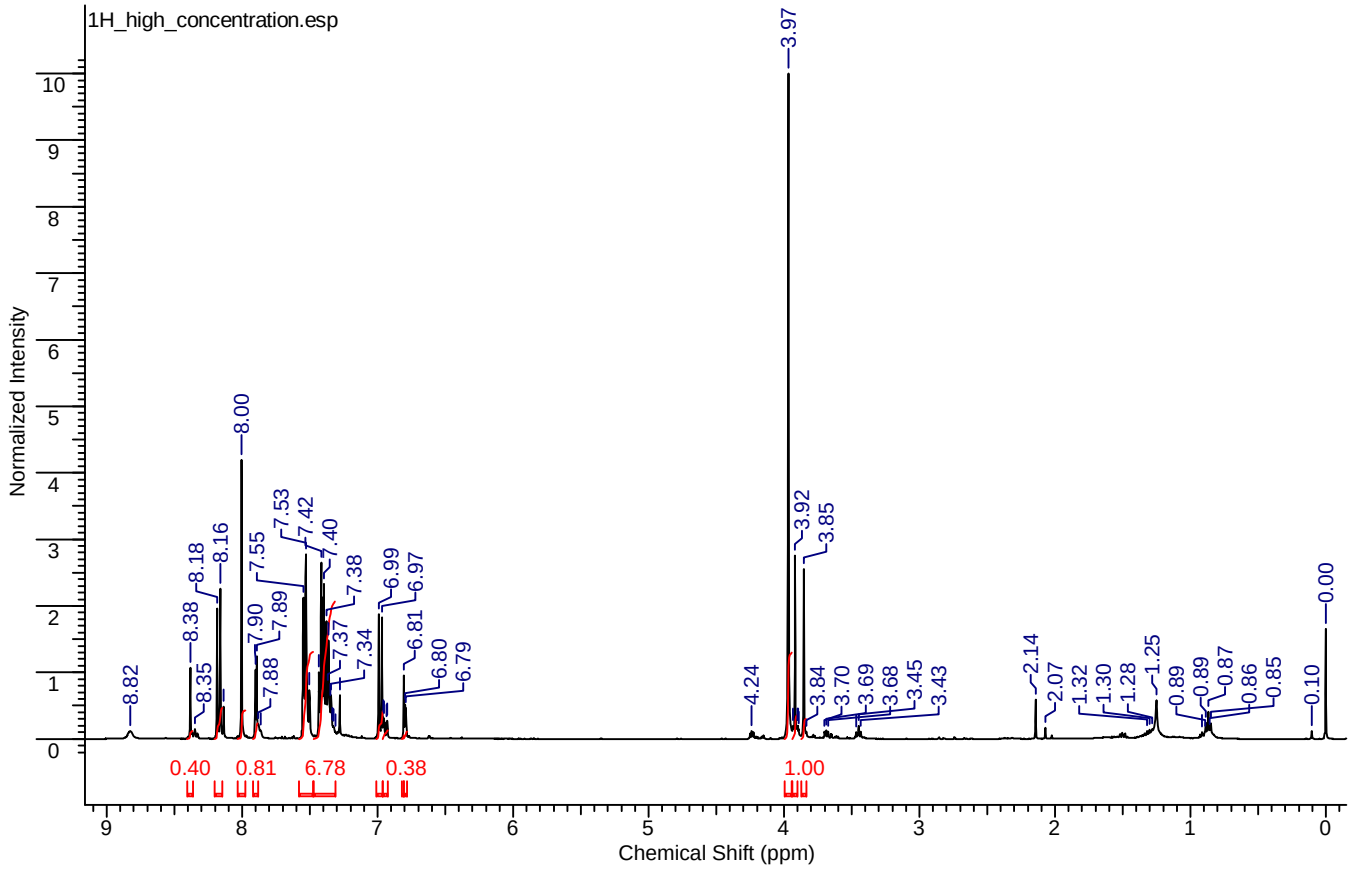


Figure 11: ^{1}H NMR spectrum of reaction mixture after bromination of 281

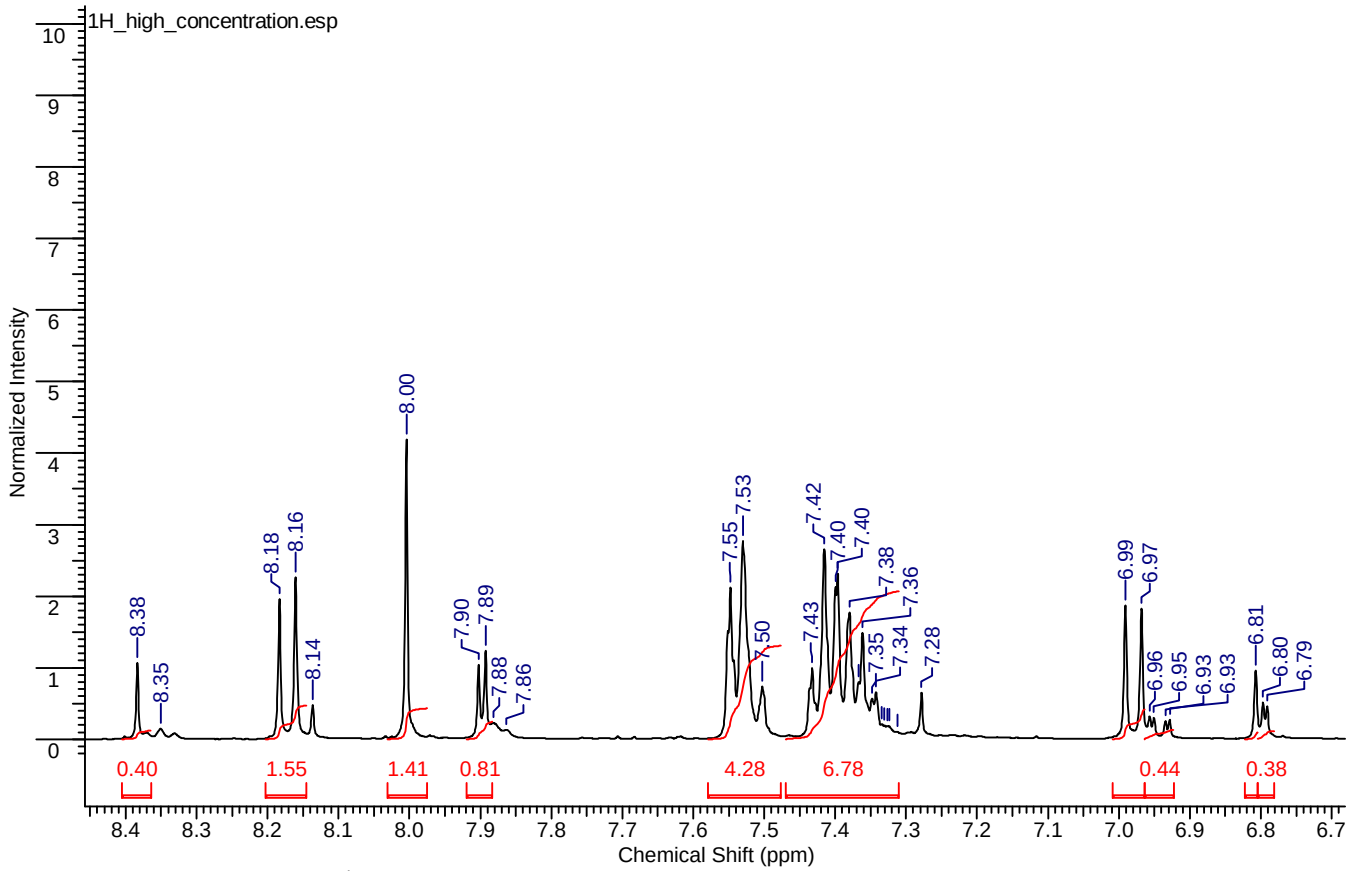


Figure 12: ^{1}H NMR spectrum of reaction mixture after bromination of 281

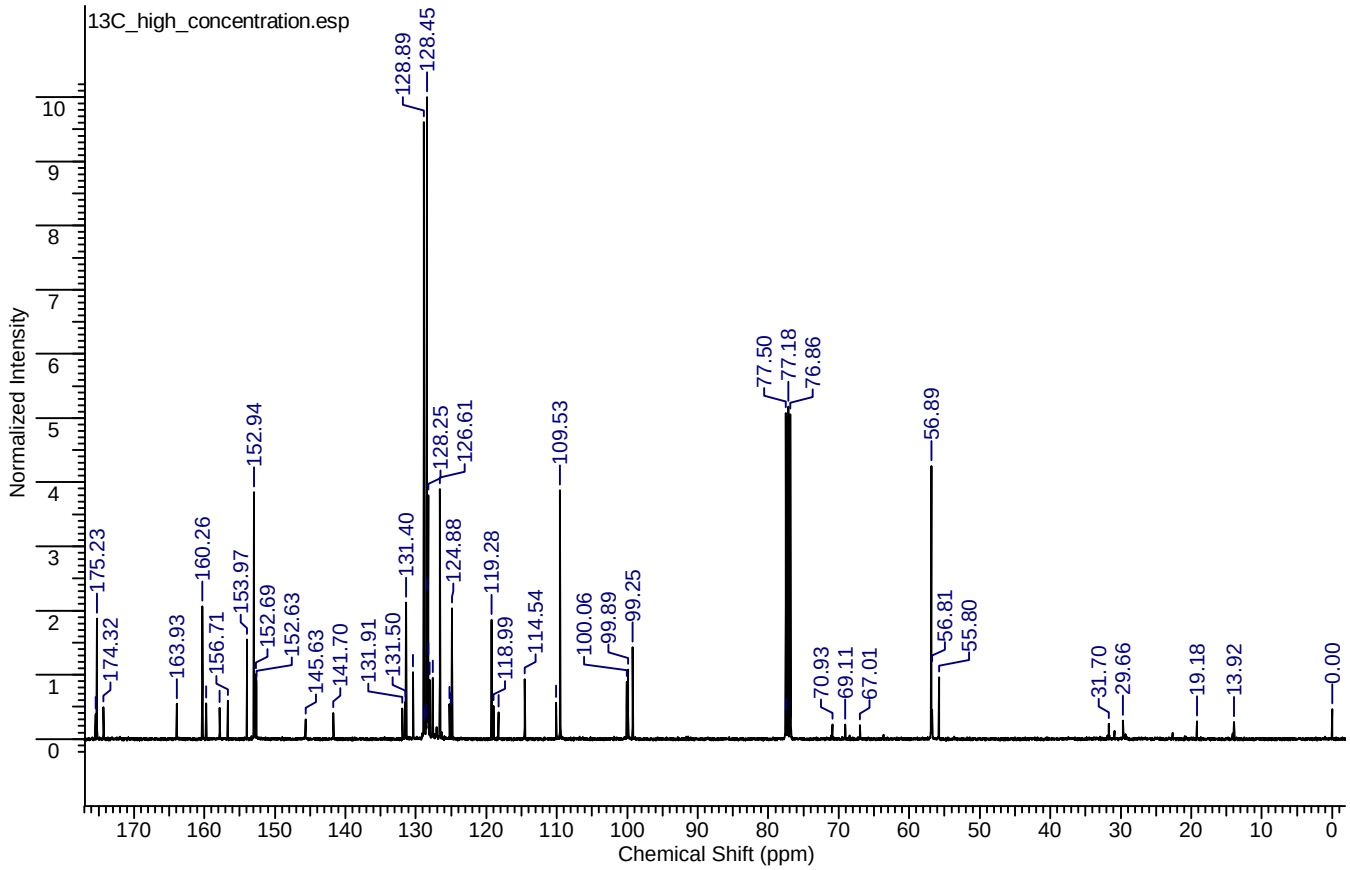


Figure 13: ^{13}C NMR spectrum of reaction mixture after bromination of 281

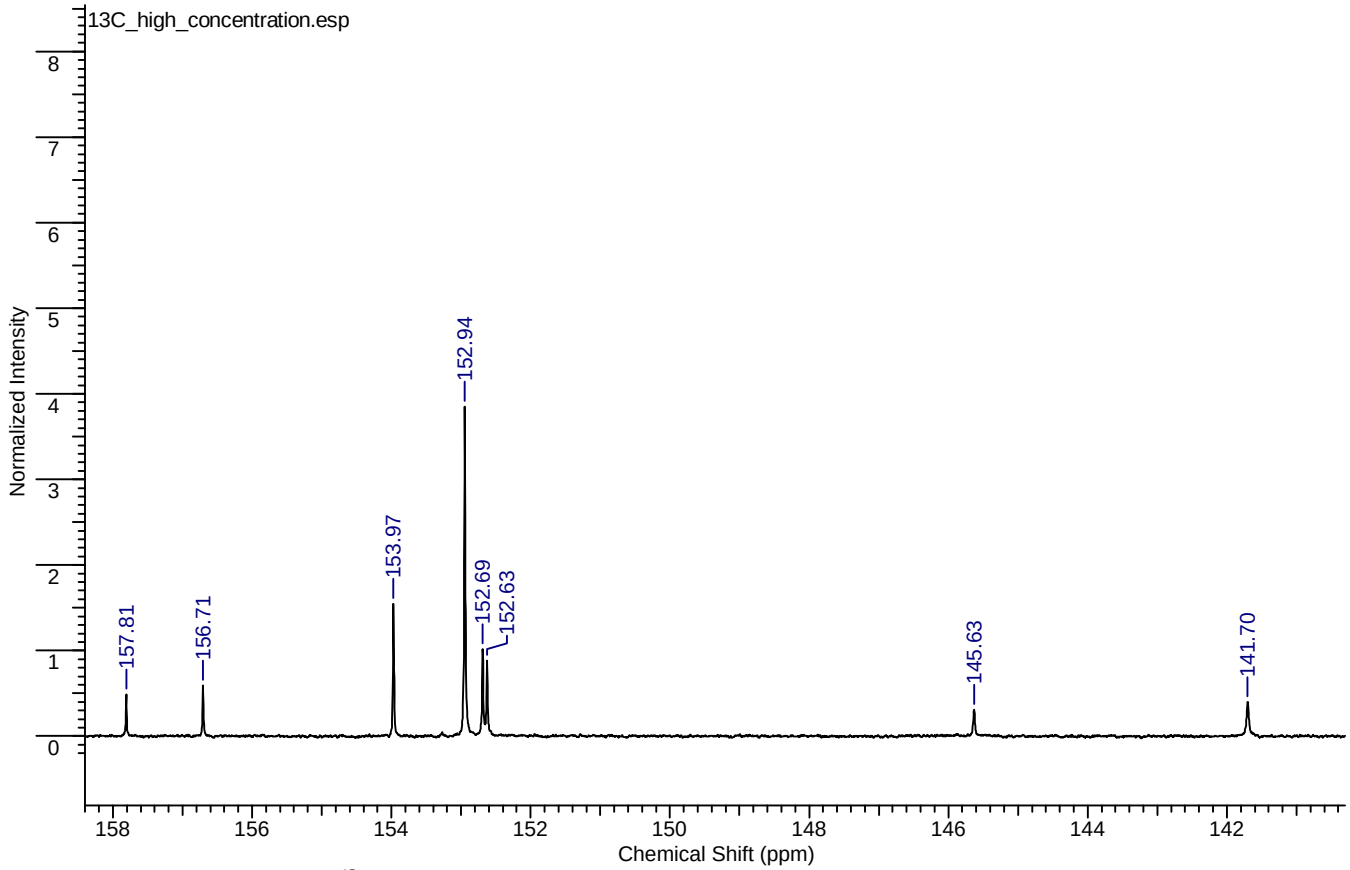
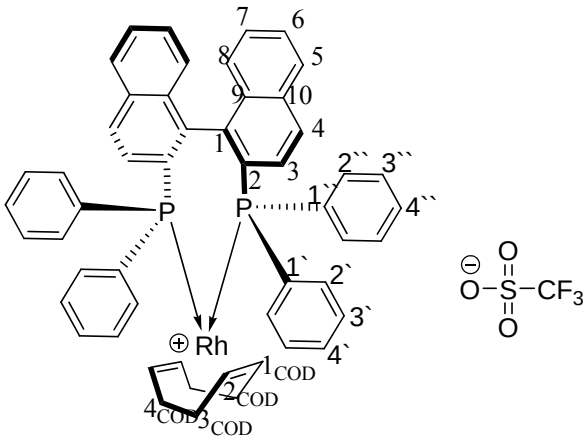


Figure 14: ^{13}C NMR spectrum of reaction mixture after bromination of 281

Rhodium (1,5-cyclooctadiene) (rac-2,2`-Bis(diphenylphosphino)-1,1`-binaphtyl) triflate, [Rh(COD)(rac-BINAP)]OTf



In glovebox 98 mg (0.21 mmol) of $[Rh(COD)_2]OTf$ and 140 mg (0.225 mmol) of rac-BINAP were placed in a glass flask, the mixture was dissolved in 2 ml of absolute CH_2Cl_2 and stirred for 3 h at r.t. The solution was evaporated to a volume of 0.1 ml and 10 ml of absolute Et_2O were added, which resulted in precipitation. The precipitate was collected by filtration and throughly washed with ether. The title complex (moderately air-stable even in solution) was washed off from the filter by CH_2Cl_2, evaporated *in vacuo* and dried in deep

vacuum. Yield – quantitative. The same procedure can be used for preparation of enantiomerically pure complex. Red or yellow crystalls. Stable at r.t. for 1 week, then decomposes. Should be stored at -20º C. The NMR-shifts are given for one enantiomer.

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 2.14 (m, 2H, a-4-H_{COD}), 2.33 (nrm, 2H, e-4-H_{COD}), 2.40 (nrm, 2H, a-3-H_{COD}), 2.59 (m, 2H, e-3-H_{COD}), 4.59 (q, J 6.2, 2H, 1-H_{COD}), 4.80 (m, 2H, 2-H_{COD}), 6.45 (d, 8.4, 2H, 8-H), 6.70 (t, 7.2, 4H, 3``-H), 6.80 (t, 7.2, 2H, 4``-H), 6.98 (t, 7.5, 7-H), 7.35 (nrm, 2H, 6-H), 7.37 (nrm, 4H, 2``-H), 7.51 (nrm, 2H, 4`-H), 7.53 (nrm, 8H, 2`- and 3`-H), 7.61 (d, 8.1, 2H, 5-H), 7.72 (d, 8.6, 2H, 4-H), 7.86 (m, 2H, 3-H).

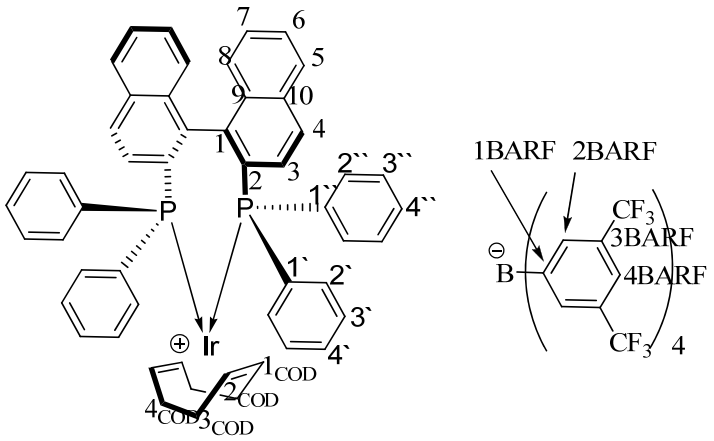
^{13}C NMR ($CDCl_3$, 150 MHz): δ = 28.76 (4-CH_{2COD}), 31.75 (3-CH_{2COD}), 97.50 (m, 2-CH_{COD}), 102.80 (m, 1-CH_{COD}), 121.10 (q, J 321.3, CF_3), 126.53 (7-CH), 126.66 (t, J 4.40, 3-CH), 126.86 (8-CH), 127.49 (6-CH), 127.71 (d, J 49.52, 1`-CP), 127.79 (t, J 5.5, 3``-CH), 127.87 (d, J 48.42, 1``-CP), 127.97 (5-CH), 128.31 (d, J 47.3, 2-CP), 128.76 (t, J 4.4, 3`-CH), 129.06 (t, J 4.4, 4-CH), 130.01 (4``-CH), 130.96 (4`-CH), 133.38 (t, J 3.3, 9-C) , 133.58 (10-C), 133.69 (t, J 4.4, 2`-CH), 134.50 (t, J 6.6, 2``-CH), 138.53 (t, 6.6, 1-C)

^{31}P NMR ($CDCl_3$, 161 MHz): δ = +26.18 (d, J 145.2)

^{19}F NMR ($CDCl_3$, 376 MHz): δ = -78.40

HRMS (ESI/FT-ICR): isotope cluster 833-835, observed (calculated): 833.1934, 100% (833.1973, 100.0%), 834.1934, 52.6% (834.2007, 56.2%), 835.1968, 17.3% (835.2040, 15.5%), 836.2078, 1.7% (836.2074, 2.8%).

Iridium (1,5-cyclooctadiene) (rac-2,2`-Bis(diphenylphosphino)-1,1`-binaphtyl) tetrakis(3,5-bis(trifluoromethyl)phenyl) borate, [Ir(COD)(rac-BINAP)]BARF, 334



A solution of 50 mg (0.0744 mmol) of $[Ir(COD)Cl]_2$ and 92.6 (0.149 mmol) of rac-BINAP in 5 ml of absolute CH_2Cl_2 was refluxed for 1 h. After cooling to r.t. 133 mg (0.15 mmol) of NaBARF were added and the mixture was stirred 2 hours (TLC controlled, eluated

by CH_2Cl_2). Purification by silica gel column chromatography (CH_2Cl_2) yielded 229 mg (86%) of [Ir(COD)(rac-BINAP)]BARF. Red crystalls. Stable at r.t. for 1 week, then decomposes. Should be stored at -20º C.

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 1.85 (m, 2H, a-4-H_{COD}), 2.08 (m, 2H, e-4-H_{COD}), 2.23 (m, 2H, a-3-H_{COD}), 2.34 (2H, m, e-3-H_{COD}), 4.20 (q, J 6.0, 2H, 1-H_{COD}), 4.49 (m, 2H, 2-H_{COD}), 6.47 (d, J 8.6, 2H, 8-H), 6.65 (t, J 7.3, 4H, 3`-H), 6.77 (t, J 7.3, 2H, 4`-H), 7.03 (t, J 7.7, 2H, 7-H), 7.24 (br t, J 9.7, 4H, 2`-H), 7.36 (t, J 7.3, 2H, 6-H), 7.52 (br s, 10H, 2``-, 3``-, 4``-H), 7.55 (br s, 4H, 4-H_{BARF}), 7.60 (d, J 8.3, 2H, 5-H), 7.69 (d, J 8.8, 2H, 4-H), 7.77 (br s, 8H, 2-H_{BARF}), 7.85 (br t, J 8.6, 2H, 3-H).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 29.29 (4-CH_{2COD}), 32.39 (3-CH_{2COD}), 85.88 (t, J 5.7, 2-CH_{COD}), 90.54 (t, J 5.7, 1-CH_{COD}), 117.46 (br s, 4-CH_{BARF}), 124.57 (q, J 273, CF_3), 126.13 (d, 57.4, 1`-C), 126.17 (d, J 58.5, 1``-C), 126.45 (t, J 4.40, 3-CH), 126.87 (7-CH), 127.01 (d, J 60.8, 2-C), 127.06 (8-CH), 127.79 (t, J 4.6, 3``-CH), 127.92 (5-CH), 127.97 (6-CH), 128.70 (t, J 4.6, 3`-CH), 128.9 (br q, J 30, 3-C_{BARF}), 130.23 (4``-CH), 131.50 (4`-CH), 133.66 (t, 4.6, 9-C), 133.69 (10-C), 133.93 (t, J 4.6, 2`-CH), 134.49 (t, J 6.9, 2``-CH), 134.82 (br s, 2-CH_{BARF}), 138.97 (t, J 6.9, 1-C), 161.74 (q 1:1:1:1:, J 50.5, 1-C_{BARF}).

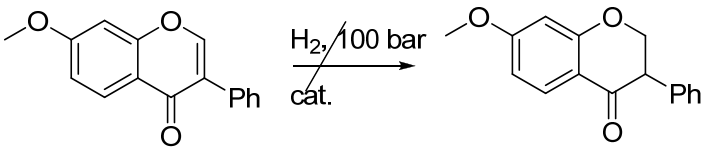
^{31}P NMR ($CDCl_3$, 161 MHz): δ = +16.0

^{19}F NMR ($CDCl_3$, 128 MHz): δ = -62.8.

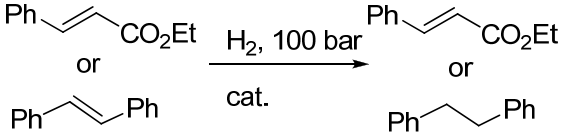
^{11}B NMR ($CDCl_3$, 376 MHz): δ = -6.9.

HRMS (ESI/FT-ICR): isotope cluster 921-926, observed (calculated): 923.2518, 100% (923.2547, 100.0%), 921.2551, 49.9% (921.2524, 59.5%), 924.2451, 67.7% (924.2581, 56.2%), 922.2594, 28.8% (922.2558, 33.5%), 925.2481, 17.5% (925.2615, 15.5%).

General procedure B



or other model flavonoids



The complex of rhodium (4-5 mg) was weighted into the glass vessel ([$Rh(PPh_3)_3Cl$] was weighted in glovebox, [Rh(COD)(rac-BINAP)]OTf – under air), it was quickly charged under air with substrate (20 equivalent, relative to the catalyst), degased or absolute solvent

(3-4 ml), optionally with triethylamine (10 or 100 eq) and thiophene (1 drop) and sealed in the 50 ml autoclave. The autoclave was purged three times with hydrogen, then charged with hydrogen to presssure of 100 bar and hydrogenated for 2-12 h. After ventilation to atmosphere the reaction mixture was subjected to GC/MS, evaporated and subjected to NMR in $CDCl_3$ or in DMSO-d_6 to show the conversion of the educt.

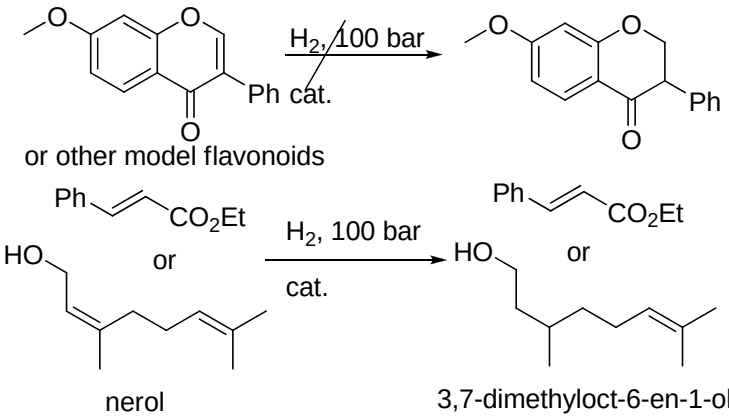
General procedure C

The complex $[Rh(COD)Cl]_2$ (4-5 mg) and rac-BINAP (2.2 eq) were weighted in glovebox into the glas flask. After extraction from the glovebox absolute or degased solvent (3-4 ml) was added under nitrogen and the mixture was stirred for 10 minutes. Substrate (20 eq), optionally triethylamine (10 or 100 eq) and thiophene (1 drop) were weighted in a glass vessel, the mixture, containing [Rh(COD)(rac-BINAP)Cl] was transferred to this glass vessel quickly under air, and it was sealed in the autoclave. Further operations acccording to the **general procedure B**.

General procedure D

The complexes or type $[Ir(COD)L_2]BARF$ and [Rh(COD)(rac-BINAP)]OTf are air- and moisture-stable, hence can be precisely weighted under air on analytical balance. The catalyst (1-3 mg) was weighted in a glas or teflon vessel. To this vessel substrate (100 eq) and absolute or degased solvent (2-3 ml) were added quickly under air, and it was sealed in the autoclave. Further operations acccording to the **general procedure B**.

General procedure E



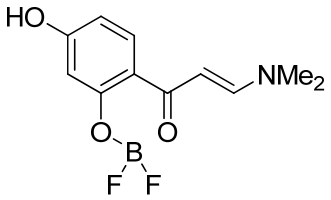
The complexes of ruthenium are very air-sensitive (oxygene causes the oxidation of ruthenium to Ru(III)), hence the autoclave should be charged in glovebox. 4-5 Mg of ruthenium complex were weighted into a glass vessel, the substrate (20 eq) and absolute or

degased solvent (3-4 ml) were added, and the vessel was sealed in the autoclave. The use of 250 ml autoclave allowed to run up to 8 reactions (in various solvents) simultaneous. The tightly closed autoclave was extracted from the glovebox, and connected to the hydrogen high-pressure cylinder. The connection hose was evacuated and purged by nitrogen three times, then an autoclave was charged with hydrogen to the pressure of 100 bar. Hydrogenation was performed overnight (ca. 12 h), and reaction mixture was analysed according to the **general procedure B**.

General procedure F

The method, applied by M. J. Fehr et al.{Fehr, 1999 #430} was used. The standard solution of $HBF_4 \cdot Et_2O$ and of DIPEA in degased MeOH were prepared and evacuated to the glovebox. 4-5 Mg of ruthenium complex were weighted into a glass vessel, then a calculated amount of the basic or acidic MeOH was added (in order to achieve wished Ru / activator ratio) followed by the absolute or degased solvent. The mixture was stirred 1.5 h in glovebox, then substrate (20 eq) was added and the vessel was sealed in the autoclave. The use of 250 ml autoclave allowed to run up to 8 reactions (vith various amount of activator) simultaneous. Further operations were performed according to the **general procedure E**.

(E)-1-(2-(difluoroboryloxy)-4-hydroxyphenyl)-3-(dimethylamino)prop-2-en-1-one



5 g (33 mmol) of resacetophenone were dissolved in 25 ml of dry DMF, to this solution 12.68 ml (0.1 mol) of $BF_3 \cdot Et_2O$ were added (temperature of reaction mixture should never exceed 60º C, the use of internal thermometer is recommended), followed by 6.03 ml (66 mmol) of $POCl_3$. The resulting brown mixture was stirred for 3 h at 40º C (ultrasonic irradiation for 2 h *vs* conventional magnetical stirring is highly recommended). The mixture was poured onto 500 ml of ice, allowed to stay for 24 h and filtrated. The brown precipitate was washed with water and dried. After drying it was refluxed with EtOH, cooled, filtrated and crystalline yellow precipitate was washed with EtOH, yielding 4.2 g (50%) of **(E)-1-(2-(difluoroboryloxy)-4-hydroxyphenyl)-3-(dimethylamino)prop-2-en-1-one**.

^{1}H NMR (DMSO, 400 MHz): δ = 3.20 (s, 3H, Me), 3.39 (s, 3H, Me), 6.05 (d, J 11.4, 1H, 2-H), 6.22 (d, J 2.5, 1H, 3-H_{Ar}), 6.40 (dd, J 2.5, J 9.0, 1H, 5-H_{Ar}), 7.90 (d, J 9.0, 1H, 6-H_{Ar}), 8.31 (d, J 11.4, 3-H), 10.59 (s, 1H, OH).

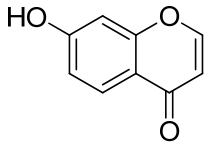
^{13}C{1H} NMR (DMSO, 100 MHz): δ = 38.51 (Me), 46.19 (Me), 87.90 (2-CH), 103.70 (3-CH_{Ar}), 108.52 (1-C_{Ar}), 109.18 (5-CH_{Ar}), 130.20 (6-CH_{Ar}), 158.67 (3-CH), 161.45 (2-C_{Ar}), 165.32 (4-C_{Ar}), 176.19 (1-C).

^{19}F NMR (DMSO, 376 MHz): δ = -142.90 (s, 0.2F, ^{10}B$\underline{F_2}$), -142.96 (s, 0.8F, ^{11}B$\underline{F_2}$).

^{11}B NMR (DMSO, 128 MHz): δ = +0.23 (s)

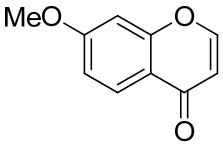
HRMS (ESI/FT-ICR), [M-F^-] 236.0888 (236.0894); [M+Na^+] observed (calculated): 278.0747 (278.0776).

7-Hydroxychromone



1 G (3.9 mmol) of **(E)-1-(2-(difluoroboryloxy)-4-hydroxyphenyl)-3-(dimethylamino)prop-2-en-1-one** was boiled in 20 ml of 37% aqueous HCl for 5 minutes. The solution has changed the colour to red. The mixture was evaporated, dried under deep vacuum, and the rest was suspended in 100 ml of water, filtrated, crystalline rest washed with water and dried, yielding 317 mg (50%) of **7-hydroxychromone**. The spectral properties correspond to those published[446].

7-Methoxychromone 53



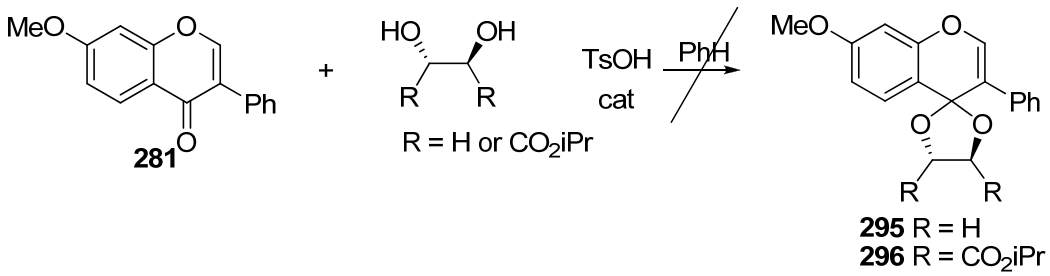
486 Mg (3 mmol) of 7-hydroxychromone and 3.732 g (27 mmol) of dry K_2CO_3 were suspended in 40 ml of dry acetone. To this suspension 0.85 ml (9 mmol) of Me_2SO_4 were added, and the resulting mixture was stirred overnight. It was poured in 400 ml of water and stirred for 2 h. The substance is good soluble in water, but was extracted with dichloromethane (5x100 ml). After drying with Na_2SO_4, filtration and evaporation of organic phase 518 mg (98%) of crude **53** were obtained (spectrally pure, but coloured in red). It was chromatographed on the column of silica gel with Et_2O, yielding 450 mg (85%) of coloured compound. Then it was dissolved in water (100 ml), treated with activated carbon (0.5 g),

refluxed for 15 min and filtrated being hot, then remainig carbon was washed with 100 ml of boiling water. Water extracts were evaporated, yielding 440 mg (83%) of pure and white **53**. Such a complicated purification is necessary in order to be sure, that no catalytic poisons are present, and the lack of hydrogenation is not connected with some impurities. Spectral properties correspond to those published[447].

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 3.84 (s, 3H, OMe), 6.21 (d, J 5.9, 1H, 3-H), 6.77 (d, J 2.2, 1H, 8-H), 6.90 (dd, J 8.8, J 2.2, 1H, 6-H), 7.72 (d, J 5.9, 1H, 2-H), 8.03 (d, J 8.8, 5-H).

^{13}C{1H} NMR ($CDCl_3$, 150 MHz): δ = 55.67 (OMe), 100.20 (8-CH), 112.73 (3-CH), 114.38 (6-CH), 118.56 (10-C), 126.96 (5-CH), 154.76 (2-CH), 158.09 (9-C), 163.94 (7-C), 176.84 (4-C).

Attempts to prepare acetals from 281.



0.5 G (2 mmol) of 7-methoxyisoflavone **281** and 0.488 g (2.1 mmol) of (+)-diisopropyl L-tartrate and catalytical quantitiy of TsOH (hydrate) were added to 30 ml of benzene and refluxed with Dean-Stark receiver overnight. The GC/MS analysis has shown only educt and no traces of product **295** in reaction mixture. The same procedure involving ethyleneglycol had the same outcome.

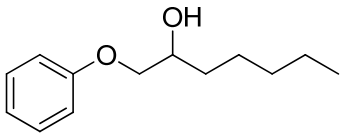
7.2 Attempts to prepare a heterogenized catalyst

tBuLi (1.5 M solution in pentane, Acros), p-bromodimethylaniline **308** (Acros), n-BuLi (as 1.6 M solution in hexane, Acros or Aldrich), lithium thienylcyanocuprate (0.25M solution in THF, Aldrich) were purshaed and used "as is". Phenylglycid **302** (Ciba) was found in collection of chemicals of AG Groth. $BF_3{\cdot}Et_2O$ (Merck) was refluxed over CaH_2 in nitrogen atmosphere, then distilled in vacuum and stored over molecular sieves (4Å) in nitrogen atmosphere at +4º C. Solid-state ^{13}C NMR CPTOSS/MAS and ^{29}Si NMR CP/MAS spectra were measured by Ulrich Haunz on Bruker Avance 400 instrument, with 100 MHz resonance frequency for ^{13}C nucleus and . IR-spectra were measured on Perkin-Elmer Spectrum 100 IR-

spectrometer with Attenuated Total Reflectance (ATR) element, i.e. the silica gel was crushed directly on diamond crystal of the ATR. ATR correction[448] was not performed.

The silica gel with grain size 60-200 μn and pore sized 150Å (Acros, product number 360085000) was used for grafting.

1-phenoxyheptan-2-ol 303



2 mmol of nBuLi were added to 7 ml of absolute THF and the mixture was cooled to -95º C in nitrogen atmosphere. 2 mmol of absolute $BF_3 \cdot Et_2O$ were added *via syringe* (temperature rised to -80º C), and after cooling to -95º C 1.33 mmol of **302** were added *via syringe* (temperature rised to -80º C). This mixture was stirred 1h, during this time the temperature rised to -60º C. The reaction was quenched by water and CH_2Cl_2, the two-phase mixture was separated, organic layer was dried by Na_2SO_4, filtrated and evaporated, giving the oil, which had crystallized in 5 minutes, giving pure 1-phenoxyheptan-2-ol **303** in quantitative yield.

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 0.94 (t, J 6.8, 3H, CH_3), 1.36 (br s, 4H, $CH_3\underline{CH_2CH_2}$), 1.43 (m, 1H, $CH_3CH_2CH_2\underline{CH_2}$), 1.51-1.65 (m, 3H, $CH_3CH_2CH_2\underline{CH_2}$ and $HOCH\underline{CH_2}CH_2$), 2.49 (br s, 1H, OH), 3.85 (t, J 9.2, 1H, OCH_2), 3.99 (dd, J 9.2, J 2.2, 1H, OCH_2), 4.02 (br m, 1H, $HO\underline{CH}$), 6.94 (d, J 7.6, 2H, 2`-H), 6.99 (t, J 7.6, 1H, 4`-H), 7.31 (t, J 7.6, 2H, 3`-H).

^{13}C{1H} NMR ($CDCl_3$, 150 MHz): δ = 15.08 (CH_3), 23.63 ($CH_3\underline{CH_2}$), 26.24 ($CH_3CH_2CH_2\underline{CH_2}$), 32.89 ($CH_3CH_2\underline{CH_2}$), 34.13 ($CH_3CH_2CH_2CH_2\underline{CH_2}$), 71.20 (OCH), 73.22 ($OCH_2$), 115.61 (2`-CH), 122.10 (4`-CH), 130.54 (3`-CH), 159.67 (1`-C).

HRMS (ESI/FT-ICR), [M+Na^+] observed (calculated): 231.1327 (231.1356)

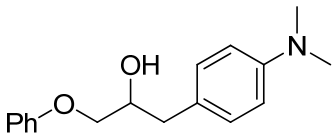
Preparation of silica gel for grafting

The silica gel is hydroxylated prior to grafting, according to the recomendation[375]. 50 G of silica gel were mixed with 200 ml of water (Milli Q) and refluxed overnight (without magnetically stirring). All volatiles were removed in vacuum of rotary evaporator, then the rest was dried for 6 hours in vacuum of oil pump at 120º C. Evidently, the elemental analysis has shown no carbon content.

Preparation of 1-(3-ylpropoxy)heptan-2-ol-grafted silica gel 305

Silica gel, prepared for grafting, was allowed to react with GLYMO according to the published procedure[380], yielding the epoxy-grafted silica gel **299**. The back-titration of epoxy-groups by $Na_2S_2O_3$ showed the content of epoxy-groups 0.5 mmol per 1 g of sample of **299**. 1.87 Ml of nBuLi (3 mmol, 1.6 M solution in hexane) were dissolved in 5 ml of absolute THF and cooled to -95º C. 0.37 Ml (3 mmol) of absolute $BF_3 \cdot Et_2O$ were added (resulted in warming to -78º C), and the resulting mixture was stirred 5 min at -78º C. To this mixture 0.5 g (0.25 mol of epoxy-groups) of silica gel **299** were added, and the mixture was stirred 30 min magnetically at -78º C, then 2 h stirred at ultrasonic at r.t. The silica gel was filtrated, washed with THF, then methanol, then acetone, then ether and dried in vacuum of oil pump. If was subjected to soxlett-extraction first by water, then by dichloromethane, and dried in vacuum of oil pump. After extraction the dried sample of **305** gave the elemental analysis as follows: 4.90% C, 1.47% H. Its ^{13}C NMR CPTOSS/MAS spectrum (100 MHz for ^{13}C nucleus, 67504 transients), ^{29}Si NMR CP/MAS spectrum (79.5 MHz for ^{29}Si nucleus, 69201 transients) and IR spectrum are presented in section 3.2

Generation of 1-(4-(dimethylamino)phenyl)-3-phenoxypropan-2-ol 310



200 Mg (1 mmol) of *p*-bromodimethylaniline **308** were dissolved in 2 ml of absolute THF, cooled to -95º C and 2 mmol of 1.5M solution of tBuLi (in pentane) were added (in nitrogen atmosphere), resulting in warming of the reaction mixture to -78º C. The mixture was stirred at -80º C for 30 min, then 1 mmol of lithium 2-thienylcyanocuprate (0.25 M solution in THF, Aldrich) was added *via syringe*, and the resulting mixture was warmed to 0º C till homogenisation (*ca* 30 sec), then cooled to -78º C and 1 mmol of phenylglycid **302** was added *via syringe*. The mixture was stirred 30 min at -78º C, then 12 h at r.t., poured in a mixture of EtOAc and saturated aqueous NH_4Cl with 25% aqueous NH_3. The phases were separated and organic phase subjected to GC/MS. If needed, the substance **310** can be purified by column chromatography, but I have not done this. GC-yield was 80%. The side-product is phenoxyacetone (10%), the other 10% is unreacted phenylglycid. The use of 1.5 eq or more of high-order cuprate is not recommended, since the GC-yield is notably reduced.

1st attempt to synthesize 1-(4-(dimethylamino)phenyl)-3-(3-ylpropoxy)propan-2-ol-grafted silica gel.

85 Mg (0.425 mmol) of *p*-bromodimethylaniline **308** were dissolved in 1 ml of absolute THF. After cooling to -78º C 0.56 ml (0.846 mmol) of tBuLi (1.5 M solution in pentane) were added within 5 min, and the mixture was stirred for 30 min. Thus, the *p*-lithiodimethylaniline **309** was generated. 1.7 Ml (0.425 mmol) of lithium thienylcyanocuprate (0.25M solution in THF) were added and the mixture warmed till homogenisation (*ca* 30 sec), then cooled to -78º C and 0.1 g (0.423 mmol) of GLYMO were added. The mixture was stirred for 12 h at r.t. 1 G of silica gel was added, and resulting mixture was stirred by ultrasonic 12 h at r.t. All volatiles were removed *in vacuo*, and the silica gel was washed by saturated aqueous solution of Na_2EDTA, then by solution of NH_3/NH_4Cl, then by saturated solution of LiCl in DMF. The silica gel remained brown, hence the Cu was adsorbed there.

2nd attempt to synthesize 1-(4-(dimethylamino)phenyl)-3-(3-ylpropoxy)propan-2-ol-grafted silica gel.

*p-L*ithiodimethylaniline **309** was generated as previously described. 1.7 Ml (0.425 mmol) of lithium thienylcyanocuprate (0.25M solution in THF) were added and the mixture was warmed till homogenisation (*ca* 30 sec), then cooled to -78º C and 0.1 g (0.423 mmol) of GLYMO were added. The mixture was stirred for 8 h at r.t. 0.22 Ml (1.7 mmol) of TMSCl were added, stirred for 4 h and all volatiles were removed *in vacuo*. The rest was redissolved in ethylacetate, quickly extracted by aqueous solution of NH_3/NH_4Cl (1:1 25% NH_3 and saturated aq. NH_4Cl), dried by Na_2SO_4, filtrated through a layer of silica gel **299** and evaporated. The rest was redissolved in toluene, then 1 g of silica gel (for grafting) was added and resulting mixture was stirred for 6 h using ultrasound. The silica gel was dried and washed by saturated aqueous Na_2EDTA, but it does not decolorize it. The silica gel remained brown, hence the Cu was adsorbed there.

3rd attempt to synthesize 1-(4-(dimethylamino)phenyl)-3-(3-ylpropoxy)propan-2-ol-grafted silica gel.

The reaction was performed as the previous, extracted by aqueous NH_3/NH_4Cl and dried by Na_2SO_4. To the dried extracts activated Carbon was added, and this was filtrated through celit. Filtrate was evaporated *in vacuo*, redissolved in absolute toluene (this solution was subjected to ^{29}Si NMR and showed two peaks in region -35 - -45 ppm, namely at -41.5 of **315** and at -42.5 of unreacted GLYMO). 1 G of silica gel (for grafting) was added to this toluene-

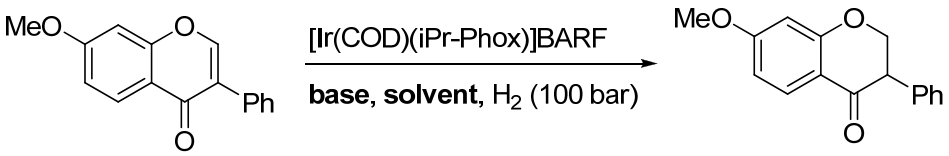
solution, and this was stirred for 24 h using ultrasound, then dried *in vacuo*. Washing by saturated aqueous Na_2EDTA does not decolorize this silica gel, hence the Cu stays adsorbed there.

7.3 Nucleophilic hydrogenation of 7-methoxyisoflavone

DIPEA, used for nucleophilic hydrogenation, was purshased from Merck, Acros, Fluka or Aldrich, and was found to be not pure enough. It was refluxed over crystalline ninhydrine (5 h) under light overpressure (50 mbar) of nitrogen, then distilled in vacuum of membrane pump (40 mbar). The distilled DIPEA was refluxed over LiH (Fluka) for 5 h (overpressure 50 mbar of hydrogen) and distilled in vacuum again. Then it was again refluxed over LiH under pressure of nitrogen and distilled in vacuum. This DIPEA doest not contain the diisopropylamine, which is deleterious for nucleophilic hydrogenation. It is best stored in nitrogen filled glovebox, in dark. 2,6-Di-*tert*-butylpyridine was purshased from Molecula, and purified similar to DIPEA (distillation in vacuum over ninhydrine, then twice over LiH).

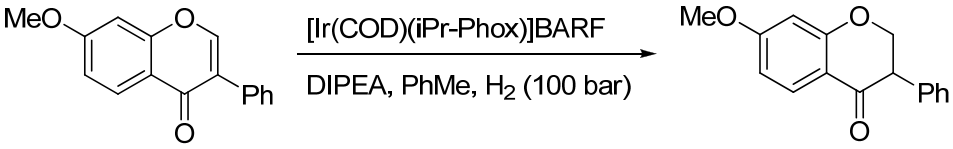
(R)-1-Phenylethanamine (Fluka) was found in collection of reagents of AG Groth and used without purification.

General procedure G (experimental procedure of nucleophilic hydrogenation).



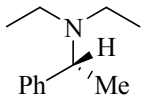
1-2 Mg of catalyst were weighted into tefon vessel, then a calculated amount of substrate (to a ratio catalyst/substrate 1/100), optionally 1-2 drops of thiophene (to suppress possible heterogeneous process), base (0.07 mL) and 5 mL of degased solvent (distilled in nitrogen-atmosphere) were added. All operations were quickly carried out under air and the vessel was sealed in stainless-steel autoclave. Autoclave was purged 3 times with hydrogen and then charged to 100 bar. After 8 hours of hydrogenation at r.t., the autoclave was unsealed and reaction mixture was subjected to gas chromatography with mass-spectral analysator (GC/MS). GC conversion was calculated from corresponding peaks' areas and was not corrected with external standard. If needed, reaction mixture was evaporated in vacuum, redissolved in $CDCl_3$ or in DMSO-D_6 and subjected to ^1H NMR, which showed the same conversion.

General procedure H (preparative procedure of nucleophilic hydrogenation).



50 Mg of substrate were weighted into tefon vessel, then a calculated amount of catalyst (to achieve wished catalyst/substrate ratio), DIPEA (500 eq. relative to Ir-complex) and 15 mL of degased toluene (distilled in nitrogen-atmosphere) were added. Further operations are similar to general procedure F. Products were purified by silica gel column chromatography, eluting by diethyl ether.

(R)-N,N-diethyl-1-phenylethanamine



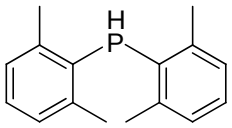
I am grateful to Anton Kotljarov for the method of alkylation, since the standrad methods were ineffective.

A mixture of 21.8 g (0.18 mol) of (R)-1-phenylethanamine, 5.8 g (0.018 mol) of tetrabutylammonium bromide, 87.2 ml (1.08 mol) of iodoethane, 28.776 g (0.72 mol) of NaOH, 49.7 g (0.36 mol) of potassium carbonate and 600 ml of toluene was refluxed during 24 hours (with protection from water by $CaCl_2$-tube). Then the mixture was cooled, toluene was evaporated and residue partitioned between water and dichloromethane. Water-layer was washed three times by dichloromethane, organic extracts were evaporated and partitioned between water and hexane. Hexane-layer was dried by Na_2SO_4, filtrated and evaporated. Residue was distilled in vacuum of oil-pump and was characterized as (R)-N,N-diethyl-1-phenylethanamine. This base was completely inactive in nucleophilic hydrogenation, probabily because of contamination with (R)-N-monoethyl-1-phenylethanamine (0.3% were present in synthesised amine, according to GC/MS). Contaminated (R)-N,N-diethyl-1-phenylethanamine was diluted by dioxane and 5 ml of BzCl were added. This mixture was stirred 48 hours (became brown), partitioned between hexane and 5N NaOH, and hexane-layer was dried over Na_2SO_4, filtrated and evaporated. Residue was distilled in vacuum of oil-pump and afforded 21 g (65%) of (R)-N,N-diethyl-1-phenylethanamine, where monoethylated amine was not detected. This amine should be used for nucleophilic hydrogenation during 1 hour, then it becames couloured and inactivated.

7.4 Nucleophilic hydrogenation: catalyst screening

$[Ir(COD)_2]BARF$ was obtained as a gift from Umicore or synthesized by the provided procedure. 1,3-dimethyl-1H-imidazol-3-ium iodide[449], 1,3-dimethyl-4,5-dihydro-1H-imidazol-3-ium tetrafluoroborate[450], NaBARF[435], oxazolines[396] are synthesized by the known procedures. 1-Cyanomethyl-3-methylimidazolium chloride synthesized with quantitative yield from $ClCH_2CN$ and 1-methylimidazole by refluxing in THF during 18 h, according to the published procedure[410]. Di-*ortho*-tolylphosphine and diphenylarsine synthesized with 61% and 64% yield, resp. from tri-*ortho*-tolylphosphine or triphenylarsine by decomposition with metallic lithium in THF, hydrolysis and vacuum-distillation[451] (ether or MTBE are ineffective, only THF should be used as a solvent). Iridium (1,5-cyclooctadiene) ((4S,5S)-(+)-O-[1-Benzyl-1-(5-methyl-2-phenyl-4,5-dihydro-oxazol-4-yl)-2-phenylethyl]-diphenyl-phosphinite) tetrakis(3,5-bis(trifluoromethyl)phenyl) borate **354** and benzo[h]quinolin-10-ol **326** were purshased from ABCR. (1S,2S)-(+)-2-Amino-1-phenyl-1,3-propanediol was purshased from Wako.

Bis(2,6-dimethylphenyl)phosphine (317g)



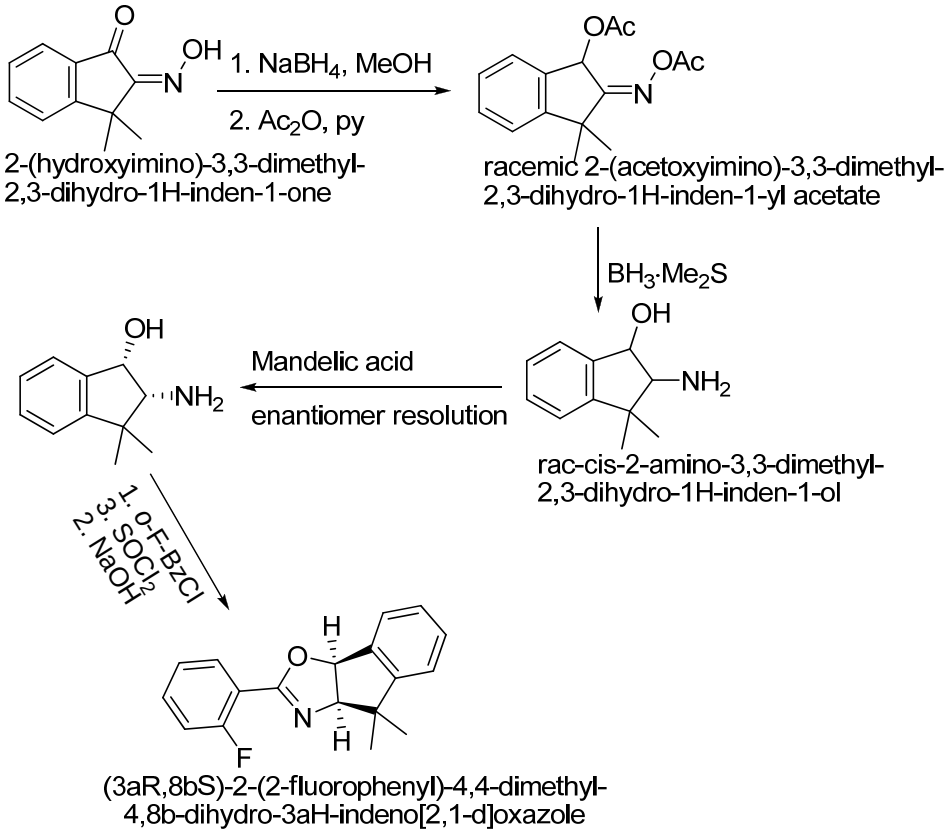
Synthesized from dixylylphosphine oxide by stirring at 70º C with triisobutylaluminium (TIBAL) in absolute toluene during 48 hours, by the known procedure[452] (DIBAL-H is ineffective, only TIBAL should be used). White crystals. Yield – 69%.

^1H NMR (C_6D_6, 400 MHz): δ = 2.22 (s, 12H, CH_3), 5.26 (d, J 231, 1H, PH), 6.83 (dd, J 7.4, J 2.3, 4H, 3-H), 6.97 (t, J 7.4, 2H, 4-H).

$^{13}C\{1H\}$ NMR (C_6D_6, 100 MHz): δ = 22.93 (d, J 10.4, CH_3), 128.48 (s, 4-C), 128.63 (d, J 2.4, 3-C), 133.38 (d, J 17.7 Hz, 1-C), 142.56 (d, J 12.0, 2-C).

^{31}P NMR (C_6D_6, 161 MHz): δ = -91.60 (d, J 231).

(3aR,8bS)-2-(2-fluorophenyl)-4,4-dimethyl-4,8b-dihydro-3aH-indeno[2,1-d]oxazole (318h).



A simplified procedure from article[453] was used for the synthesis of this compound, and the full synthetic procedure is given below.

2-(Hydroxyimino)-3,3-dimethyl-2,3-dihydro-1H-inden-1-one[454] was recrystallized from toluene. A 3-Neck 1L flask equipped with reflux-condenser and internal thermometer was charged with a solution of 18.4 g (97 mmol) of 2-(hydroxyimino)-3,3-dimethyl-2,3-dihydro-1H-inden-1-one in 460 ml methanol (under nitrogen) and cooled to -20º C. 16.56 G (438 mmol) of $NaBH_4$ were added through the remaining neck and the mixture was stirred for 1 hour with cooling (reaction is so vigorous, that refluxing begins), then for 10 h in an ice-bath. A mixture was evaporated in vacuum, and suspended in 368 ml of pyridine (with vigorous shaking under nitrogen). 184 ml of acetic anhydride was added and vigorous shaking continued, resulting in violett coloring which changed to yellow within 30 sec. After 12 hours the mixture was evaporated in vacuum and the rest triturated in 800 ml of water to give crude **racemic 2-(acetoxyimino)-3,3-dimethyl-2,3-dihydro-1H-inden-1-yl acetate**. It was recrystallized from mixture toluene/hexane 1/3 to give white crystals with a yield of 70%.

3-Neck 100 mL flask, equipped with reflux-condenser and internal thermometer, was charged with a solution of 1g (3.63 mmol) of **racemic 2-(acetoxyimino)-3,3-dimethyl-2,3-dihydro-1H-inden-1-yl acetate** in 20 ml THF (under nitrogen) and cooled to -20º C. The remaining neck was sealed with a rubber septum. 1.4 ml (14.72 mmol) of borane-

dimethylsulfide complex (94%, Acros) was added *via syringe* through septum. The mixture was heated and refluxed for 3 h, then cooled to -20ºC and 3.4 ml of 1N HCl was added (under air) which resulted in refluxing. After cooling, a mixture was poured in 2N KOH and 5 times extracted with CH_2Cl_2. The organic extracts were dried with Na_2SO_4, filtrated and evaporated, giving pure white ***rac*-*cis*-2-amino-3,3-dimethyl-2,3-dihydro-1H-inden-1-ol**. This substance is very unstable, it epimerizes upon storage, and should be used in 2-3 days. The method is scaleable up to 20 g of **2-(acetoxyimino)-3,3-dimethyl-2,3-dihydro-1H-inden-1-yl acetate**.

Although in the original article[453] the use of borane-THF complex is described, this leads to a mixture of the other compounds, but not to the target. A communication with Atsushi Sudo revealed that the borane-dimethylsulfide complex should be used.

Racemic *cis*-2-amino-3,3-dimethyl-2,3-dihydro-1H-inden-1-ol was resolved as described in literature[453]

In absolute dioxane under nitrogen 1.665 g (9.4 mmol) **(1S,2R)-2-amino-3,3-dimethyl-2,3-dihydro-1H-inden-1-ol** and 2.6 ml (19 mmol) of NEt_3 were dissolved. With cooling to 0º C 1.2 ml (9.9 mmol) of 2-fluorobenzoyl chloride were added *via syringe* and stirred for 8 h at r.t. 13.4 Ml (184.7 mmol) of $SOCl_2$ were added *via syringe* (cooling to 0º C) and the mixture was stirred for 2 h, then evaporated in vacuum, suspended in 5N NaOH and extracted 5 times with CH_2Cl_2. After drying with Na_2SO_4, filtration and evaporation the rest was redissolved in absolute Et_2O, 3.4 g (23.9 mmol) of Na_2SO_4 and 3.4 g (85 mmol) of NaOH dust (Aldrich) were added, and the whole stirred for 48 h in a sealed flask (r.t.). The water was added, and organic layer separated. Adsorption on silica with subsequent column chromatography on 200 g of silica (Et_2O-pentane 2/3) gave crystalline off-white **(3aR,8bS)-2-(2-fluorophenyl)-4,4-dimethyl-4,8b-dihydro-3aH-indeno[2,1-d]oxazole 318h** with a yield of 30%. Unfortunately, the target compound is only a by-product. The formula of the main product, which is less polar and comes first from column, is not assigned. The spectral properties of **318h** correspond to those published[455].

General detailed procedure I for the synthesis of 286a, 286b, 286c, 286d, 286k. Diphenylphosphine, lithium diphenylphosphide and all ligands **316** are very toxic and pyrophoric compounds. Up to anion-exchange, all operations must be carried out strictly under nitrogen (or argon) in a well-ventilated fume hood.

A 2-neck 10 mL flask, rubber-septum, magnetic stirrer, 1 mL syringe, needle and a stopcock were evacuated to the nitrogen filled glovebox. The magnetic stirrer was placed in the flask, one neck was sealed with septum and the other with stopcock. Diphenylphosphine

(0.33 mmol) was weighted in syringe and the septum was punctured with this syringe in the glovebox. Then this system was extracted from the glovebox, the stopcock was connected with nitrogen-line and opened (see Figure 15).

4 ml of ether were added *via syringe* through septum, and diphenylphosphine was dissolved there (syringe from diphenylphosphine repeatedly washed with reaction mixture). 0.33 Mmol of n-butyllithium (1.6 M solution in hexane) were added to this mixture *via syringe* through septum at r.t. and this yellow mixture was stirred for 5 min (lithium diphenylphosphide in ether was generated). 0.3 Mol of the liquid oxazoline (**318a, 318b, 318c, 318d, 318k)** were weighted in syringe (allowed on air) and added to the reaction mixture through septum (syringe was repeatedly washed with reaction mixture). The reaction was allowed to be stirred overnight (for about 10 hours). At this point a gas chromatography with mass-sensitive analyzer was performed, which showed a conversion of **318** over 90% into the ligand **316**. The mixture was evaporated in the stream of nitrogen (the septum was simply removed).

0.15 mmol of $[Ir(COD)Cl]_2$ and 3 ml of CH_2Cl_2 were added to the rest and a reflux condenser sealed by paraffin oil sealed bubbler with nitrogen inlet was mounted (Figure 16), which allowed to perform the reaction in the stream of nitrogen (and not under pressure). Nitrogen should come through reflux condenser, and the remainig neck of the reaction-flask was sealed with a stopper. The mixture was refluxed for 2 hours (refluxing is necessary otherwise the yield is understated).

After cooling the air-stable complex of iridium is formed, hence all operations would be made on air. 0.33 mmol of NaBARF were added and this mixture was stirred at r.t. for 1-3 hours (anionic exchange could be monitored by TLC eluting by dichloromethane, *Rf* of [Ir(COD)Cl(Phox)] is 0, that of [Ir(COD)(Phox)]BARF is 0.75-1). Then 1 g of silica gel was added, and the mixture was evaporated under vacuum. This silica was placed on top of the column, filled with 20 g of silica gel, and the desired complex was eluted by CH_2Cl_2. The complexes **286** are coloured, hence eluation can easily be observed. The eluant was evaporated in vacuum (without heating), and the complex dried under deep vacuum.

The procedure is scalable up to 400 mg of $[Ir(COD)Cl]_2$ (further scaling was not checked).

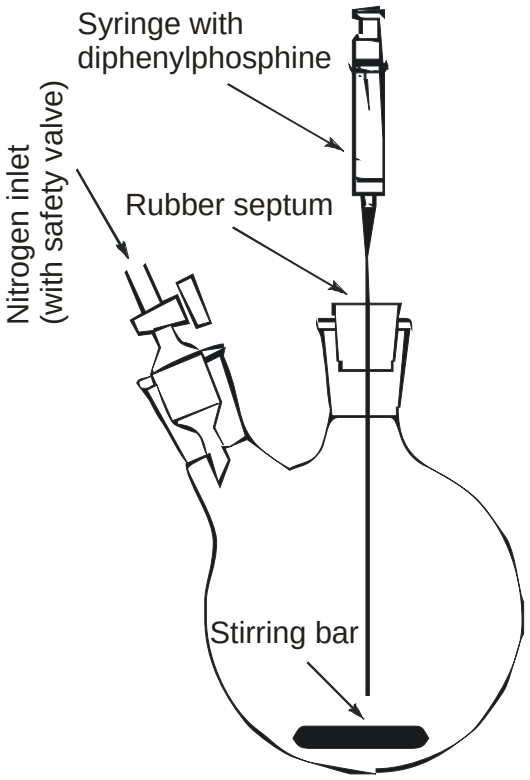


Figure 15

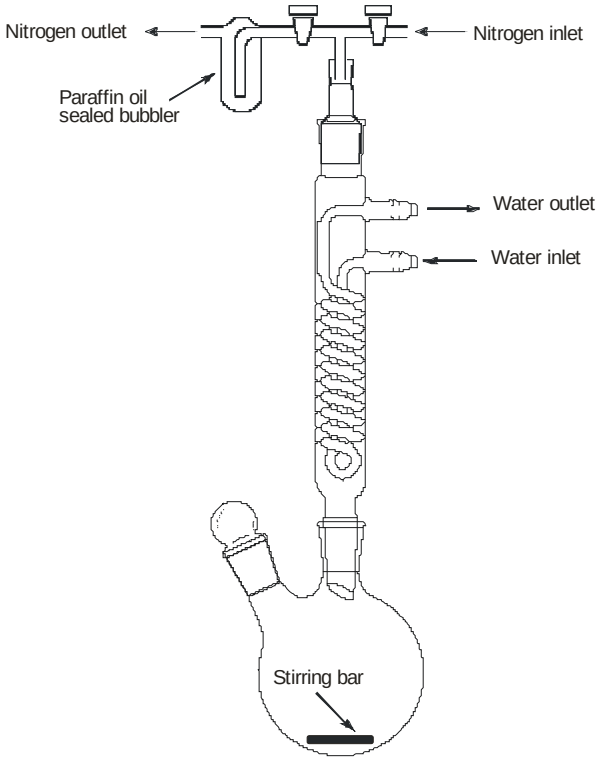
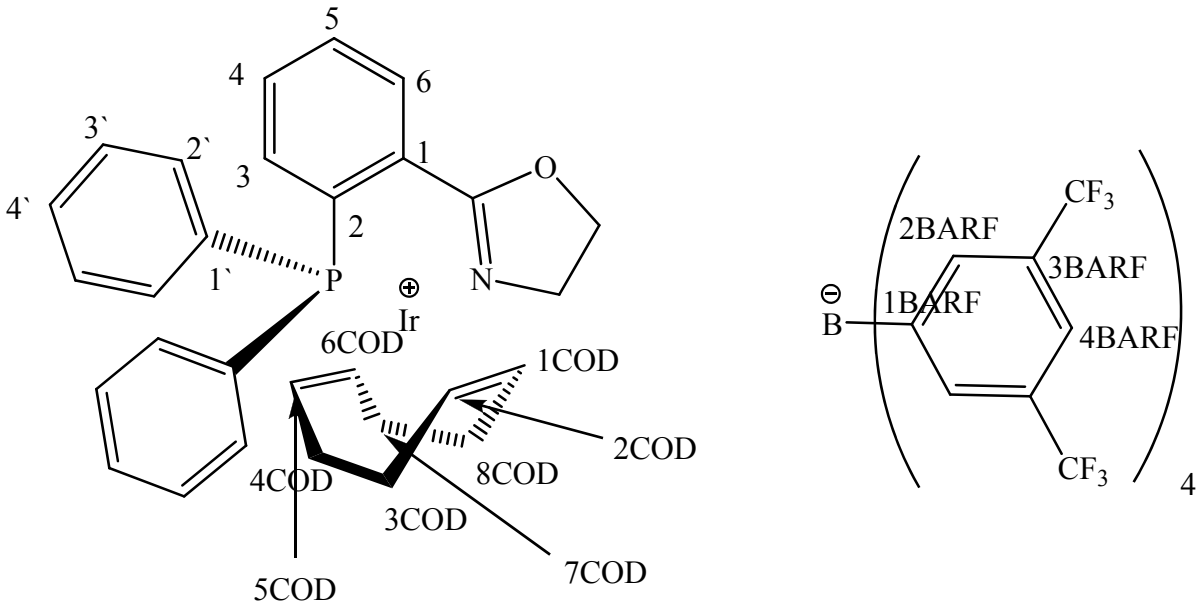


Figure 16

Iridium (1,5-cyclooctadiene) (2-(2-(diphenylphosphino)phenyl)-4,5-dihydrooxazole) tetrakis(3,5-bis(trifluoromethyl)phenyl) borate 286a.



Yield: 74%. Red crystals. Unstable on storage at r.t. even in crystalline form. Should be stored at -20º C.

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 1.93 (m, 2H, a-4-H_{COD} and a-8-H_{COD}), 2.05 (m, 2H, a-3-H_{COD} and a-7-H_{COD}), 2.26 (m, 4H, e-3-H_{COD}, e-4-H_{COD}, e-7-H_{COD}, e-8-H_{COD}), 3.16 (br s, 2H, 5- and 6-H_{COD}), 4.09 (t, J 10, 2H, NCH_2), 4.48 (t, J 10, 2H, OCH_2), 5.08 (br s, 2H, 1- and 2-H_{COD}), 7.43 (dd, J 11.44, J 8.22, 2`-H), 7.49 (m, 6H, 3-, 4- and 3`-H), 7.54 (br s, 4H, 4-H_{BARF}), 7.60 (m, 3H, 5- and 4`-H), 7.74 (br s, 8H, 2-H_{BARF}), 8.05 (m, 1H, 6-H).

^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz): δ = 32.13 (d, J 3.44, 4- and 8-CH_{2COD}), 29.70 (3- and 7-CH_{2COD}), 54.55 (NCH_2), 64.28 (5- and 6-CH_{COD}), 68.39 (OCH_2), 95.14 (d, J 11.47, 1-2 and 2-CH_{COD}), 117.50 (br s, 4-CH_{BARF}), 124.55 (q, J 273, CF_3), 126.20 (d, J 60, 1`-C), 128.68 (d, J 8.8, 1-C), 128.9 (br q, J 30, 3-$C_{BARF}$), 129.36 (d, J 9.9, 3`-C), 129.39 (d, J 46.11, 2-C), 132.15 (d, J 1.61, 5-CH), 132.47 (d, J 2.41, 4`-CH), 133.23 (d, J 9.9, 3-CH), 133.35 (d, J 8.0, 6-CH), 133.89 (d, J 6.9, 4-CH), 134.18 (d, J 12.1, 2`-CH), 134.81 (br s, 2-CH_{BARF}), 161.72 (q 1:1:1:1:, J 50.5, 1-C_{BARF}), 165.68 (d, J 8.0, N=C).

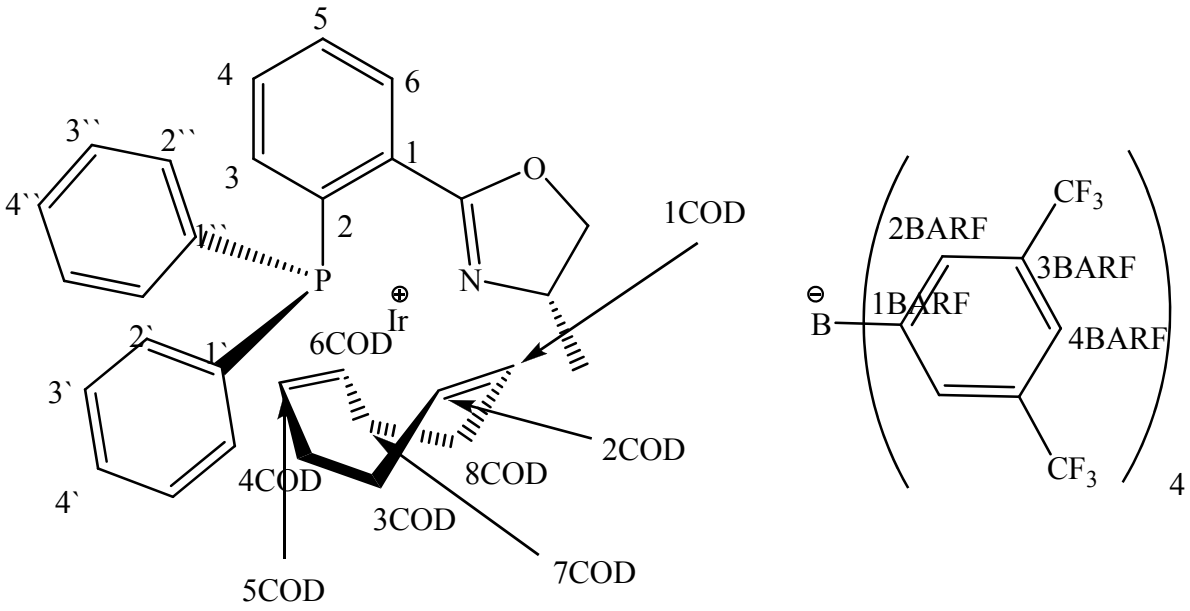
^{31}P NMR ($CDCl_3$, 161 MHz): δ = +16.1.

^{19}F NMR ($CDCl_3$, 128 MHz): δ = -62.8.

^{11}B NMR ($CDCl_3$, 376 MHz): δ = -6.9.

HRMS ESI/FT-ICR: isotope cluster 630-634, observed (calculated): 630.1679, 66.0% (630,1671, 59,5%); 631.1721, 20.5% (633,1728, 31.4%); 631.1856, 12.1% (631,1704, 18.7%); 632.1688, 100.0% (632,1694, 100%); 633.1714, 33.4% (633,1728, 31.4%); 634.1739, 6.8% (634,1761, 4.7%).

Racemic iridium (1,5-cyclooctadiene) (2-(2-(diphenylphosphino)phenyl)-4-methyl-4,5-dihydrooxazole) tetrakis(3,5-bis(trifluoromethyl)phenyl) borate 286b.



Assignment for (S)-enantiomer

Yield: 80%. Red crystals. Very stable on storage even in $CDCl_3$-solution at r.t. (minimum 6 months). Unstable on storage in toluene.

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 1.05 (d, J 5.7, Me), 1.47 (nrm, 1H, a-4-H_{COD}), 1.65 (nrm, 1H, a-8-H_{COD}), 2.03 (nrm, 1H, e-4-H_{COD}), 2.06 (nrm, 1H, e-8-H_{COD}), 2.45 (nrm, 3H,a-7-H_{COD} and 3-H_{COD}), 2.53 (nrm, 1H, e-7-H_{COD}), 3.14 (br m, 5-H_{COD}), 3.36 (br m, 6-H_{COD}), 4.18 (dd, J 9.0, J 3.9, 1H, OCH_2), 4.27 (br s, 1H, NCHMe), 4.46 (d, J 9.0, 1H, OCH_2), 4.97 (br s, 1- and 2-H_{COD}), 7.14 (dd, J 11.3, J 6.6, 2H, 2`-H), 7.41 (nrm, 1H, 3-H), 7.46 (nrm, 2H, 3`-H), 7.47 (nrm, 1H, 4`-H), 7.48 (nrm, 2H, 3``-H), 7.54 (br s, 4H, 4-$H_{BARF}$), 7.55 (nrm, 1H, 4``-H), 7.60 (nrm, 4H, 4-, 5- and 2``-H), 7.74 (br s, 8H, 2-H_{BARF}), 8.07 (m, 1H, 6-H).

^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz): δ = 23.16 (Me), 26.47 (8-CH_{2COD}), 28.59 (4-CH_{2COD}), 32.22 (3-CH_{2COD}), 36.06 (7-CH_{2COD}), 61.52 (NCHMe), 63.80 (6-CH_{COD}), 63.92 (5-CH_{COD}), 74.24 (OCH_2), 93.54 (d, J 13.2, 1-CH_{COD}), 96.49 (d, J 12.1, 2-CH_{COD}), 117.5(br s, 4-CH_{BARF}), 121.81 (d, J 58.3, 1`-C), 124.55 (q, J 273, $CF_3$), 128.65 (d, J 29.7, 2-C), 128.9 (br q, J 30, 3-$C_{BARF}$), 128.98 (d, J 11.0, 3`-CH), 129.12 (d, J 50.6, 1``-C), 129.60 (d, J 11.0, 3``-CH), 129.70 (d, J 15.4, 1-C), 132.23(d, J 3.3, 4`-CH), 132.25 (br s, 5-CH), 132.70 (d, J 2.2, 4``-CH), 133.11 (d, J 9.9, 2`-CH), 133.39 (br s, 3-CH), 133.46 (d, J 7.7, 6-CH), 133.99 (d, J 6.6, 4-CH), 134.81 (br s, 2-CH_{BARF}), 161.72 (q 1:1:1:1, 1-C_{BARF}), 163.73 (d, J 6.6, N=C).

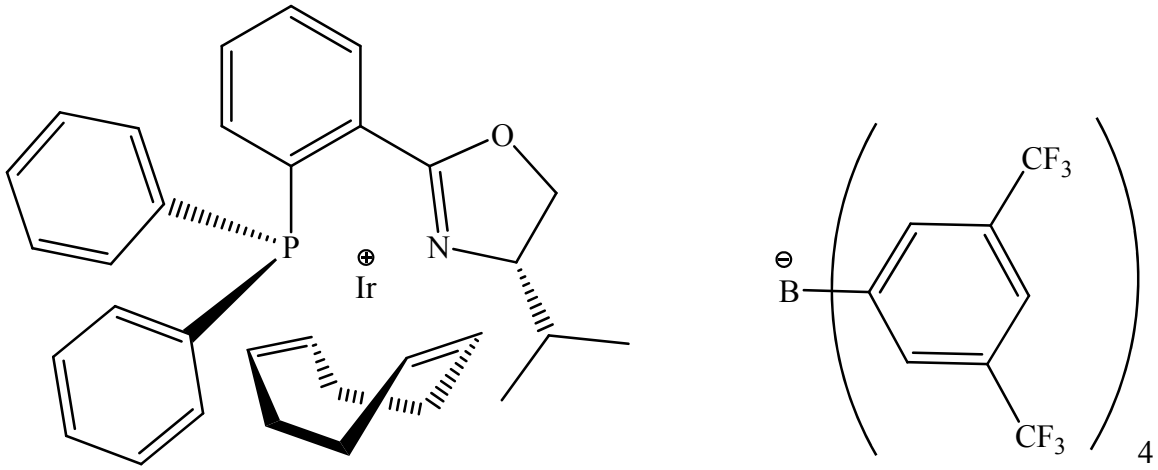
^{31}P NMR ($CDCl_3$, 161 MHz): δ = +17.6.

^{19}F NMR ($CDCl_3$, 128 MHz): δ = -62.8.

^{11}B NMR ($CDCl_3$, 376 MHz): δ = -6.9.

HRMS ESI/FT-ICR: isotope cluster 644-648, observed (calculated): 644.1833, 56.6% (644,1827, 59.5%); 645.1880, 17.6% (645,1861, 19.3%); 646.1851, 100.0% (646,1851, 100.0%); 647.1901, 33.7% (647,1884, 32.4%); 648.1949, 5.9% (648,1918, 5.1%).

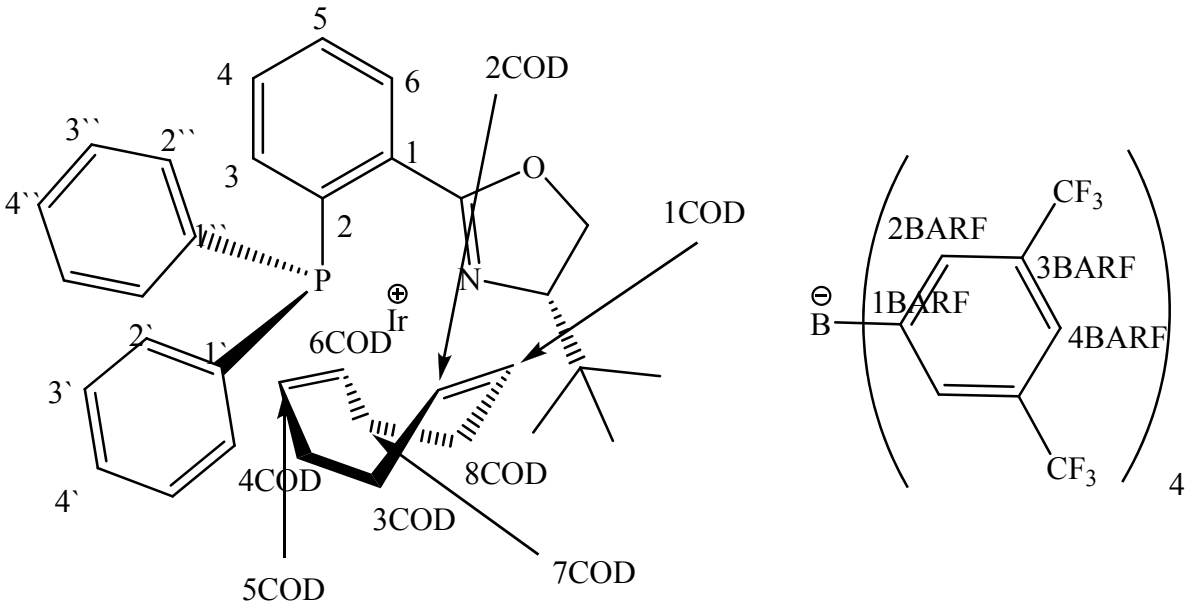
Iridium (1,5-cyclooctadiene) ((S)-2-(2-(diphenylphosphino)phenyl)-4-isopropyl-4,5-dihydrooxazole) tetrakis(3,5-bis(trifluoromethyl)phenyl) borate (4c).



Yield: 81% (best yield found in literature is 91%[456]). Red crystals. Very stable on storage even in $CDCl_3$-solution at r.t. (minimum 6 months). Unstable on storage in toluene.

HRMS ESI/FT-ICR: isotope cluster 672-676, observed (calculated): 672.2204, 48.0% (672,2140, 59.5%); 673.2255, 24.5% (673,2174, 20.6%); 674.2145, 100.0% (674,2164, 100%); 675.2125, 46.9% (675,2197, 34.6%); 676.2201 7.0% (676,2231, 5.8%).

Iridium (1,5-cyclooctadiene) ((S)-4-tert-butyl-2-(2-(diphenylphosphino)phenyl)-4,5-dihydrooxazole) tetrakis(3,5-bis(trifluoromethyl)phenyl) borate 286d.



Yield: 79.7%. Red crystals. Very stable on storage even in $CDCl_3$-solution at r.t. (minimum 6 months). Unstable on storage in toluene.

$[\alpha]_D^{21}$=-155 (c 0.105, $CHCl_3$)

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 0.63 (s, 9H, Me), 1.43(nrm, 1H, a-4-H_{COD}) 1.6 (nrm, 1H, a-8-H_{COD}), 2.0 (nrm, 2H, e-4- and e-8-H_{COD}), 2.47 (nrm, 2H, a-3- and a-7-H_{COD}), 2.40 (nrm, 1H, e-3-H_{COD}), 2.55 (nrm, 1H, e-7-H_{COD}), 3.04 (br s, 1H, NOE with 7.11 ppm, 5-H_{COD}), 3.5 (br s, 1H, NOE with 7.46 ppm, 6-H_{COD}), 3.94 (dd, J 9.4, J 2.6, NCH*t*Bu) 4.32 (t, J 9.4, 1H, OCH_2), 4.58 (dd, J 9.4, J 2.6, 1H, OCH_2), 4.95 (br m, 1- and 2-H_{COD}), 7.11 (br m, 2H, 2`-H), 7.32 (nrm, 1H, 3-H), 7.43 (nrm, 2H, 3`-H), 7.46 (nrm, 2H, 2``-H), 7.49 (nrm, 1H, 4`-H), 7.50 (nrm, 2H, 3``-H), 7.54 (br m, 4H, 4-H_{BARF}), 7.55 (nrm, 1H, 4``-H), 7.62 (nrm, 2H, 4- and 5-H), 7.74 (br s, 8H, 2-H_{BARF}), 8.20 (m, 1H, 6-H).

^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz): δ = 25.09 (Me), 25.51 (8-CH_{2COD}), 28.16 (4-CH_{2COD}), 32.70 (3-CH_{2COD}), 34.42 ($\underline{C}Me_3$), 36.8 (7-CH_{2COD}), 62.74 (5-CH_{COD}), 63.37 (6-CH_{COD}), 69.82 (OCH_2), 74.47 (N$\underline{CH}$*t*Bu), 93.28 (d, J 13.8, 1-CH_{COD}), 97.57 (d, J 10.3, 2-CH_{COD}), 117.50 (br s, 4-CH_{BARF}), 122.31 (d, J 57.4, 1`-C), 124.55 (q, J 273, $CF_3$), 127.61 (d, J 48.2, 1-C), 128.83 (d, J 10.3, 3`-CH), 128.9 (br q, J 30, 3-C_{BARF}), 129.12 (d, J 13.8, 1-C), 129.60 (d, J 51.6, 1``-C), 129.70 (d, J 11.5, 3``-CH), 132.09 (4`-CH), 132.58 (d, J 1.6, 5-H), 132.62 (4``-CH), 133.19 (d, J 10.3, 2`-CH), 133.98 (d, J 8.0, 6-CH), 134.20 (d, J 14.9, 2``-CH), 134.23 (d, J 6.9, 4-CH), 134.81 (br s, 2-CH_{BARF}), 134.93 (d, J 2.4, 3-CH), 161.72 (q 1:1:1:1, J 50.5, 1-C_{BARF}), 164.03 (d, J 4.6, N=C).

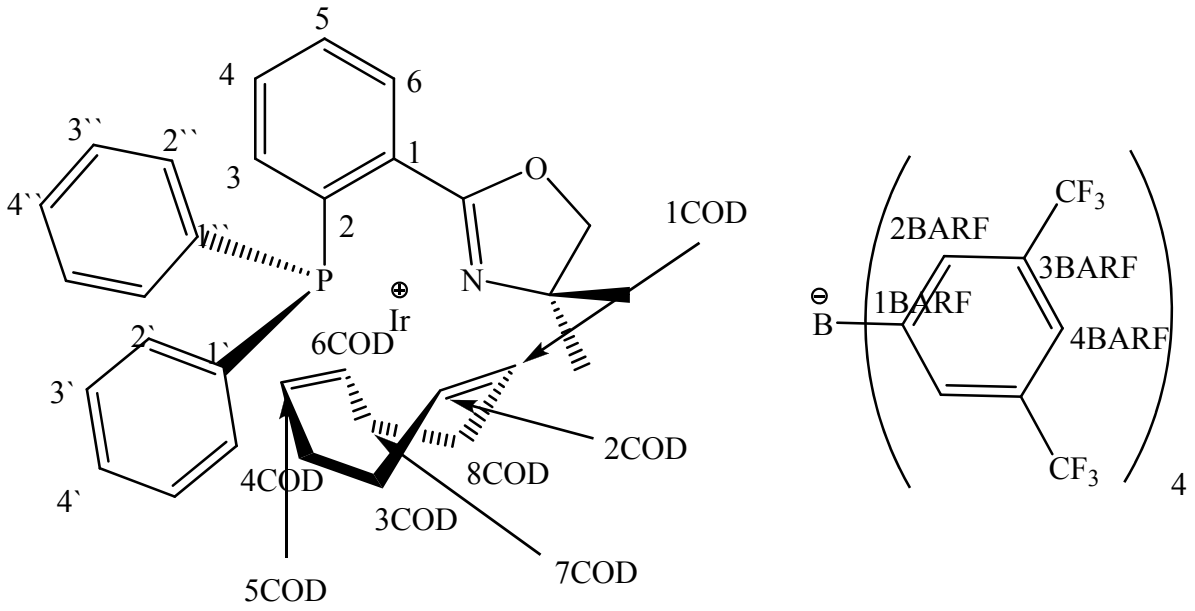
^{31}P NMR ($CDCl_3$, 161 MHz): δ = +17.5.

^{19}F NMR ($CDCl_3$, 128 MHz): δ = -62.8.

^{11}B NMR ($CDCl_3$, 376 MHz): δ = -6.9.

HRMS ESI/FT-ICR: isotope cluster 686-690, observed (calculated): 686.2380, 52.7% (686,2297, 59.5%); 687.2416, 13.1% (687,2330, 21.2%); 688.2323, 100.0% (688,2320, 100%); 689.2315, 43.8% (689,2354, 35.7%); 690.2344, 4.9% (690,2387, 6.2%).

Iridium (1,5-cyclooctadiene) (2-(2-(diphenylphosphino)phenyl)-4,4-dimethyl-4,5-dihydrooxazole) tetrakis(3,5-bis(trifluoromethyl)phenyl) borate 286k.



Yield: 68%. Red crystals. Very unstable even in crystalline state at r.t. Should be stored at -20º C.

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 1.31 (s, 6H, Me), 1.82 (nrm, 2H, a-4- and a-4-H_{COD}), 2.01 (nrm, 2H, e-4- and e-8-H_{COD}), 2.22 (nrm, 4H, 3- and 7-H_{COD}), 3.27 (br s, 2H, 5- and 6-H_{COD}), 3.87 (s, 2H, OCH_2), 5.40 (br s, 2H, 1- and 2-H_{COD}), 7.31 (br s, 4H, 2``- and 3``-H), 7.44 (3-H), 7.48 (nrm, 3H, 2`- and 4``-H), 7.54 (br s, 5H, 4`-H and 4-$H_{BARF}$), 7.59 (nrm, 5- and 3`-H), 7.60 (nrm, 4-H), 7.74 (br s, 8H, 2-H_{BARF}), 7.84 (m, 6-H).

^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz): δ = 27.81 (Me), 29.70 (br s, 3- and 7-CH_{2COD}), 31.90 (br s, 4- and 8-CH_{2COD}), 61.72 (5- and 6-CH_{COD}), 73.12 (OCH_2), 82.47 (N<u>C</u>Me_2), 93.64 (d, J 13.2, 1- and 2-CH_{COD}), 117.50 (br s, 4-CH_{BARF}), 124.55 (q, J 273, CF_3), 125.29 (d, J 7.68, 2-C), 125.74 (1`-C), 128.9 (br q, J 30, 3-C_{BARF}), 129.52 (4``-CH), 129.28 (d, J 11.0, 2``-CH), 129.91 (d, J 62.6, 1``-C), 131.23 (d, J 5.5, 1-C), 131.71 (br s, 3-CH), 131.90 (d, J 7.7, 6-CH), 131.99 (5-CH), 132.53 (4`-CH), 133.39 (d, J 6.6, 3C, 4-CH and 3`-CH), 134.07 (br s, 4C, 2`- and 3``-CH), 134.81 (br s, 2-CH_{BARF}), 161.72 (q 1:1:1:1, J 50.5, 1-C_{BARF}), 165.49 (d, J 7.8, N=C).

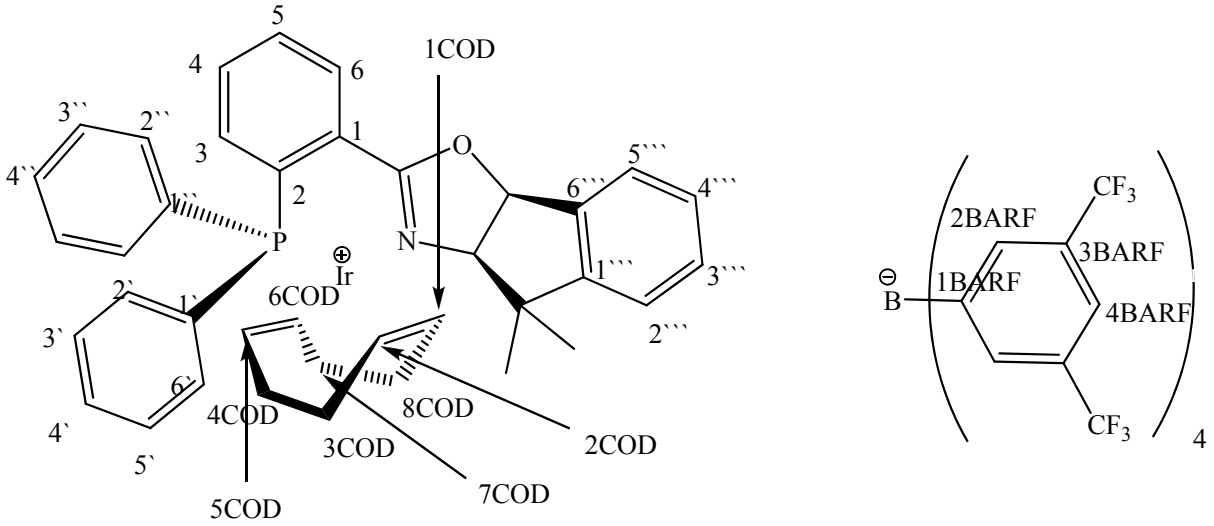
^{31}P NMR ($CDCl_3$, 161 MHz): δ = +21.8.

^{19}F NMR ($CDCl_3$, 128 MHz): δ = -62.8.

^{11}B NMR ($CDCl_3$, 376 MHz): δ = -6.9.

HRMS ESI/FT-ICR: isotope cluster 658-662, observed (calculated): 658.1974, 50.7% (658.1984, 59.5%); 659.2018, 16.7% (659.2017, 19.9%); 660.2012, 100.0% (660.2007, 100%); 661.2029, 32.2% (661.2041, 33.5%); 662.2083, 2.4% (662.2074, 5.4%).

Iridium (1,5-cyclooctadiene) ((3aR,8bS)-2-(2-(diphenylphosphino)phenyl)-4,4-dimethyl-4,8b-dihydro-3aH-indeno[2,1-d]oxazole) tetrakis(3,5-bis(trifluoromethyl)phenyl) borate 286h.



The 2-neck 10 mL flask, two rubber-septa, magnetic stirrer, teflon stopcock with upper and bottom laps, syringe and needle were evacuated to the nitrogen filled glovebox. **318h** (0.3 Mmol) was weighted and placed between the closed stopcock and its upper lap, sealed by septum. The bottom lap of the stopcock seals one neck of the flask, the other neck is sealed by septum and punctured by syringe with diphenylphosphine (0.33 mml). The system is extracted from the glovebox and a septum of the flask is punctured with nitrogen inlet. Ether (1 ml) and n-BuLi (0.33 mmol) are added through septum as described in **general procedure I** in order to generate lithium diphenylphosphide. The upper septum of the stopcock was punctured by a syringe with 4 ml of ether (at this point the system should look like in Figure 17), the stopcock was opened and **318h** was washed off by ether to reaction mixture. After overnight stirring the generated ligand was allowed to react with $[Ir(COD)Cl]_2$ as described in the **general procedure I**.

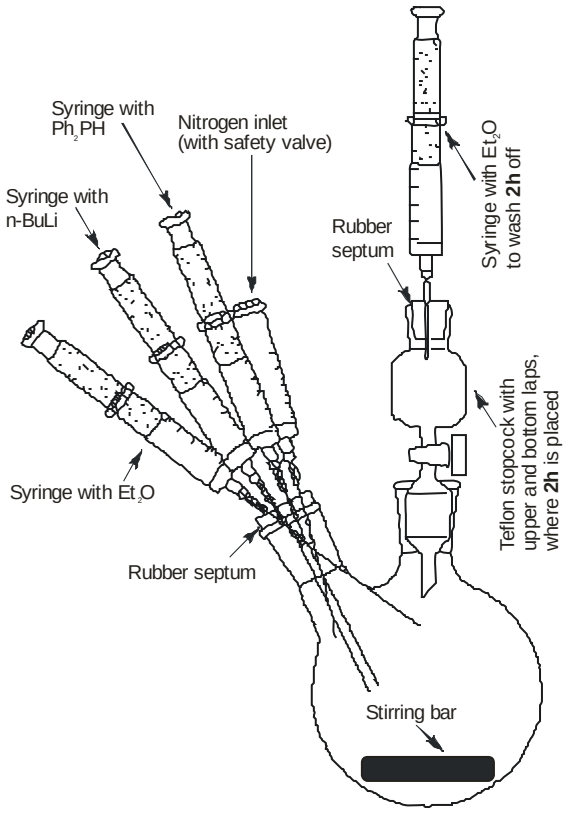


Figure 17

Yield: 79.6%. Red crystals. Very stable on storage even in $CDCl_3$-solution at r.t. (minimal 6 month). Unstable on storage in toluene.

$[\alpha]_D^{21}$=0 (c 0.105, $CHCl_3$, no rotation), $[\alpha]_{546}^{21}$=+ 156 (c 0.105, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 600 MHz, r.t.): δ = 0.76 (s, 3H, Me), 1.41 (s, 3H, Me), 1.47 (nrm, 1H, a-7-H_{COD}), 1.72 (nrm, 1H, a-3-H_{COD}), 2.01 (e-7-H_{COD}), 2.12 (nrm, 1H, e-3-H_{COD}), 2.42 (nrm, 1H, a-8-H_{COD}), 2.49 (a-4-H_{COD}), 2.52 (nrm, e-8-H_{COD}), 2.63 (e-4-H_{COD}), 3.03 (br s, 1H, NOE with 7.10 ppm, 6-H_{COD}), 3.54 (br s, 1H, NOR with 7.42 ppm, 5-H_{COD}), 5.12 (m, 1H, NOE with 4.69 ppm, 1-H_{COD}), 5.16 (m, 1H, 2-H_{COD}), 4.96 (d, J 8.5, 1H, NCH), 6.17 (d, J 8.5, 1H, OCH), 7.03 (d, J 7.6, 1H, 2```-H), 7.10 (dd, J 11.5, J 7.6, 2H, 2``-H), 7.24 (br d, J 8.2, 1H, 3-H), 7.28 (m, 1H, 4```-H), 7.37 (t, J 7.6, 1H, 3```-H), 7.38 (nrm, 1H, 4`-H), 7.42 (nrm, 5H, 2`-, 6`- and 3``- and 4``-H), 7.47 (m, 3H, 3`-, 5`- and 5```-H), 7.54 (br s, 4H, 4-H_{BARF}), 7.56 (t, J 7.6, 1H, 4-H), 7.61 (t, J 7.6, 1H, 5-H), 7.74 (br s, 8H, 2-H_{BARF}), 8.31 (ddd, J 8.2, J 4.1, J 1.1, 1H, 6-H).

^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz): δ = 26.8 (Me), 31.2 (Me), 25.7 (d, J 2.3, 3-CH_{2COD}), 28.1 (7-CH_{2COD}), 32.5 (8-CH_{2COD}), 36.2 (4-CH_{2COD}), 49.5 ($\underline{C}Me_2$), 62.9 (5-CH_{COD}), 63.9 (6-CH_{COD}), 79.09 (NCH), 87.8 (OCH), 91.2 (d, J 13.7, 2-CH_{COD}), 96.8 (d, J 10.0, 1-CH_{COD}), 117.50 (br s, 4-CH_{BARF}), 123.00 (d, J 58.5, 1``-C), 123.12 (2```-CH), 124.55 (q, J 273, CF_3), 126.30 (5```-CH), 127.59 (d, J 48.2, 2-C), 128.51 (4```-CH), 128.77 (2`- and 6-`CH), 128.9

(br q, J 30, 3-C_{BARF}), 128.99 (d, J 51.6, 1`-C), 129.58 (d, J 13.8, 1-C), 129.64 (d, J 11.5, 3``-CH), 131.82 (3```-CH), 132.10 (d, J 2.3, 5`-CH), 132.44 (d, J 2.3, 3`-CH), 132.52 (d, J 2.3, 5-CH), 133.21 (d, J 10.3, 2``-CH), 133.23 (6```-CH), 133.94 (d, J 11.5, 6-CH), 133.99 (4`-CH), 134.05 (4``-CH), 134.11 (d, J 6.9, 4-CH), 134.81 (br s, 2-CH_{BARF}), 135.35 (s, 3-CH), 150.87 (1```-CH), 161.72 (q 1:1:1:1, J 50.5, 1-C_{BARF}), 163.97 (d, J 5.7, C=N).

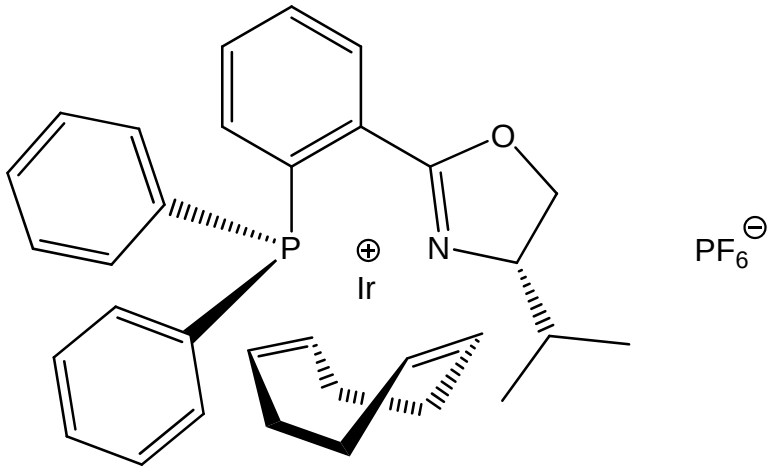
^{31}P NMR ($CDCl_3$, 161 MHz): δ = +16.5.

^{19}F NMR ($CDCl_3$, 128 MHz): δ = -62.8.

^{11}B NMR ($CDCl_3$, 376 MHz): δ = -6.9.

HRMS ESI/FT-ICR: isotope cluster 746-750, observed (calculated): 746.2302, 54.0% (746.2297, 59.5%); 747.2313, 21.8% (747.2330, 24.5%); 748.2293, 100.0% (748.2320, 100.0%); 749.2287, 42.5% (749.2354, 41.1%); 750.2255, 9.3% (750.2387, 8.2%).

Iridium (1,5-cyclooctadiene) ((S)-2-(2-(diphenylphosphino)phenyl)-4-isopropyl-4,5-dihydrooxazole) hexafluorophosphate 286j.



Up to anion-exchange everything was made by **general procedure I**. Solution of 1 mmol KPF_6 in 2 ml water was added to the complex with coordinated Cl. Two-phase system was vigorously stirred for 2 hours (anion-exchange could be monitored with TLC on silica gel with CH_2Cl_2-MeOH 20/1 eluent). The organic layer was separated with the help of syringe, and the aqueous rest was extracted 5 times with CH_2Cl_2. Joined organic extracts were dried over Na_2SO_4, filtrated, and filtrate evaporated. The rest was redissolved in minimal amount of CH_2Cl_2 and the target complex was precipitated with 100 ml Et_2O, filtrated, washed off from filter with CH_2Cl_2, evaporated and dried in deep vacuum.

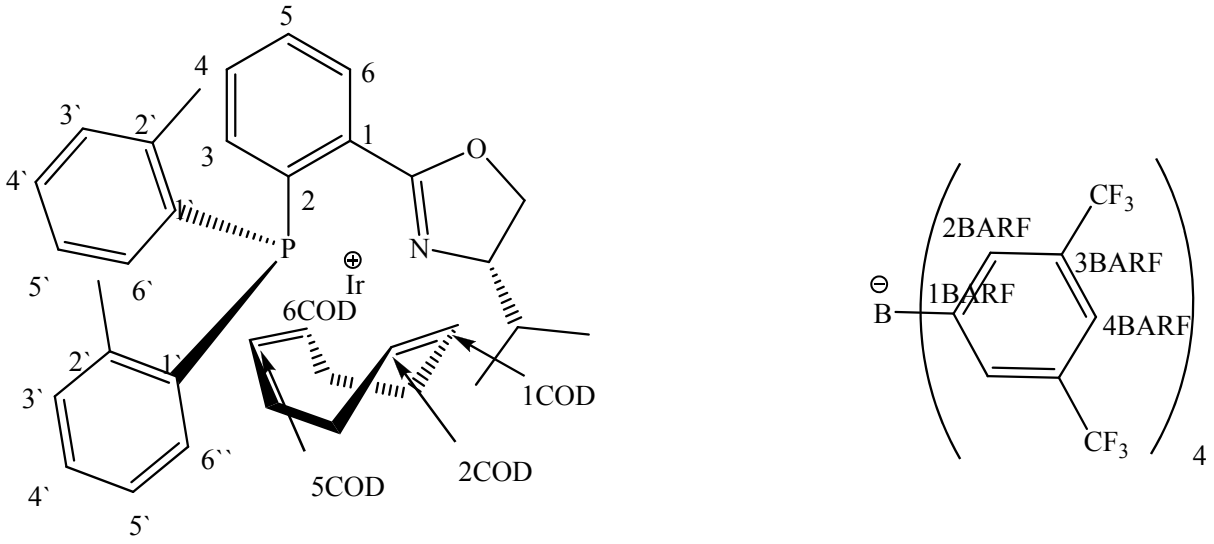
Yield:78% (best yield found in literature is 82%[457]). Red crystals. Unstable on storage in solution, but stable in crystalline state. Can be stored at r.t., but better at -20º C.

HRMS ESI/FT-ICR: isotope cluster 672-676, observed (calculated): 672.2162, 47.9% (672.2140, 59.5%); 673.2257, 13.1% (673.2174, 20.6%); 674.2150, 100.0% (674.2164, 100%); 675.2244, 32.1% (675.2197, 34.6%); 676.2269, 3.6% (676.2231, 5.8%).

General procedure J for the synthesis of 286e, 286f.

Bis(*o*-tolyl)phosphine (**317e**) is crystalline, that is why it was weighted in the glovebox directly in the 2-neck reaction-flask. There is no need to use syringe in the glovebox. Further operations according to **general procedure I**.

Iridium (1,5-cyclooctadiene) ((S)-2-(2-(dio-tolylphosphino)phenyl)-4-isopropyl-4,5-dihydrooxazole) tetrakis(3,5-bis(trifluoromethyl)phenyl) borate (286e).



Yield: 85%. Red crystals. Very stable on storage even in $CDCl_3$-solution at r.t. (minimum 6 months). Unstable on storage in toluene.

$[\alpha]_D^{20}$=-97 (c 0.13, $CHCl_3$)

^{31}P NMR (1,2,4-trichlorobenzene, 161 MHz, 140ºC): +12.5

^{1}H NMR ($CDCl_3$, 600 MHz, r.t., full assignment is not possible, tetntative assignment is given): δ = 0,05 (br s, 3H), 0.87 (br s, 3H, Me); 1.41 (br s, 1H, Me), 1.58 (br m, 1H); 1.95 (br s, 1H) 2.04 (br m, 2H, CHMe$_2$ and e-3-H$_{COD}$); 2.31 (br s, 1H); 2.35 (s, 6H, 2`-Me and 2``-Me); 2.42 (br m, 2H, e-8-CH$_{COD}$); 3.30 (br s, 2H, 5- and 6-H$_{COD}$); 4.15 (br s, 1H, OCH$_2$); 4.32 (t, J 9.54 Hz, 1H, OCH$_2$); 4.43 (br s, 1H, NCH); 4.68 (br q, J 6.7 Hz, NOE with 2.05 ppm, 1H, 1-CH$_{COD}$); 4.98 (br s, 1H, 2-CH$_{COD}$); 7.21 (br s, 2H, 6`-H); 7.37 (br s, 2H, 3`-H); 7.43 (br s, 2H, 4`-H); 7.52 (br s, 4H, BARF); 7.58 (br s, 3H, 3-, 4- and 5-H); 7.72 (br s, 8H, BARF); 8.09 (br m, 1H, 6-H).

$^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 150 MHz, r.t., assignment is not possible): δ = 12.31; 13.26; 18.71; 24.0; 27.90; 29.71; 31.17; 32.41; 21.97; 35.30; 36.16; 68.18; 70.32; 68.9; 94.6; 117.46 (BARF); 124.55 (q, J 273 Hz, BARF); 127.08 (d, J 8 Hz); 128.9 (br q, J 30Hz, BARF); 129.51; 132.11; 132.46 (d, J 8 Hz); 132.62; 133.66; 133.71; 133.81 (d, J 8 Hz); 134.81 (BARF); 135.3; 161.72 (q, J 50.5 Hz, BARF); 163.88

^{31}P NMR ($CDCl_3$, 161 MHz, r.t.): 8.54 (br s, 0.9 P); 16.14 (br s, 1 P).

^{19}F NMR ($CDCl_3$, 128 MHz, r.t.): δ = -62.8.

^{11}B NMR ($CDCl_3$, 376 MHz, r.t.): δ = -6.9.

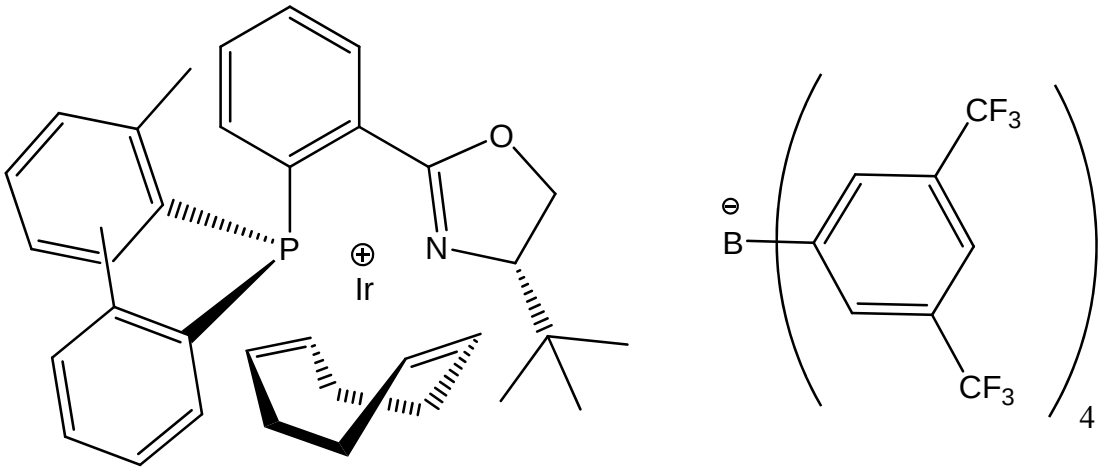
^{1}H NMR ($CDCl_3$, 400 MHz, -40ºC): δ = -0.09 (d, J 6.64 Hz, 1H); 0.12 (d, J 6.6 Hz, 1.6 H); 0.84 (d, J 7 Hz, 1.3 H); 0.92 (d, J 6.6 Hz, 1.8 H); 1.37 (br s, 1.2 H); 1.55 (br s, 1.3 H); 1.85-2.04 (br m, 4.9 H); 2.22-2.57 (br m, 8.6 H); 2.82 (br s, 0.4 H); 3.15 (br s, 0.4 H); 3.28-3.39 (br m, 1.65H); 4.1-4.2 (br m, 0.9 H); 4.32-4.44 (br m, 1.3 H); 4.50 (br d, J 7 Hz, 0.6 H); 4.67 (br s, 1 H); 4.93-5.08 (br m, 0.9 H); 6.63 (m , 0.8 H); 6.91 (m, 0.7 H); 7.07 (m, 0.7 H); 7.18-7.26 (m, 1.7 H); 7.34-7.70 (m, 12 H); 7.75 (br s, 8H, BARF); 8.07 (br m, 1H); 9.07 (m, 0.5 H)

$^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 150 MHz, -40ºC): δ = 11.94; 13.26; 18.69; 23.45 (br s); 23.79 (d, J 8); 24.67 (d, J 5.7); 25.32; 26.77 (d, J 8); 27.36; 27.67; 29.70 (br s); 32.12; 32.24; 32.27; 33.06; 35.38 (br s); 36.23 (br s); 64.07; 65.04; 66.42; 67.51; 67.81; 68.05; 69.66; 69.88; 88.31 (d, J 12.6); 89.20 (br d, J 13.8); 94.03 (d, J 10.3); 94.76 (br d, J 9.2); 117.36 (BARF); 117.51 (d, J 57.0); 117.67; 120.39 (d, J 53.92); 124.55 (q, J 273, BARF); 125.99; 126.31 (d, J 4.6); 126.43; 126.77; 126.84 (d, J 4.6); 126.99 (d, J 6.9); 127.07 (d, J 8.0); 127.70 (d, J 12.6); 127.68; 128.29 (d, J 19.5); 128.9 (br q, J 30); 129.17; 131.7-132.4 (m); 133.2-133.7 (m); 133.89; 134.38; 134.53 (BARF); 135.83; 140.57 (d, J 9.2); 141.51 (d, J 9.2); 142.60; 142.70; 140.80; 143.45; 161.72 (q, J 50.5 Hz, BARF); 163.16 (d, J 4.6); 163.76 (d, J 8.0)

^{31}P NMR ($CDCl_3$, 161 MHz, -40ºC): δ = 8.21 (s, 0.75 P); 15.75 (s, 1 P)

HRMS ESI/FT-ICR: isotope cluster 644-648, observed (calculated): 700.2441, 51.1% (700,2453, 59.5%); 701.2434, 17.0% (701,2487, 21.9%); 702.2472, 100.0% (702,2477, 100.0%); 703.2477, 33.9% (703,2510, 36.8%); 704.2539, 5.6% (703,2510, 6.6%).

Iridium (1,5-cyclooctadiene) ((S)-4-tert-butyl-2-(2-(di(*o*-tolyl)phosphino)phenyl)-4,5-dihydrooxazole) tetrakis(3,5-bis(trifluoromethyl)phenyl) borate (4f).



Yield: 83% (best yield found in literature is 72%[341]). Orange crystals. Very stable on storage even in $CDCl_3$-solution at r.t. (minimum 6 months). Unstable on storage in toluene.

HRMS ESI/FT-ICR: isotope cluster 714-718, observed (calculated): 714.2635, 62.4% (714,2610, 59.5%); 715.2706, 25.4% (715,2643, 22.5%); 716.2624, 100.0% (716,2633, 100%); 717.2667, 44.8% (717,2667, 37.9%); 718.2744, 8.7% (718,2700, 7.0%).

General procedure K for the synthesis of 286i, 286l.

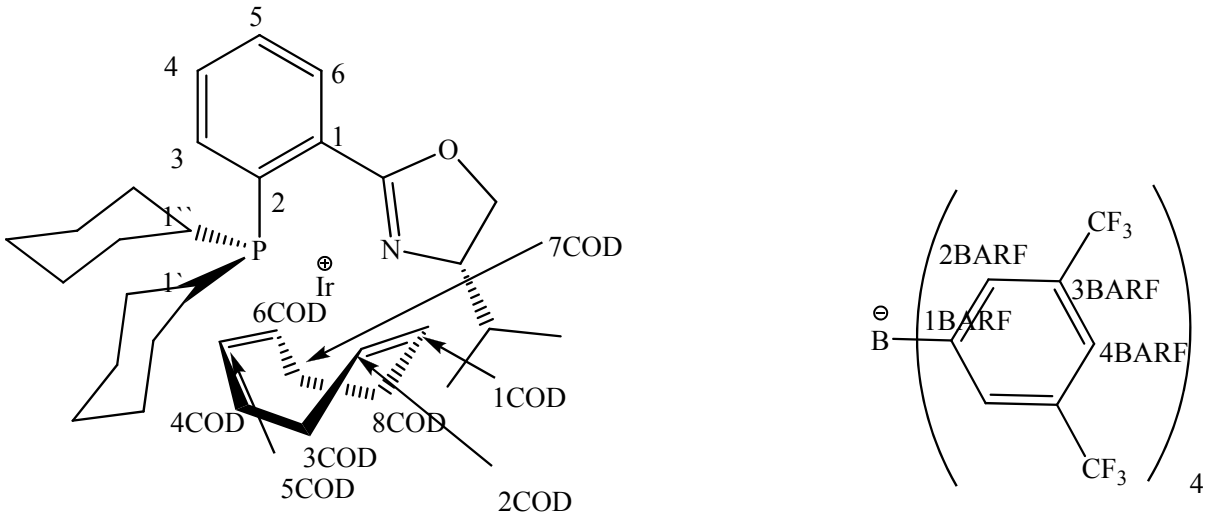
The 2-neck 10 mL flask, rubber-septum, magnetic stirrer, 1 mL syringe, needle and a stopcock were evacuated to nitrogen filled glovebox. Magnetic stirrer was placed in flask, one neck sealed with septum and the other with stopcock. Dicyclohexylphosphine (**317i**, 0.33 mmol) was weighted in syringe and the septum was punctured with this syringe in glovebox. Then this system was extracted from the glovebox, the stopcock connected with nitrogen-line and opened (see Figure 15).

4 Ml of MTBE were added *via syringe* through septum. After dissolving of phosphine (1 min) 0.33 mmol of n-butyllithium (1.6 M solution in hexane) were added to this mixture *via syringe* through septum at r.t. and this colourless mixture was stirred for 30 min. Then 0.3 mol of **318** were weighted in syringe (allowed on air) and added to the reaction mixture through septum. The syringe was washed with the reaction mixture. The septum was removed and a reflux condenser, sealed by paraffin oil sealed bubbler with nitrogen inlet, was built. Under nitrogen, coming from this bubbler, the stopcock from the flask was removed and the neck was sealed (Figure 16).

The mixture was refluxed for 12 hours and cooled. At this point a gas chromatography with mass-sensitive analyzer was performed, which showed a conversion of **318** over 80% into the ligand **316**. The mixture was evaporated in the stream of nitrogen through side-neck, 0.15 mmol of $[Ir(COD)Cl]_2$ and 3 ml of CH_2Cl_2 were added, and the mixture was refluxed for

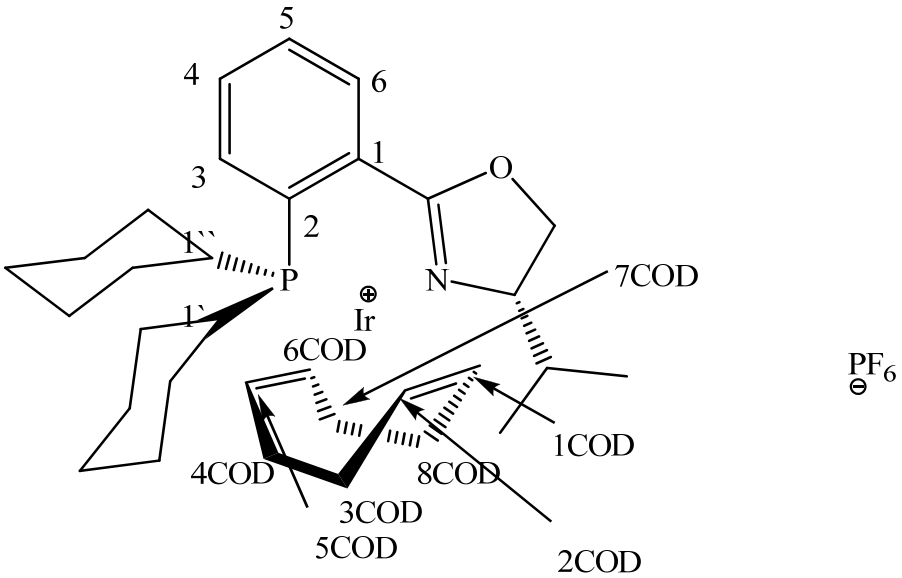
4 hours (Figure 16). At this point an air-stable complex of iridium is formed, hence all operations could be made on air. Anion-exchange to BARF was made according to the **general procedure I** (for **286i**), an exchange to PF_6 similar to that for complex **286j**.

Iridium (1,5-cyclooctadiene) ((S)-2-(2-(dicyclohexylphosphino)phenyl)-4-isopropyl-4,5-dihydrooxazole) tetrakis(3,5-bis(trifluoromethyl)phenyl) borate (286i)



Yield: 70%. This complex was catalytically active in stilbene hydrogenation, but contaminated by dicyclohexylphosphine oxide, and the contaminant was not removed even by gradient column chromatography (hexane-dichloromethane). The synthesis of analytically pure **286i** is described below.

Iridium (1,5-cyclooctadiene) ((S)-2-(2-(dicyclohexylphosphino)phenyl)-4-isopropyl-4,5-dihydrooxazole) hexafluorophosphate (286l)



Yield: 68%. Red crystals. Very unstable on storage even in crystalline state at r.t. (stable for 1 day, then decomposes). Should be stored at -20º C

$[\alpha]_D^{19}$=-136 (c 0.11, $CHCl_3$)

^{1}H NMR ($CDCl_3$, 600 MHz, r.t.): δ = 0.80 (d, J 6.6, 3H, Me), 1.08 (d, J 6.9, 3H, Me), 1.15-1.4 (nrm, 8H, Cy), 1.4-1.5 (nrm, 2H, Cy), 1.70-1.95 (nrm, 10H, Cy), 1.61 (nrm, 1H, a-4-H_{COD}), 1.66 (nrm, 1H, a-8-H_{COD}), 2.07 (nrm, 2H, $\underline{CH}Me_2$ and e-8-H_{COD}), 2.13 (nrm, 2H, e-4-H_{COD} and 1`-H), 2.29 (nrm, 1H, a-3-H_{COD}), 2.49 (nrm, 4H, e-3-H_{COD}, 7-H_{COD} and 1``-H), 3.69 (br s, 1H, 5-H_{COD}), 4.15 (br s, 1H, 6-H_{COD}), 4.32 (m, 1H, NCH), 4.62 (d, J 5.9, 2H, OCH_2), 4.74 (m, NOE with 2.07, 4.32 and 4.62 ppm, 1H, 1-H_{COD}), 5.13 (br s, NOE with 4.32 and 4.62 ppm, 1H, 2-H_{COD}), 7.67 (pseudo-t, J 7.8, 1H, 5-H), 7.78 (m, 2H, 3- and 4-H), 8.31 (dd, J 7.9, J 2.9, 1H, 6-H).

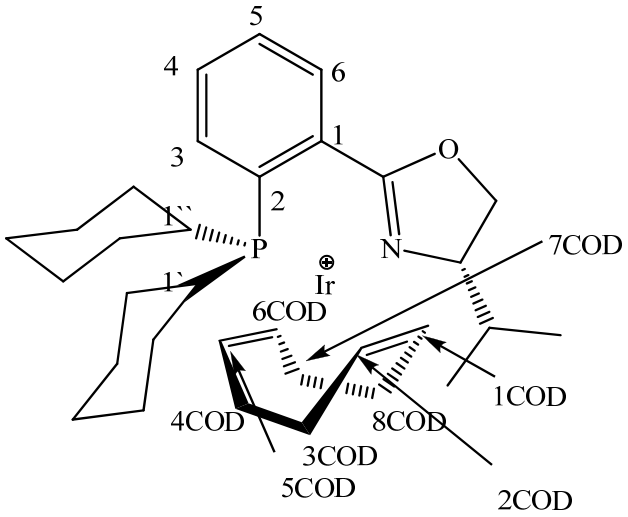
^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz): δ = 14.84 (Me), 19.26 (Me), 25.87 (Cy), 26.03 (Cy), 26.09 (8-CH_{2COD}), 26.94 (d, J 8.0, Cy), 27.02 (d, J 9.2, Cy), 27.13 (d, J 11.5, Cy), 27.32 (d, J 9.2, Cy), 28.12 (d, J 3.4, Cy), 29.11 (Cy), 29.44 (4-CH_{2COD}), 29.98 (Cy), 30.65 (Cy), 31.65 (3-CH_{2COD}), 32.09 (d, J 27.5, 1``-CH), 32.96 ($\underline{CH}Me_2$), 36.15 (7-CH_{2COD}), 41.95 (d, J 26.4, 1`-CH), 59.86 (5-CH_{COD}), 61.92 (6-CH_{COD}), 68.20 (OCH_2), 70.19 (NCH), 89.90 (d, J 11.5, 1-CH_{COD}), 95.46 (d, J 11.5, 2-CH_{COD}), 126.80 (d, J 35.6, 2-C), 129.45 (d, J 9.2, 1-C), 131.74 (d, J 2.3, 5-CH), 132.43 (d, J 1.2, 3-CH), 133.87 (d, J 5.7, 4-CH), 134.07 (d, J 8.0, 6-CH), 164.34 (d, J 5.7, N=C).

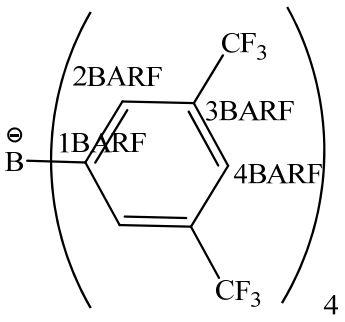
^{31}P NMR ($CDCl_3$, 161 MHz): δ = +10.1 (ligand), -143.7 (sep, J 714 Hz, PF_6).

^{19}F NMR ($CDCl_3$, 128 MHz): δ = -73.6 (J 714 Hz).

HRMS ESI/FT-ICR: isotope cluster 684-688, observed (calculated): 684.3051, 53.8% (684.3079, 59.5%); 685.3070, 17.3% (685.3113, 20.6%); 686.3089, 100.0% (686.3103, 100%); 687.3071, 33.1% (687.3136, 34.6%); 688.3137, 5.4% (688.3170, 5.8%).

Iridium (1,5-cyclooctadiene) ((S)-2-(2-(dicyclohexylphosphino)phenyl)-4-isopropyl-4,5-dihydrooxazole) tetrakis(3,5-bis(trifluoromethyl)phenyl) borate 286i from **286l**





50 Mg (0.06 mmol) of **286l** and 54 mg (0.061 mmol) of NaBARF were dissolved in 5 ml of dichloromethane. The anion-exchange was monitored by TLC on silica gel eluting with CH_2Cl_2. *Rf* of **286i** is 0, that of **286i** is 0.9. In 2 hours the mixture was adsorbed on silica gel and chromatographed according to the **general procedure I**.

Yield: 71%. Red crystals. Stable on storage in crystalline form at r.t. for at least 1 week. Nevertheless, it should be stored at -20º C.

$[\alpha]_D^{19}$=-48 (c 0.135, $CHCl_3$)

^{1}H NMR ($CDCl_3$, 600 MHz, r.t.): δ = 0.77 (d, J 6.4, 3H, Me), 1.00 (d, J 7.0, 3H, Me), 1.19-1.35 (nrm, 8H, Cy), 1.37-1.50 (nrm, 2H, Cy), 1.66-1.93 (nrm, 10H, Cy), 1.61 (nrm, 2H, a-4- and a-8-H_{COD}), 2.01 (nrm, 1H, e-8-H_{COD}), 2.07 (m, 1H, $\underline{CH}Me_2$), 2.14 (nrm, 1H, e-4-H_{COD}), 2.07 (nrm, 1H, a-7-H_{COD}), 2.22 (nrm, 1H, 1`-H), 2.23 (nrm, 1H, a-3-H_{COD}), 2.38 (nmr, 1H, e-3-H_{COD}), 2.46 (nrm, 1H, e-7-H_{COD}), 2.47 (nrm, 1H, 1``-H), 3.72 (br s, 5-CH_{COD}), 4.16 (dt, J 8.8, J 2.9, 1H, NCH), 4.19 (br s, 1H, 6-CH_{COD}), 4.32 (t, J 9.4, 1H, OCH_2), 4.55 (dd, J 9.4, J 2.9, 1H, OCH_2), 4.66 (m, NOE with 4.16, 2.07, 0.77 ppm, 1H, 1-H_{COD}), 4.86 (br s, NOE with 4.16 ppm, 1H, 2-H_{COD}), 7.54 (br s, 4H, 4-H_{BARF}), 7.55 (m, 1H, 5-H), 7.66 (t, J 7.6, 1H, 4-H), 7.74 (br s and d, J 8.8, 9H, 2-H_{BARF} and 3-H), 8.21 (dd, J 10.6, J 2.4, 1H, 6-H).

^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz): δ = 14.53 (Me), 19.16 (Me), 25.76 (Cy), 26.00 (2C, Cy and 8-CH_{2COD}), 26.91 (d, J 9.2, Cy), 26.99 (d, J 9.2, Cy), 27.12 (d, J 11.47, Cy), 27.37 (d, J 10.3, Cy), 28.23 (d, J 2.3, Cy), 29.18 (Cy), 29.43 (4-CH_{2COD}), 30.18 (Cy), 30.68 (Cy), 31.57 (3-CH_{2COD}), 32.20 (d, J 28.7, 1``-C), 32.87 ($\underline{CH}Me_2$), 36.04 (d, J 3.5, 7-CH_{2COD}), 42.18 (d, J 27.5, 1`-C), 60.82 (5-CH_{COD}), 62.92 (6-CH_{COD}), 67.87 (OCH_2), 70.27 (NCH), 89.43 (d, J 13.8, 1-CH_{COD}), 94.14 (d, J 10.3, 2-CH_{COD}), 117.50 (br s, 4-CH_{BARF}), 124.55 (q, J 273, CF_3), 127.04 (d, J 35.6, 2-C), 128.9 (br q, J 30, 3-C_{BARF}), 129.16 (d, J 11.5, 1-C), 131.84 (5-CH),

132.38 (s, 3-CH), 134.03 (d, J 6.9, 6-CH), 134.81 (br s, 2-CH_{BARF}), 133.94 (d, J 5.7, 4-CH), 161.72 (q 1:1:1:1, J 50.5, 1-C_{BARF}), 164.4 (d, J 5.8, N=C).

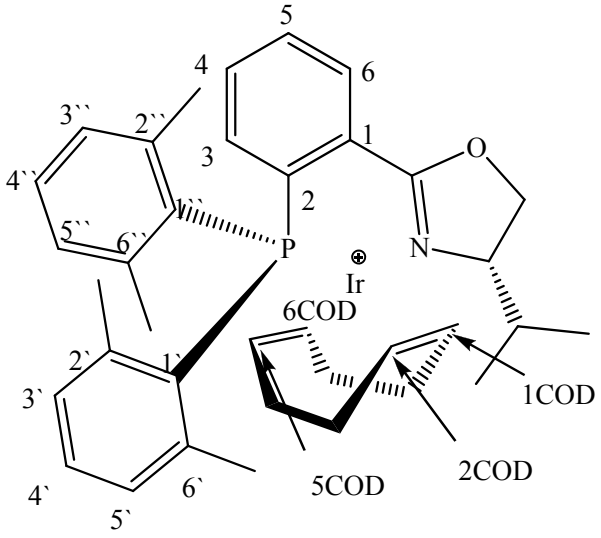
^{31}P NMR ($CDCl_3$, 161 MHz): δ = +10.4.

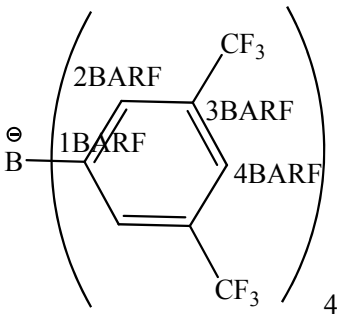
^{19}F NMR ($CDCl_3$, 128 MHz): δ = -62.8.

^{11}B NMR ($CDCl_3$, 376 MHz): δ = -6.9.

HRMS ESI/FT-ICR: isotope cluster 684-688, observed (calculated): 684.3045, 53.7% (684.3079, 59.5%); 685.3143, 19.3% (685.3113, 20.6%); 686.3098, 100.0% (686.3103, 100%); 687.3043, 34.3% (687.3136, 34.6%); 688.3145, 8.0% (688.3170, 5.8%).

Iridium (1,5-cyclooctadiene) ((S)-2-(2-(bis(2,6-dimethylphenyl)phosphino)phenyl)-4-isopropyl-4,5-dihydrooxazole) tetrakis(3,5-bis(trifluoromethyl)phenyl) borate 286g.





Dixylylphosphine (**317g**) is crystalline, that is why it was weighted in the glovebox directly in the 2-neck reaction-flask. There is no need to use syringe in the glovebox. Further operations according to the **general procedure K**.

Yield: 66.9%. This complex was catalytically active in stilbene hydrogenation, but spectrally impure. It cannot be purified even by gradient column chromatography (hexane-dichloromethane). Yellow crystals, unstable even in crystalline state at r.t. Should be stored at -20º C.

$[\alpha]_D^{21}$=-19(c 0.12, $CHCl_3$), $[\alpha]_{546}^{21}$=-48 (c 0.12, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 600 MHz, r.t.): δ = 0.48 (d, J 6.7, 3H, Me_{iPr}), 1.01 (d, J 6.7, 3H, Me_{iPr}), 1.85 (s, 3H, 6``-Me), 2.00 (s, 3H, 2``-Me), 2.22 (s, 3H, 2`-Me), 2.50 (m, 1H, CHMe_2), 3.19 (m, 1H, 5-H_{COD}), 3.29 (m, 1H, 6-H_{COD}), 4.40 (br d, J 8.1, 2H, OCH_2), 4.63 (br td, J 8.1, J 2.5, 1H, NCH), 4.70 (m, NOE with 3.29 ppm, with 1.76 ppm, 1H, 2-H_{COD}), 5.24 (m, 1H,

NOE with 2.5 ppm, 4.63 ppm), 6.86 (br s, 1H, 4`-H), 7.05 (nrm, 2H, 3`- and 5`-H), 7.15 (nrm, 2H, 3``- and 5``-H), 7.37 (nrm, 1H, 4``-H), 7.54 (br s, 4H, 4-H_{BARF}), 7.55 (t, J 7.5, 1H, 5-H), 7.66 (t, J 7.5, 1H, 4-H), 7.74 (br s, 8H, 2-H_{BARF}), 8.05 (dd, J 10.3, J 7.5, 1H, 3-H), 8.27 (t, J 7.5, 1H, 6-H), CH_{2COD} and 6`-Me are not distinguishable, since the compound is not spectrally pure.

$^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 150 MHz): δ = 7.53 (6`-Me), 13.78 ($Me_{iPr}$), 19.01 ($Me_{iPr}$), 22.78 (2C, 2`-Me and 2``-Me), 26.73 (6``-Me), 29.94 (CHMe$_2$), 44.66 (6-CH_{COD}), 66.90 (5-CH_{COD}), 67.04 (OCH_2), 79.38 (d, J 23.8, 1-CH_{COD}), 81.75 (NCH), 103.05 (s, 2-CH_{COD}), 117.50 (br s, 4-CH_{BARF}), 123.42 (d, J 16.5, 3`-CH), 124.55 (q, J 273, CF_3), 126.00 (d, J 12.8, 1-C), 126.28 (d, J 56.82, 1``-C), 128.9 (br q, J 30, 3-$C_{BARF}$), 129.76 (d, J 47.7, 2-C), 130.32 (d, J 7.3, 4`-CH), 130.51 (d, J 88.0, 1`-C), 130.74 (d, J 7.3, 3``-CH), 130.76 (d, J 12.8, 6`-CMe), 131.14 (d, J 7.3, 5``-CH), 131.48 (s, 4``-CH), 131.68 (s, 5`-CH), 131.82(5-CH), 131.98 (d, J 7.3, 4-CH), 134.81 (br s, 2-CH_{BARF}), 134.85 (d, J 7.3, 6-CH), 135.53 (s, 3-CH), 140.35 (d, J 9.2, 2``-CMe), 141.27 (d, J 9.2, 6``-CMe), 141.45 (d, J 1.6, 2`-CMe), 161.72 (q 1:1:1:1, J 50.5, 1-C_{BARF}), 163.8 (d, J 5.5, N=C), CH_{2COD} are not distinguishable, since the compound is not spectrally pure.

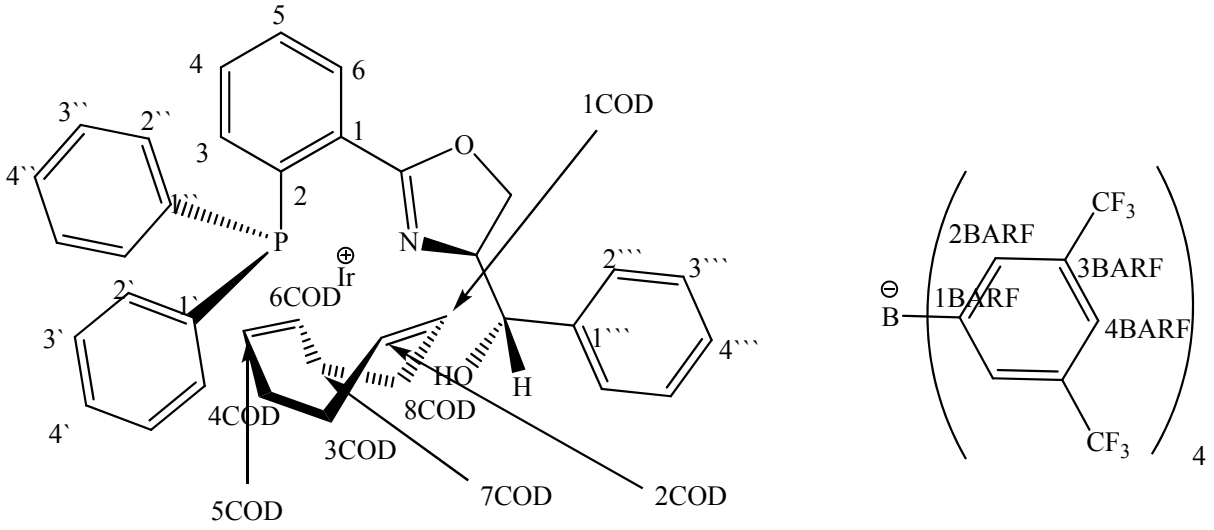
^{31}P NMR ($CDCl_3$, 161 MHz): δ = +20.8.

^{19}F NMR ($CDCl_3$, 128 MHz): δ = -62.8.

^{11}B NMR ($CDCl_3$, 376 MHz): δ = -6.9.

HRMS ESI/FT-ICR: isotope cluster 728-732, observed (calculated): 728.2704, 78.4% (728.2766, 59.5%); 729.2763, 28.2% (729.2800, 23.2%); 730.2783, 100.0% (730.2790, 100.0%); 731.2773, 35.7% (731.2823, 38.9%); 732.2912, 5.4% (732.2857, 7.4%).

Iridium (1,5-cyclooctadiene) ((S)-((S)-2-(2-(diphenylphosphino)phenyl)-4,5-dihydrooxazol-4-yl)(phenyl)methanol) tetrakis(3,5-bis(trifluoromethyl)phenyl) borate 286m.



41.3 Mg (0.152 mmol) of **318m** were dissolved in 5 ml of abs. Et_2O (under nitrogen). To this solution 0.64 ml of 0.5N $KPPh_2$ (0.32 mmol) in THF (Aldrich) at r.t. were added and this mixture was stirred overnight (for about 10 h) at r.t. Degased water (a few drops) was added and all volatiles (including diphenylphosphine) were removed in vacuum of the oil-pump with heating (60º C).

The rest was redissolved in 5 ml of abs. CH_2Cl_2. This solution showed one signal at -6 ppm (consistent with[360]) in ^{31}P NMR. 50 Mg (0.0744 mmol) of $[Ir(COD)Cl]_2$ were added to this solution and it was stirred at r.t. for 2 hours (refluxing leads to complex decomposition). ^{31}P NMR of this solution showed one singlet at +20 ppm. From this point everything was made under air. 135 Mg (0.152 mmol) of NaBARF were added and the mixture was stirred for 2 h. The mixture was adsorbed on 1 g of silica gel and the column chromatography was performed on 20 g of silica gel according to **the general procedure I** with the mixture CH_2Cl_2-Hexane (2/1). The first spot represents some by-products, whereas the more polar second spot represents the title compound.

Yield: 34%. Red crystals. After dissolving in $CDCl_3$ begins to decompose in 1 h. Very unstable even in crystalline state at r.t. Should be stored at -20º C or colder.

$[\alpha]_D^{25}$=-113 (c 0.11, $CHCl_3$)

^1H NMR ($CDCl_3$, 600 MHz, r.t.): δ = 1.44 (nrm, 1H, a-4-H_{COD}), 1.57 (nrm, 1H, a-8-H_{COD}), 2.01 (nrm, 1H, e-8-H_{COD}), 2.05 (nrm, 1H, e-4-H_{COD}), 2.41 (nrm, 1H, a-7-H_{COD}), 2.47 (nrm, 1H, a-3-H_{COD}), 2.52 (nrm, 1H, e-3-H_{COD}), 2.53 (nrm, 1H, e-7-H_{COD}), 3.21 (s, 1H, NOE with 7.14 ppm, 5-H_{COD}), 3.38 (s, 1H, 6-H_{COD}), 3.72 (m, 2H, OCH_2), 4.13 (m, 1H, NCH), 4.68 (br s, 2-H_{COD}), 4.82 (s, 1H, NOE with 4.13 ppm, 1-H_{COD}), 5.68 (d, J 3.5, CHOH), 7.14 (br s, 2H, 2`-H), 7.26 (s under signal of $CHCl_3$, 2```-H), 7.44 (nrm, 1H, 3-H), 7.46 (nrm, 1H, 4```-

H), 7.47 (nrm, 3H, 4`- and 3```-H), 7.49 (nrm, 2H, 3`-H), 7.54 (br s, 4H, 4-H_{BARF}), 7.57 (nrm, 1H, 4``-H), 7.58 (nrm, 2H, 3``-H), 7.65 (nrm, 2H, 2``-H), 7.66 (nrm, 1H, 4-H), 7.70 (nrm, 1H, 5-H), 7.74 (br s, 8H, 2-H_{BARF}), 8.31 (m, 1H, 6-H), OH-exchanged.

$^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 150 MHz): δ = 26.37 (8-CH_{2COD}), 28.52 (4-CH_{2COD}), 32.24 (7-CH_{2COD}), 36.15 (3-CH_{2COD}), 64.12 (5-CH_{COD}), 64.42 (6-CH_{COD}), 64.54 (OCH_2), 74.27 (NCH), 83.33 (CHOH), 93.76 (d, J 13.8, 1-CH_{COD}), 97.08 (d, J 11.5, 2-CH_{COD}), 117.50 (br s, 4-CH_{BARF}), 121.20 (d, J 58.5, 1`-C), 124.55 (q, J 273, CF_3), 124.85 (2```-CH), 128.51 (d, J 48.19, 2-C), 128.63 (d, J 12.6, 1-C), 128.9 (br q, J 30, 3-C_{BARF}), 129.15 (d, J 11.5, 3`-CH), 129.75 (3```-CH), 129.82 (d, J 53.9, 1``-C), 130.04 (3``-CH), 130.18 (4```-CH), 130.40 (4`-CH), 132.46 (4``-CH), 132.59 (5-CH), 132.99 (d, J 14.5, 2`-CH), 133.84 (s, 3-CH), 133.86 (d, J 8.0, 6-CH), 134.41 (d, J 12.6, 3C, 4- and 2``-CH), 134.81 (br s, 2-CH_{BARF}), 136.93 (1```-C), 161.72 (q, 1:1:1:1, J 50.5, 1-C_{BARF}), 164.67 (d, J 5.7, N=C).

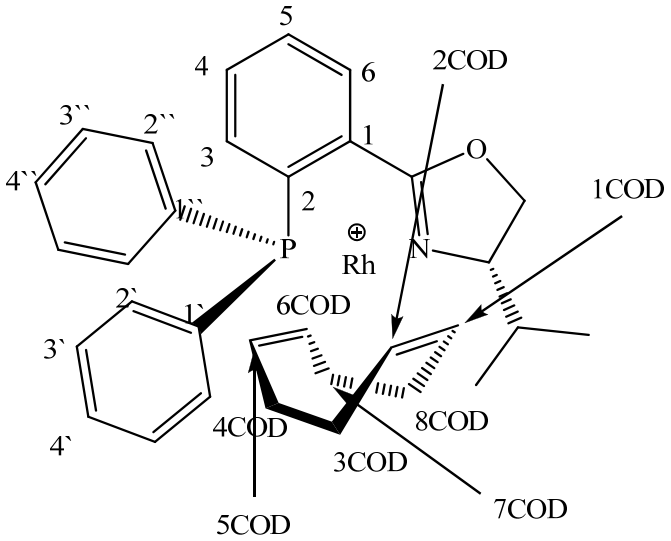
^{31}P NMR ($CDCl_3$, 161 MHz): δ = +16.9.

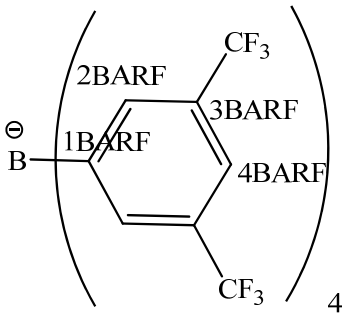
^{19}F NMR ($CDCl_3$, 128 MHz): δ = -62.8.

^{11}B NMR ($CDCl_3$, 376 MHz): δ = -6.9.

HRMS ESI/FT-ICR: isotope cluster 736-740, observed (calculated): 736.2111, 54.1% (736.2090, 59.5%); 737.2136, 22.5% (737.2123, 23.2%); 738.2131, 100.0% (738.2113, 100.0%); 739.2160, 35.5% (739.2146, 38.9%), 740.2230, 5.4% (740.2180, 7.4%).

Rhodium (1,5-cyclooctadiene) ((S)-2-(2-(diphenylphosphino)phenyl)-4-isopropyl-4,5-dihydrooxazole) tetrakis(3,5-bis(trifluoromethyl)phenyl) borate 319.





According to the **general procedure I**, but $[Rh(COD)Cl]_2$ was taken instead of iridium-complex.

Yield: 86%. Yellow crystals. Stable in $CDCl_3$ solution at -20º C for at least 2 weeks. Should be stored at -20º C in crystalline form.

$[\alpha]_D^{21}$ -41 (c 0.11, $CHCl_3$)

^1H NMR ($CDCl_3$, 600 MHz, r.t.): δ = -0.15 (d, J 6.6, 3H, Me), 0.80 (d, J 7.0, 3H, Me), 1.85 (nrm, a-4-H_{COD}), 1.95 (nrm, 2H, $\underline{CH}Me_2$ and a-8-H_{COD}), 2.13 (nrm, 1H, e-4-H_{COD}), 2.19 (nrm, 1H, e-8-H_{COD}), 2.45 (nrm, 1H, a-3-H_{COD}), 2.50 (nrm, 1H, a-7-H_{COD}), 2.69 (nrm, e-3-H_{COD}), 2.79 (nrm, 1H, e-7-H_{COD}), 3.51 (br s, NOE with 7.05 ppm, 1H, 5-H_{COD}), 3.59 (br s, NOE with 7.05, 7.68 ppm, 1H, 6-H_{COD}), 3.79 (br d, J 8.7, 1H, NCH), 4.29 (t, J 9.4, 1H, OCH_2), 4.33 (dd, J 9.4, J 3.5, 1H, OCH_2), 5.27 (br s, 2H, 1- and 2-H_{COD}), 7.05 (nrm, 2H, 2`-H), 7.33 (br dd, J 9.0, J 7.0, 1H, 3-H), 7.41 (t, J 7.2, 2H, 3`-H), 7.50 (br s, 3H, 4`- and 3``-H), 7.54 (br s, 4H, 4-$H_{BARF}$), 7.56 (nrm, 1H, 4``-H), 7.61 (nrm, 2H, 4- and 5-H), 7.68 (nrm, 2H, 2``-H), 7.74 (br s, 8H, 2-H_{BARF}), 8.09 (m, 1H, 6-H).

$^{13}C\{^1H\}$ NMR ($CDCl_3$, 150 MHz): δ = 12.29 (Me), 18.79 (Me), 26.33 (8-CH_{2COD}), 28.65 (4-CH_{2COD}), 30.70 (3-CH_{2COD}), 32.44 ($\underline{CH}Me_2$), 35.33 (7-CH_{2COD}), 67.74 (OCH_2), 70.90 (NCH), 77.61 (d, J 11.5, 6-CH_{COD}), 79.05 (d, J 12.6, 5-CH_{COD}), 105.52 (dd, J 11.5, J 8.0, 1-CH_{COD}), 107.66 (dd, J 9.2, J 6.9, 2-CH_{COD}), 117.45 (br s, 4``-CH), 117.50 (br s, 1-$CH_{BARF}$), 124.33 (d, J 49.3, 1`-C), 124.55 (q, J 273, $CF_3$), 128.52 (d, J 40.2, 2-C), 128.54 (d, J 14.9, 1-C), 128.9 (br q, J 30, 3-$C_{BARF}$), 129.03 (d, J 10.3, 3`-CH), 129.13 (1``-C), 129.80 (d, J 10.3, 3``-CH), 131.81 (d, J 2.3, 4`-CH), 132.20 (d, J 2.3, 5-CH), 132.64 (d, J 2.3, 4-CH), 132.86 (d, J 10.3, 2`-CH), 133.64 (d, J 8.0, 6-CH), 133.72 (d, J 13.8, 3-CH), 134.46 (d, J 12.6, 2``-CH), 134.81 (br s, 2-CH_{BARF}), 161.72 (q 1:1:1:1, J 50.5, 1-C_{BARF}), 163.81 (d, J 8.0, N=C).

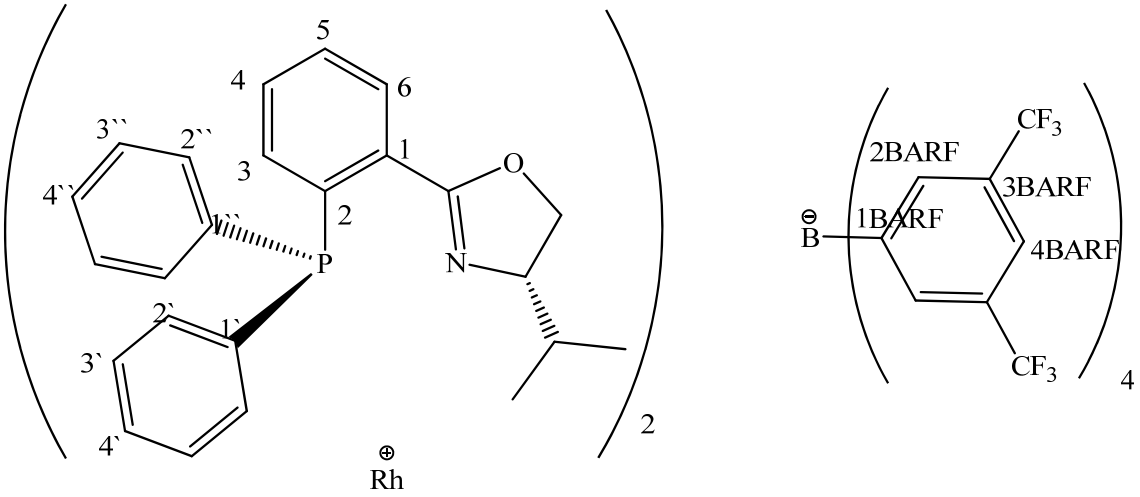
^{31}P NMR ($CDCl_3$, 161 MHz): δ = +30.7 (d, J 154.1).

^{19}F NMR ($CDCl_3$, 128 MHz): δ = -62.8.

^{11}B NMR ($CDCl_3$, 376 MHz): δ = -6.9.

HRMS ESI/FT-ICR: isotope cluster 584-586, observed (calculated): 584.1588, 100.0% (584.1590, 100%); 585.1596, 32.3% (585.1623, 34.6%); 586.1613, 5.3% (586.1657, 5.8%).

Rhodium cis- bis ((S)-2-(2-(diphenylphosphino)phenyl)-4-isopropyl-4,5-dihydrooxazole) tetrakis(3,5-bis(trifluoromethyl)phenyl) borate 320.



Synthesized from 84 mg (0.405 mmol) of **318c**, 84 mg (0.451 mmol) of **317a**, 0.451 mmol of n-BuLi, 40 mg (0.081 mmol) of $[Rh(COD)Cl]_2$ and 144 mg (0.162 mmol) of NaBARF according the **general procedure I**. After anion-exchange the mixture was adsorbed on silica gel and evaporated. The column was packed in hexane and silica with adsorbed complex placed on top. The whole column was first eluated with ca 100 ml of hexane in order to remove cyclooctadiene, then with CH_2Cl_2 in order to eluate the title complex.

Yield: 81.6%. Brown crystals. Unstable at r.t. even in crystalline form, should be stored at -20º C.

$[\alpha]_D^{21}$ -687 (c 0.115, $CHCl_3$)

^1H NMR ($CDCl_3$, 600 MHz, r.t.): δ = 0.44 (d, J 6.8, 3H, Me), 1.09 (d, J 6.8, 3H, Me), 2.09 (m, CHMe$_2$), 3.85 (m, 1H, NCH), 4.39 (m, 2H, OCH_2), 6.87 (br s, 4H, 2`- and 3-`H), 6.96 (br m, 1H, 3-H), 7.12 (t, J 7.48, 1H, 4`-H), 7.33 (t, J 7.48, 2H, 3``-H), 7.42 (nrm, 1H, 4``-H), 7.45 (nrm, 1H, 4-H), 7.49 (nrm, 1H, 5-H), 7.53 (nrm, 2H, 2``-H), 7.54 (br s, 4H, 4-H_{BARF}), 7.74 (br s, 8H, 2-H_{BARF}), 7.96 (br d, J 7.5, 6-H).

$^{13}C\{^1H\}$ NMR ($CDCl_3$, 150 MHz): δ = 16.06 (Me), 20.69 (Me), 32.46 (CHMe$_2$), 69.25 (OCH_2), 73.47 (NCH), 117.50 (br s, 4-CH_{BARF}), 124.55 (q, J 273, CF_3), 127.97 (br s, 3`-CH), 128.11 (t, J 6.9, 1-C), 128.34 (t, J 4.6, 3``-CH), 128.9 (br q, J 30, 3-$C_{BARF}$), 129.69 (4`-CH), 130.41 (5-CH), 130.76 (t, J 20.7, 1``-C), 131.18 (4``-CH), 131.41 (br s, 6-CH), 132.52 (br s, 2`-CH), 132.71 (s, 3-CH), 132.92 (br s, 4-CH), 134.43 (dd, J 20.7, J 17.2, 2-C), 134.72 (t, J 5.7, 2``-CH), 134.81 (br s, 2-CH_{BARF}), 161.72 (q, 1:1:1:1, J 50.5, 1-C_{BARF}), 163.63 (m, N=C), 1``-C is undistinguished, since the broad signal at 6.87 ppm shows no cross-peaks in HMBC-spectrum.

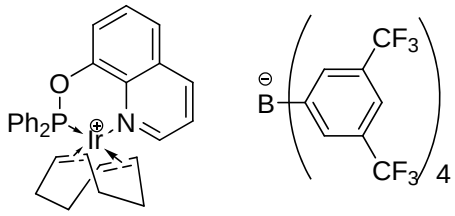
^{31}P NMR ($CDCl_3$, 161 MHz): δ = +49.3 (d, J 174.8).

^{19}F NMR ($CDCl_3$, 128 MHz): δ = -62.8.

^{11}B NMR ($CDCl_3$, 376 MHz): δ = -6.9.

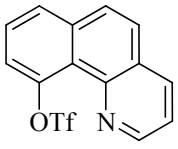
HRMS ESI/FT-ICR: isotope cluster 849-852, observed (calculated): 849.2263, 100.0% (849.2246, 100%); 850.2285, 49.2% (850.2280, 51.9%); 851.2387, 10.4% (851.2313, 13.2%).

Iridium (8-(diphenylphosphinooxy)quinoline) (1,5-cyclooctadiene) tetrakis(3,5-bis(trifluoromethyl)phenyl) borate 322



To a solution of 23.4 mg (0.162 mmol) of 8-hydroxyquinoline in 1 ml Et_2O 0.1 ml (0.16 mmol) of n-BuLi (1.6M hexane solution) were added. After stirring for 10 min 36.5 mg (0.162 mmol) of Ph_2PCl were added and stirred for 2 h. At this point the mixture was analysed by ^{13}P NMR, and showed one singlet at +121 ppm, which is assigned with 8-(diphenylphosphinooxy)quinoline **324**[458]. The ether was evaporated, and 54.2 mg (0.081 mmol) of $[Ir(COD)Cl]_2$ in 2 ml CH_2Cl_2 added. The mixture obtained was refluxed for 2 h, cooled, and 143.2 mg (0.162 mmol) of NaBARF were added. After overnight stirring the wished complex was separated by silica gel column chromatography (CH_2Cl_2, *Rf* 0.9). This complex decomposes after its formation, and cannot be isolated in pure form at r.t. The product was characherized by ^{31}P NMR, having only one peak at +107 ppm. During 1 day it could catalyze nucleophilic or electrophilic hydrogenation. In the latter case I checked the hydrogenation of stilbene in CH_2Cl_2.

Benzo[h]quinolin-10-yl trifluoromethanesulfonate 327



0.5 G (2.6 mmol) of benzo[h]quinolin-10-ol (ABCR) were dissolved in absolute Et_2O (with sonication) 1.6 ml (2.6 mmol) of 1.6M solution of nBuLi in hexane were added at r.t., which resulted in heating and in precipitation of lithium phenolate. With cooling to 0º C 0.43 ml (2.6 mmol) of Tf_2O were added, which resulted in complete dissolution. The mixture was stirred overnight (control by TLC is not possible since the product is instantly hydrolized on

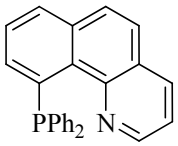
silica gel), very fast extracted with water (3 times), dried by Na_2SO_4, filtrated, washed by ether, evaporated and dried. Yield 0.84 g (100%). Yellow crystals, should be stored in glovebox.

^{1}H NMR (400MHz, $CDCl_3$): δ = 7.56-7.63 (m, 2H), 7.69 (t, J 8.0, 1H), 7.77 (d, J 8.8, 1H), 7.84 (d, J 8.8, 1H), 7.96 (dd, J 8.0, J 1.2, 1H), 8.21 (dd, J 8.0, J 1.8, 1H), 9.10 (dd, J 4.3, J 1.6, 1H).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 119.16 (q, J 320.4), 121.79, 122.66, 124.13, 127.38, 127.46, 127.48, 127.98, 129.11, 135.95, 136.35, 144.85, 147.93, 148.18.

^{19}F NMR (376 MHz, $CDCl_3$): δ = -74.43.

10-(Diphenylphosphino)benzo[h]quinoline 325



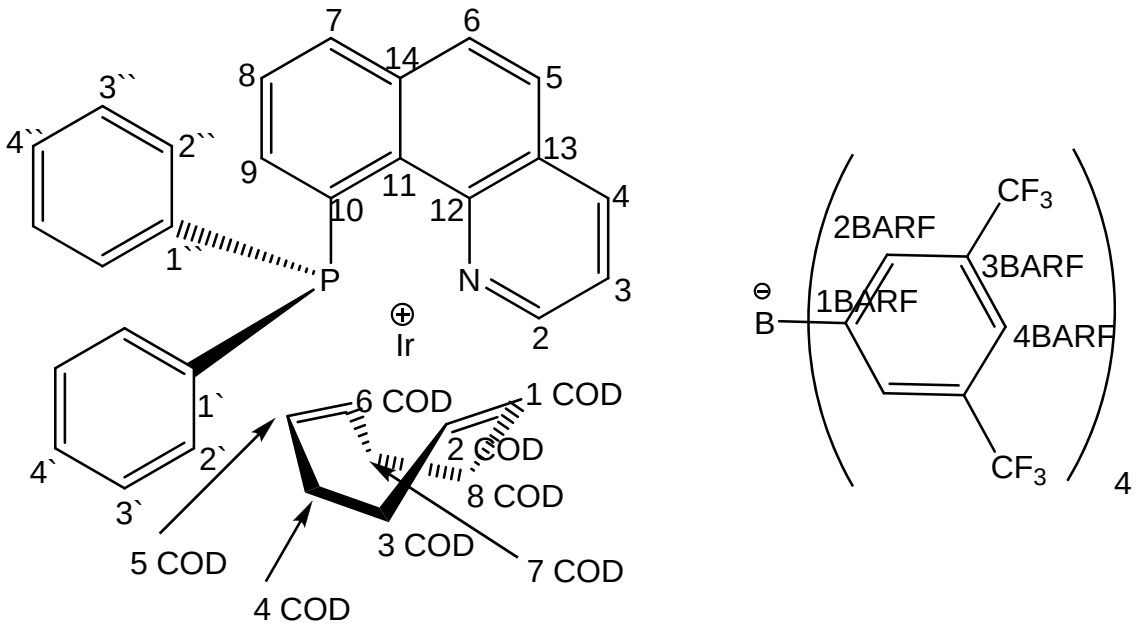
A solution of $LiPPh_2$ in 70 ml of Et_2O was generated from 630 mg (3.38 mmol) $HPPh_2$ and 2.11 ml of 1.6M solution of nBuLi according to the **general procedure I**. The solution of 740 mg (2.26 mmol) of Benzo[h]quinolin-10-yl trifluoromethanesulfonate in 20 ml Et_2O was added at r.t., and the resulting mixture was stirred for 7 days. The formed precipitate was filtrated, washed with absolute Et_2O and dried. Yield 380 mg (82%). This compound is moderately air-stable, being in crystalline form. It is insoluble in common organic solvents, in DMF and in DMSO. It is good soluble in CF_3CO_2D, where it forms a mixture of salts and this solution is not appropriate for NMR (too much of signals). It was charaterized by ^{31}P NMR, HRMS and through its derivative (complex **323**).

^{31}P NMR ($CDCl_3$, 161 MHz): δ = -0.85

^{31}P NMR (CF_3CO_2D, 161 MHz): δ = +3.6

HRMS ESI/FT-ICR [M+Na^+], observed (calculated): 386.1069 (386.1069)

Iridium (10-(Diphenylphosphino)benzo[h]quinoline) (1,5-cyclooctadiene) tetrakis(3,5-bis(trifluoromethyl)phenyl) borate 323



Synthesis of unpure complex. The solution of 35 mg (0.096 mmol) of 10-(diphenylphosphino)benzo[h]quinoline and 32.3 mg (0.048 mmol) of $[Ir(COD)Cl]_2$ in 2 ml of absolute CH_2Cl_2 was refluxed for 2 h in nitrogen atmosphere. After cooling to r.t. 86 mg (0.096 mmol) of NaBARF were added, and the resulting mixture was stirred 2 h at r.t. Column chromatography (CH_2Cl_2) yielded 76 mg (51%) of red complex, which decomposes after its formation, and cannot be isolated in pure form at r.t. This product was characherized by ^{31}P NMR, having only one peak at +26.7 ppm. During 2 days it could catalyze electrophilic hydrogenation. In the latter case I checked the hydrogenation of stilbene in CH_2Cl_2 or in PhMe.

Synthesis of pure complex. The solution of 108.2 mg (0.3 mmol) of 10-(diphenylphosphino)benzo[h]quinoline and 100 mg (0.15 mmol) of $[Ir(COD)Cl]_2$ in 10 ml of absolute CH_2Cl_2 was refluxed for 2 h in nitrogen atmosphere. The mixture was cooled to -50º C and 264 mg (0.3 mmol) of NaBARF were added. After stirring at -50º C for 24 h the mixture was chromatographed (eluent: CH_2Cl_2) on 50 g of silica gel at -40º C (the special equipment that allows performing of column chromatography at cooling should be used). The solvent was quickly removed in vaccum of oil pump at 0º C, then the substance was dried in vacuum at r.t. for 30 min, followed by drying at -40º C for 24 h.

Yield: 245 mg (53%). The solution of this complex in $CDCl_3$ is stable at r.t. *ca* 2 min.

^1H NMR ($CDCl_3$, 400 MHz, -40º C): δ = 1.48 (br m, 1H, a-7-H_{COD}), 1.69 (br m, 1H, a-3-H_{COD}), 2.01 (br m, 1H, e-7-H_{COD}), 2.09 (br m, 1H, e-3-H_{COD}), 2.30 (br m, 2H, 8-H_{COD}), 2.70 (br m, 2H, 4-H_{COD}), 3.60 (br m, 1H, 6-H_{COD}), 3.71 (br s, 1h, 5-H_{COD}), 4.09 (br s, 1H, 1-H_{COD}), 4.35 (br m, 1H, 2-H_{COD}), 7.26-7.37 (br nrm, 2H, 3``-H), 7.37-7.48 (nrm, 4H, 4`-H, 2``-H and

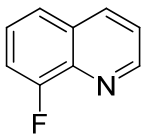
3-H), 7.52-7.59 (br nrm, 10H, 4-H_{BARF}, 2`-H, 3`-H, 4``-H and 5-H), 7.76-7.84 (br nmr, 9H, 4-H_{BARF} and 8-H), 7.87 (d, J 8.0, 1H, 6-H), 8.01 (dd, J 11.7, J 7.4, 1H, 7-H), 8.13 (d, J 8.2, 1H, 9-H), 8.14 (d, J 8.6, 1H, 4-H), 9.16 (d, J 5.3, 1H, 2-H).

$^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz, -40º C): δ = 26.36 (3-CH_{2COD}), 27.86 (7-CH_{2COD}), 32.62 (8-CH_{2COD}), 37.12 (4-CH_{2COD}), 63.53 (6-CH_{COD}), 65.95 (5-CH_{COD}), 97.25 (d, J 10.0, 1-CH_{COD}), 99.19 (d, J 13.8, 2-CH_{COD}), 117.43 (br s, 4-CH_{BARF}), 121.50 (d, J 47.6, 10-C), 122.05 (d, J 57.5, 1``-C), 124.00 (3-CH), 124.27 (q, J 273, $CF_3$), 125.88 (5-CH), 128.6 (br q, J 30, 3-$C_{BARF}$), 129.27-129.52 (br s, 3`-CH and 3``-CH), 129.42 (d, 52.9, 1`-C), 129.71 (d, J 4.6, 13-C), 129.82 (d, J 9.2, 8-CH), 130.69 (br s, 6-CH), 130.90 (2``-CH), 131.03 (2`-CH), 131.08 (br d, J 2.3, 7-CH), 131.85 (br d, J 2.3, 4``-CH), 132.35 (br d, J 1.5, 4`-CH), 133.13 (br s, 9-CH), 133.27 (d, J 10.0, 11-C), 134.57 (br s, 2-CH_{BARF}), 136.44 (d, J 9.2, 14-C), 139.66 (4-CH), 143.45 (d, J 3.1, 12-C), 151.95 (2-CH), 161.55 (q 1:1:1:1, J 49.9, 1-C_{BARF}).

^{31}P NMR ($CDCl_3$, 161 MHz, -40º C): δ = +27.01.

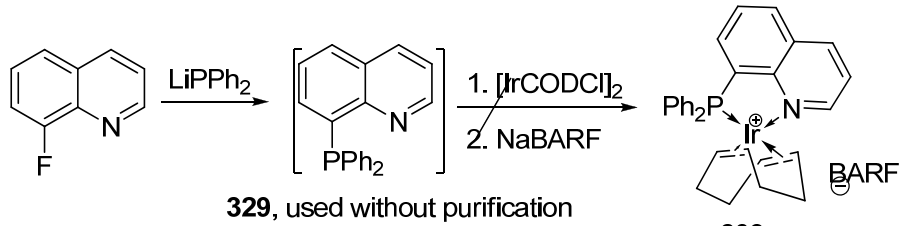
HRMS ESI/FT-ICR: isotope cluster 662-666, observed (calculated): 664.1753, 100.0% (664.1745, 100%); 662.1734, 52.0% (662.1722, 59.5%); 665.1801, 26.5% (665.1779, 35.7%); 663.1771, 15.0% (663.1755, 21.2%); 666.1850, 4.5% (666.1812, 6.2%).

8-Fluoroquinoline 328 by reaction of Skraup



9.66 Ml (0.1 mol) of 2-fluoroaniline, 14.6 ml (0.2 mol) of glycerol, 27.05 ml of sulfuric acid, 1.67 g (0.006 mol) of $FeSO_4 \cdot 7H_2O$ and 10.03 ml (0.1 mol) of nitrobenzene were heated to 80º C with stirring during 5 h. After cooling 40 g of NaOH and 20 ml of water were added and stirred for 30 min (pH should be alkaline). All volatiles were removed under deep vacuum at heating to 250º C overnight and collected in nitrogen-cooled trap. The collected substances were analysed by GC/MS and assigned to be the wished 8-fluoroquinoline, ubsubstituted quinoline, aniline, diazobenzene and two unassigned substances. The mixture was separated by silica gel column chromatography (Et_2O-pentane 4/6) and the aimed 8-fluoroquinoline was obtained after driying of the appropriate fractions. Yield – 2.2 g (15%). This method is very inefficient and cannot be recommended. Spectral properties are in agreement with that published[459].

Attempt to synthesize Iridium (1,5-cyclooctadiene) (8-(diphenylphosphino)quinoline) tetrakis(3,5-bis(trifluoromethyl)phenyl) borate 330.

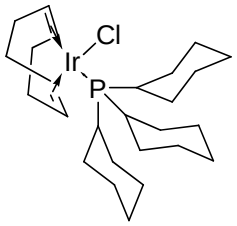


329, used without purification

330

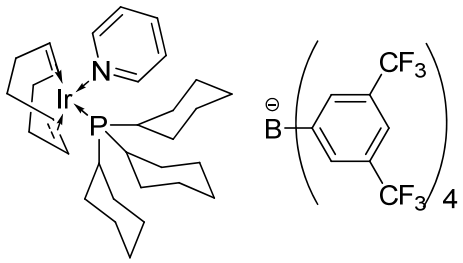
8-(Diphenylphosphino)quinoline **329** was generated according to the **general procedure I**, and the reaction mixture was analyzed by GC/MS and by ^{31}P NMR. One peak was observed at -11.5 ppm, according to the published value[460]. The solution of the ligand in CH_2Cl_2 was subjected to complexation, accroding the **general procedure I**, resulting in no complex, which could be chromatographed on silica gel.

Iridum (1,5-cyclooctadiene) (tricyclohexylphosphine) chloride, [Ir(COD)(PCy_3)Cl]



51.8 Mg (0.0772 mmol) of $[Ir(COD)Cl]_2$ and 43.3 mg (0.154 mmol) of PCy_3 were stirred 30 min at r.t. in 2 ml of absolute CH_2Cl_2. The mixture was evaporated, redissolved in 1 ml of CH_2Cl_2, and 10 ml of pentane were added. The formed precipitate was filtrated, washed with pentane, washed off from the filter by CH_2Cl_2, evaporated and dried in deep vacuum. Yield of [Ir(COD)(PCy_3)Cl] was 76 mg (80%). Spectral properties are in accordance with that published[461]. Additional portion of pure [Ir(COD)(PCy_3)Cl] can be isolated from the mother liquor by silica gel chromatography (MeOH, *Rf* 0.4).

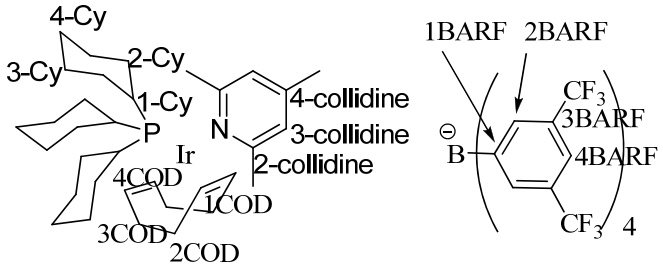
Iridum (1,5-cyclooctadiene) (pyridine) (tricyclohexylphosphine) tetrakis(3,5-bis(trifluoromethyl)phenyl) borate, [Ir(COD)(Py)(PCy_3)]BARF, 331



The procedure, found in[347], is fully not reproducible in my hands.

50 Mg (0.081 mmol) of [Ir(COD)(PCy_3)Cl], 80 mg (0.09 mmol) of NaBARF and 5 drops of pyridine were stirred 3 h in 2 ml of absolute CH_2Cl_2. Magnesium sulfate was added (to adsorb the formed NaCl), filtrated and washed with CH_2Cl_2. The filtrate was evaporated, the rest was redissolved in 2 ml of absolute CH_2Cl_2 and the wished [Ir(COD)(Py)(PCy_3)]BARF was precipitated by 50 ml of absolute pentane, collected by filtration, washed off from the filter by CH_2Cl_2, evaporated and dried in a deep vacuum. Yield – 123 mg (quantitative). Spectral properties are in accordance with the published[347].

Iridum (1,5-cyclooctadiene) (2,4,6-trimethylpyridine) (tricyclohexylphosphine) tetrakis(3,5-bis(trifluoromethyl)phenyl) borate, [Ir(COD)(sym-collidine)(PCy_3)]BARF, 332



Synthesized from [Ir(COD)(PCy_3)Cl] similar to [Ir(COD)(Py)(PCy_3)]BARF, using sym-collidine instead of pyridine. Yield – 80%.

^{1}H NMR (600MHz, $CDCl_3$): δ = 0.99 (m, 6H, a-3-H_{Cy}), 1.12 (m, 3H, a-4-H_{Cy}), 1.39 (m, 6H, a-2-H_{Cy}), 1.67 (m, 5H, e-4-H_{Cy} and a-2-H_{COD}), 1.77 (m, 8H, e-2-H_{Cy} and a-3-H_{COD}), 1.84 (m, 3H, e-3-H_{COD}), 1.93 (m, 3H, 1-H_{Cy}), 2.18 (m, 2H, e-2-H_{COD}), 2.29 (br s, 5H, e-3-H_{COD} and 4-$Me_{collidine}$), 3.05 (s, 6H, 2-$Me_{collidine}$), 3.68 (br s, 1H, 1-H_{COD}), 4.19 (br s, 1H, 4-H_{COD}), 7.02 (s, 2H, 3-$H_{collidine}$), 7.54 (br s, 4H, 4-H_{BARF}), 7.72 (br s, 8H, 2-H_{BARF}).

^{13}C NMR (150MHz, $CDCl_3$): δ = 20.25 (4-C<u>Me</u>$_{collidine}$), 25.81 (s, 4-CH_{2COD}), 26.67 (2-C<u>Me</u>$_{collidine}$), 27.51 (d, J 10.3, 3-CH_{2COD}), 29.86 (s, 2-CH_{2Cy}), 35.74 (d, J 21.8, 1-CH_{Cy}), 60.74 (4-CH_{COD}), 87.58 (d, J 11.5, 1-CH_{COD}), 117.43 (br s, 4-CH_{BARF}); 124.54 (q, J 272.3, CF_3), 126.05 (3-$CH_{collidine}$), 128.9 (br q, J 30, 3-C_{BARF}), 134.79 (br s, 2-CH_{BARF}), 151.37 (4-$C_{collidine}$), 157.40 (2-$C_{collidine}$), 161.69 (q 1:1:1:1, J 50.5 1-CB_{BARF}).

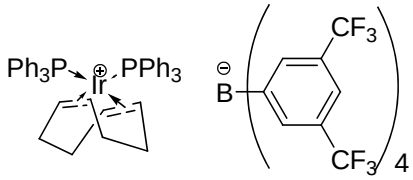
^{31}P NMR ($CDCl_3$, 161 MHz): δ = +7.75.

^{19}F NMR ($CDCl_3$, 128 MHz): δ = -62.8.

^{11}B NMR ($CDCl_3$, 376 MHz): δ = -6.9.

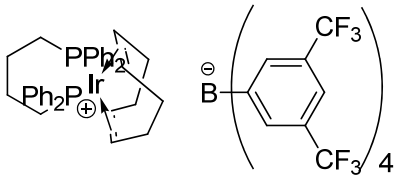
HRMS ESI/FT-ICR: isotope cluster 700-704, observed (calculated): 702.3787, 100% (702.3780, 100.0%), 700.3798, 51.6% (700.3756, 59.5%), 703.3833, 35.2% (703.3813, 36.8%), 701.3824, 19.9% (701.3790, 21.9%), 704.3873, 7.0%(704.3847, 6.6%).

Iridum (1,5-cyclooctadiene) bis(triphenylphosphine) tetrakis(3,5-bis(trifluoromethyl)phenyl) borate 333



A solution of 78 mg (0.3 mmol) of PPh_3 and 50 mg (0.0744 mmol) of $[Ir(COD)Cl]_2$ in 5 ml of absolute CH_2Cl_2 was refluxed for 1 h in nitrogen atmosphere. After cooling 132 mg (0.15 mmol) of NaBARF were added and resulting mixture stirred for 2 h. Column chromatography (CH_2Cl_2) yielded 200 mg (79%) of $[Ir(COD)(PPh_3)_2]$BARF. Spectral properties are in accordance with that published[462].

Iridum (1,5-cyclooctadiene) (1,4-bis(diphenylphosphino)butane) tetrakis(3,5-bis(trifluoromethyl)phenyl) borate, [Ir(COD)(DPPB)]BARF, 335

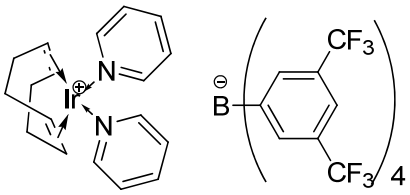


The method, found in article[406], was applied. No method could give the pure [Ir(COD)(DPPB)]BARF, propably, the latter slowly decomposes at r.t.

51.4 Mg (0.076 mmol) of $[Ir(COD)Cl]_2$ and 171.5 mg (0.2 mmol) of NaBARF were dissolved in 25 ml of THF and cooled to 0º C. A solution of 65.2 mg (0.153 mmol) of DPPB in 10 ml THF was added dropwise *via syringe* and this mixture was stirred 2 h at r.t. THF was evaporated in a stream of hitrogen, 20 ml of absolute toluene was added, filtrated, and the filtrate was evaporated and dried in vacuum of an oil pump (evaporation only at r.t., without heating). 161 mg of red substance is obtained. It is dirty [Ir(COD)(DPPB)]BARF (according to ^{1}H NMR), but has only one peak in ^{31}P NMR at +15 ppm. It cannot be purified by silica gel chromatography at r.t., since after contact with silica gel it becomes yellow (i.e. the 16-electron red complex coordinates the silica gel).

HRMS ESI/FT-ICR: isotope cluster 725-729, observed (calculated): 727.2250, 100% (727.2234, 100.0%), 725.2197, 53.4% (725.2211, 59.5%), 728.2218, 37.1% (728.2268, 38.9%), 726.2304, 10.7% (726.2245, 23.2%), 729.2295, 9.8% (729.2302, 7.4%).

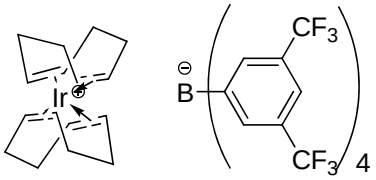
Iridum (1,5-cyclooctadiene) bis(pyridine) tetrakis(3,5-bis(trifluoromethyl)phenyl) borate 336



The method, described in[45] was unreproducible in my hands.

105 Mg (0.156 mmol) of $[Ir(COD)Cl]_2$ and 0.05 ml of pyridine were refluxed in 5 ml of absolute CH_2Cl_2 for 4 h. After cooling 278 mg (0.313 mmol) of NaBARF were added and this mixture was stirred for 10 min. 2 Ml of water were added, and the two-phase mixture was stirred for 1 h. Organic phase was extracted 3 times with water, then joined aqueous extracts were reextracted 3 times with CH_2Cl_2. Joined organic extracts were dried by Na_2SO_4, filtrated, washed by CH_2Cl_2, evaporated and dryed in deep vacuum. Yield 410 mg (99.2%). The substance is very unstable, and should be used over a period of 1-2 days. Spectral properties are in accordance with that published[45].

Iridium bis(1,5-cyclooctadiene) tetrakis(3,5-bis(trifluoromethyl)phenyl) borate ($[Ir(COD)_2]BARF$)

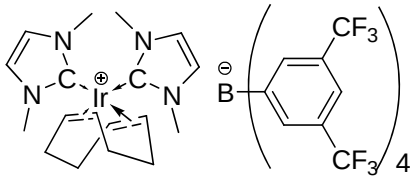


To a solution of 30.1 mg (0.044 mmol) $[Ir(COD)Cl]_2$ and 77.4 mg (0.088 mmol) of NaBARF in 1.5 ml of CH_2Cl_2 0.1 ml of freshly distilled 1,5-cyclooctadiene were added. The mixture was stirred for 30 min, then Na_2SO_4 was added to adsorb the formed NaCl. The mixture was filtrated, throughly washed by CH_2Cl_2, evaporated to 0.25 ml and 10 ml of pentane was added. The formed crystalline $[Ir(COD)_2]BARF$ was collected by filtration, washed off from the filter by CH_2Cl_2 and dried in vacuum. Should be stored at -20º C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.26 (m, 8H, CH_2), 2.41 (m, 8H CH_2), 5.00 (s, 8H, CH_{COD}), 7.56 (s, 4H, 4-H_{BARF}), 7.71 (s, 8H, 2- and 6-H_{BARF}).

^{19}F NMR (376 MHz, $CDCl_3$): δ = -62.8.

Iridium bis(imidazol-3-ene) (1,5-cyclooctadiene) tetrakis(3,5-bis(trifluoromethyl)phenyl) borate, [Ir(COD)(IMe)$_2$]BARF, 337



Under nitrogen to a suspension of 23.1 mg (0.103 mmol) of 1,3-dimethyl-1H-imidazol-3-ium iodide[449] in 5 ml THF 0.064 ml (0.103 mmol) of n-BuLi (1.6M solution in hexane) were added and stirred for 2 h. 65.5 Mg (0.0516 mmol) of [Ir(COD)$_2$]BARF were added and stirred for 28 h ar r.t. Reaction was quenched by methanol and adsorbed on silica gel. Column chromatography on 9 g of silica gel (under air, eluent - CH_2Cl_2, *Rf* 0.9) gave 30 mg (42%) of orange crystalline [Ir(COD)(IMe)$_2$]BARF.

^{1}H NMR (400MHz, $CDCl_3$): δ = 1.95 (m, 4H, CH_{2COD}), 2.21 (m, 4H, CH_{2COD}), 3.76 (s, 4H, CH_{COD}), 3.79 (s, 12H, Me), 6.73 (s, 4H, $CH_{imidazolene}$), 7.52 (s, 4H, 4-H_{BARF}), 7.71 (s, 8H, 2- and 5-H_{BARF}).

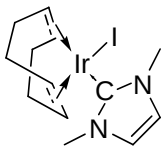
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 31.14 (CH_2), 37.49 (Me), 76.78 (CH_{COD}), 117.50 (br s, 4-CH_{BARF}); 122.60 ($CH_{imidazolene}$), 124.53 (q, J 272.3, CF_3), 128.9 (br q, J 30, 3-CCF_3), 134.80 (br s, 2- and 6-CH_{BARF}), 161.74 (q 1:1:1:1, J 50.5 CB_{BARF}), 177.70 ($C_{carbene}$).

^{11}B NMR (128 MHz, $CDCl_3$): δ = -6.9.

^{19}F NMR (376 MHz, $CDCl_3$): δ = -62.8.

HRMS ESI/FT-ICR: isotope cluster 491-496, observed (calculated): 493.1952, 100% (493.1943, 100.0%), 491.1902, 43.0% (491.1920, 59.5%), 495.2173, 20.2% (495.2010, 1.8%), 494.1980, 16.0% (494.1977, 19.5%), 492.1993, 9.9% (492.1953, 11.6%), 494.1914 (1.5%), 493.1987 (1.1%).

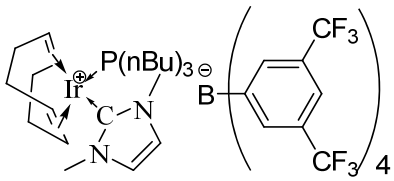
Iridium (1,5-cyclooctadiene) (imidazol-3-ene) iodide, [Ir(COD)(IMe)I], 340



The procedure, found in[347, 408], is not reproducible in my hands. But I have found, what modification should be done, in order to synthesize the wished complex.

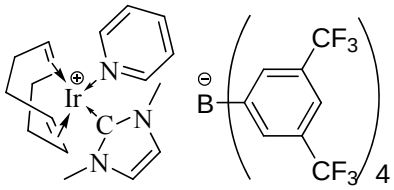
A solution of 50 mg (0.0744) mol of $[Ir(COD)Cl]_2$, 0.313 ml (0.3 mmol) of 0.95M NaOMe (solution in MeOH) in 1 ml of absolute MeOH was stirred for 5 h. 33.3 Mg (0.15 mol) of 1,3-dimethylimidazolium iodide were added and the resulting suspension was stirred for another 5 h. All volatiles were removed *in vacuo* the rest dissolved in 1 ml of absolute CH_2Cl_3 and 3 ml of absolute pentane were added. It resulted in precipitation of some orange by-product, while the wished yellow [Ir(COD)(IMe)I] **340** is soluble in pentane. The mixture was filtrated, throughly washed with pentane, then filtrate was evaporated and dried in a deep vacuum. Yield – 30 mg (38%). Alternatively the complex can be purified by silica gel column chromatography (MeOH, *Rf* 0.4). Spectral properties are in agreement with that published[408].

Iridum (1,5-cyclooctadiene) (1,3-dimethylimidazol-2-ene) (tri-n-butylphosphine) tetrakis(3,5-bis(trifluoromethyl)phenyl) borate, [Ir(COD)(IMe)(P(nBu)$_3$)]BARF, 338



15 Mg (0.0287 mmol) of [Ir(COD)(IMe)I], 25.4 mg (0.0287 mmol) of NaBARF and 3 drops of $P(nBu)_3$ were stirred in 1 ml of absolute CH_2Cl_2 for 1 h at r.t. Pentane was added and the formed precipitate was filtrated and throughly washed with pentane. Crystalline rest was washed off from the filter by CH_2Cl_2 and purified by silica gel chromatography (CH_2Cl_2) to give 33 mg (78%) of desired [Ir(COD)(IMe)(P(nBu)$_3$)]BARF. Spectral properties are in accordance with that published[347].

Iridum (1,5-cyclooctadiene) (1,3-dimethylimidazol-2-ene) (pyridine) tetrakis(3,5-bis(trifluoromethyl)phenyl) borate, [Ir(COD)(IMe)(Py)]BARF, 339



15 Mg (0.0287 mmol) of [Ir(COD)(IMe)I], 25.4 mg (0.0287 mmol) of NaBARF and 3 drops of pyridine were stirred in 2 ml of absolute CH_2Cl_2 for 3 h at r.t. The mixture was adsorbed on silica gel and subjected to column chromatography (CH_2Cl_2) to give 23 mg

(59%) of desired [Ir(COD)(IMe)(Py)]BARF. The complex is very unstable, it was destoroyed before 2D NMR spectra and HRMS were measured.

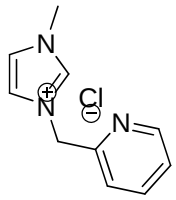
^{1}H NMR (400MHz, $CDCl_3$): δ = 1.91 (m, 4H, a-CH_{2COD}), 2.31 (m, 4H, e-CH_{2COD}), 3.60 (s, 2H, CH_{COD}), 3.92 (br s, 8H, Me and CH_{COD}), 6.88 (s, $CH_{imidazolene}$), 7.30 (br t, J 6.6, 2H, 3-H_{Py}), 7.51 (br s, 4H, 4-H_{BARF}), 7.59 (br t, J 6.6, 1H, 4-H_{Py}), 7.71 (br s, 8H, 2-H_{BARF}), 8.46 (br d, J 6.6, 2H, 2-H_{Py}).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.82, 32.31, 36.80, 64.34, 84.38, 122.67, 117.50 (br s, 4-CH_{BARF}), 124.53 (q, J 272.3, CF_3), 126.76, 128.9 (br q, J 30, 3-CCF_3), 134.80 (br s, 2- and 6-CH_{BARF}), 138.36, 149.94, 161.74 (q 1:1:1:1, J 50.5 CB_{BARF}), 176.42.

^{11}B NMR (128 MHz, $CDCl_3$): δ = -6.95.

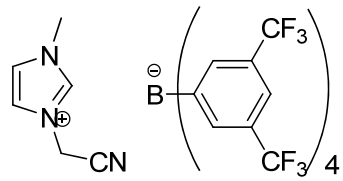
^{19}F NMR (376 MHz, $CDCl_3$): δ = -62.81.

1-methyl-3-(2-pyridylmethyl)imidazolium chloride



0.734 G (4.48 mmol) of 2-(chloromethyl)pyridine hydrochloride were dissolved in 10 ml of water, 10 ml of CH_2Cl_2 were added, and the saturated solution of $NaHCO_3$ was added dropwise in order to achieve pH 8[463]. The phases were separated, organic phase was dried by Na_2SO_4, filtrated, washed by CH_2Cl_2 and evaporated. The resulting 2-(chloromethyl)pyridine (obtained in quantitative yield) was mixed with 0.32 g (3.9 mmol) of 1-methylimidazole and 5 ml of THF, and the resulting mixture was refluxed for 24 h, then cooled to r.t. The obtained oil was triturated in THF, filtrated and dried, resulting in hygroscopic product in yield of 25%. Spectral properties are in accordance with that published[464].

1-Cyanomethyl-3-methylimidazolium tetrakis(3,5-bis(trifluoromethyl)phenyl) borate



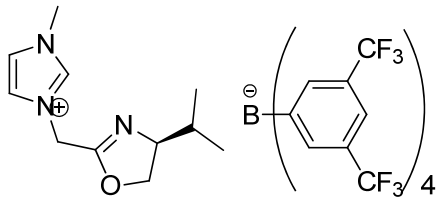
20 Mg (0.124 mmol) of 1-cyanomethyl-3-nethylimidazolium chloride and 100 mg (0.113 mmol) of NaBARF were mixed in 5 ml of CH_2Cl_2 and stirrred 10 h at r.t. The mixture

was washed twice with water, dried by Na_2SO_4, filtrated, washed with CH_2Cl_2, evaporated and dried. Yield – 114 mg (100%).

^{1}H NMR (400MHz, DMSO): δ = 3.88 (s, 3H, Me), 5.56 (s, 2H, CH_2), 7.61 (br s, 8H, 2-H_{BARF}), 7.69 (br s, 4H, 4-H_{BARF}), 7.77 (s, 1H, NCHCHN), 7.87 (s, 1H, NCHCHN), 9.22 (s, 1H, NCHN).

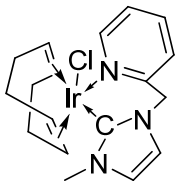
^{13}C{^{1}H} NMR (100 MHz, DMSO): δ = 36.17, 36.83, 114.86, 117.81 (br s, 4-CH_{BARF}); 122.71, 124.13 (q, J 272.3, CF_3), 124.51, 128.62 (br q, J 30, 3-CCF_3), 134.17 (br s, 2- and 6-CH_{BARF}), 137.88, 161.07 (q 1:1:1:1, J 49.8, CB_{BARF}).

(S)-3-((4-isopropyl-4,5-dihydrooxazol-2-yl)methyl)-1-methyl-1H-imidazol-3-ium tetrakis(3,5-bis(trifluoromethyl)phenyl) borate 345



107 Mg (0.108 mmol) of **1-Cyanomethyl-3-methylimidazolium tetrakis(3,5-bis(trifluoromethyl)phenyl) borate**, 27 mg (0.2618 mmol) fo (S)-valinol and 10 mg (0.0275 mmol) of $Zn(OTf)_2$ were mixed in 5 ml of absolute toluene and refluxed for 4 days (in the atmosphere of nitrogen). All volatiles were removed *in vacuo*, and the rest was purified using neutral Alox (10 G, Brokmann act. III) column chromatography (CH_2Cl_2, 0.5 L). Only 30 mg (26%) of the purposeful salt were eluated. Further eluation with methanol (0.5 L) gave a white crystalline compound, but not the target one. Spectral properties are in accordance with the published[346, 362].

Iridum (1,5-cyclooctadiene) (1-methyl-3-(2-pyridylmethyl)imidazol-2-ene) chloride, 347



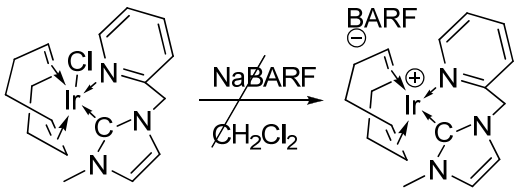
Synthesized from 31.2 mg (0.149 mmol) of 1-methyl-3-(2-pyridylmethyl)imidazolium chloride, 60 mg (0.089 mmol) of $[Ir(COD)Cl]_2$ and 61.9 mg (0.267 mmol) of Ag_2O in CH_2Cl_2, according to the published procedure[465], but the product was purified by precipitation

with pentane from CH_2Cl_2. The pure product is soluble in pentane, while the impurities stay in precipitate. The evaporation of mother liquor and drying in a deep vacuum gave 27 mg (33%) of yellow crystalline product.

^{1}H NMR (400MHz, $CDCl_3$): δ = 1.63 (br s, 2H, a-CH_{2COD}), 1.72 (br s 2H, a-CH_{2COD}), 2.14 (br s, 2H, e-CH_{2COD}), 2.26 (br s, 2H, e-CH_{2COD}), 2.79 (br s, 1H, CH_{COD}), 2.95 (br s, 1H, CH_{COD}), 3.99 (s, 3H, Me), 4.54 (br s, 1H, CH_{COD}), 4.63 (br s, 1H, CH_{COD}), 5.52 (d, J 14.8, 1H, NCH_2), 5.89 (d, J 14.8, 1H, NCH_2), 6.83 (d, J 2.0, $CH_{imidazolene}$), 6.93 (d, J 1.6, $CH_{imidazolene}$), 7.24 (t, J 5.5, 1H, 5-$H_{pyridine}$), 7.50 (d, J 7.8, 1H, 3-$H_{pyridine}$), 7.69 (td, J 7.8, J 1.6, 1H, 4-$H_{pyridine}$), 8.60 (d, J 5.5, 1H, 6-$H_{pyridine}$).

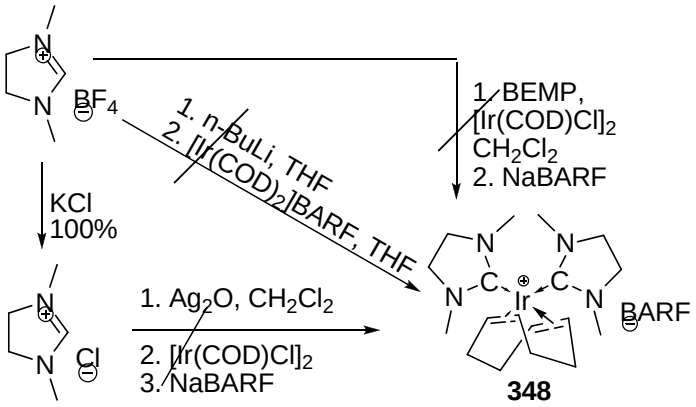
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 27.99, 37.46, 55.87, 120.63, 122.19, 123.12, 123.49, 128.79, 137.20, 150.15, 155.96, 179.63, one CH_{COD} is hidden under $CDCl_3$-signal.

Attempt to synthesize Iridum (1,5-cyclooctadiene) (1-methyl-3-(2-pyridylmethyl)imidazol-2-ene) tetrakis(3,5-bis(trifluoromethyl)phenyl) borate, 346



27 Mg (0.05 mmol) of complex **347** were dissolved in absolute CH_2Cl_2, 53 mg (0.06 mmol) of NaBARF were added, resulting in immediate change of colour from yellow to orange, and in 30 seconds – to pale yellow. Nothing could be eluated with CH_2Cl_2 on TLC of the reaction mixture. The orange complex is the presumable wished product, which is inherently unstable at r.t. (probabily because of *ortho*-metallation of pyridine).

Attempts to synthesize Iridum (1,5-cyclooctadiene) bis(1,3-dimethylimidazolidine-2-ene) tetrakis(3,5-bis(trifluoromethyl)phenyl) borate, 348



1st attempt. This method was effective in case of complex **337**. 38.7 Mg (0.208 mmol) of **1,3-dimethyl-4,5-dihydro-1H-imidazol-3-ium tetrafluoroborate** were suspended in 2 ml of THF. 0.13 Ml (0.208 mmol) of 1.6 M hexane solution of nBuLi were added, and the mixture was stirred overnight at r.t. 132 mg (0.104 mmol) of $[Ir(COD)_2]BARF$ were added to this mixture, and stirred for 12 h. The TLC has shown no complex, eluated by CH_2Cl_2, hence the purposeful **348** was not generated.

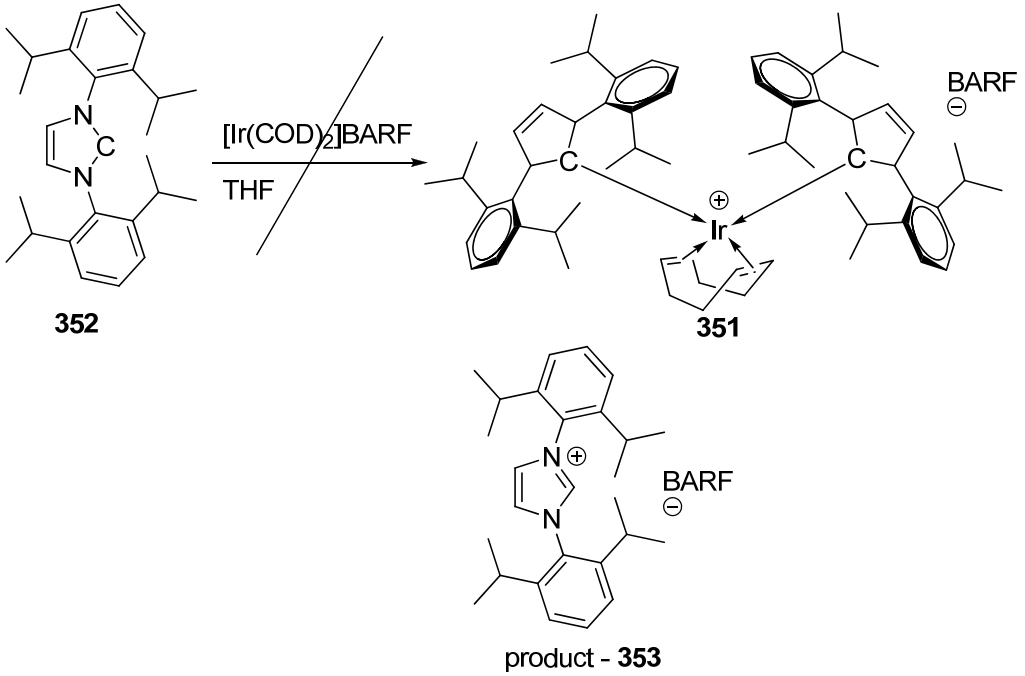
2nd attempt. 1 G (5.38 mmol) of **1,3-dimethyl-4,5-dihydro-1H-imidazol-3-ium tetrafluoroborate** and 400 mg (5.38 mmol) were mixed in water, which resulted in immediate precipitation of KBF_4. It was filtrated (do not wash it with water), and filtrate concentrated and dried in vacuum of oil pumf, affording **1,3-dimethyl-4,5-dihydro-1H-imidazol-3-ium chloride** as yellow oil with yield of 105%, hence slightly contaminated with KBF_4. It is not soluble in CH_2Cl_2, and the method of its purification was not found. In the next reaction it was taken crude.

This method was effective for the preparation of complex **346**. 50.8 mg (0.377 mmol) of **1,3-dimethyl-4,5-dihydro-1H-imidazol-3-ium chloride** and 44 mg (0.191 mmol) of Ag_2O were refluxed in absolute CH_2Cl_2 under nitrogen atmosphere. After cooling to r.t. 60.2 Mg (0.0896 mmol) of $[Ir(COD)Cl]_2$ were added, and the solution was refluxed for 90 min. After cooling to r.t. 159 mg (0.179 mmol) of NaBARF were added, and the mixture was stirred at r.t. for 4 h. Column chromatography of the mixture (**general procedure I**) afforded 17 mg of yellow crystalline product. Its NMR spectra do not correspond to those, expected for the complex **348**.

3rd attempt. This method was found in dissertation[362], it should be effective namely for saturated imidazolenes. 55.3 Mg (0.298 mmol) of **1,3-dimethyl-4,5-dihydro-1H-imidazol-3-ium tetrafluoroborate**, 81.7 mg (0.298 mmol) of BEMP (Aldrich) and 50 mg (0.0744 mmol)

of $[Ir(COD)Cl]_2$ were stirred in 7.5 ml of absolute THF for 24 h at r.t. 132 Mg (0.149 mmol) of NaBARF were added, and resulting mixture was stirred for 2 h. Column chromatography of the mixture (**general procedure I**) afforded 179 mg of yellow crystalline product. Its NMR spectra do not correspond to those, expected for the complex **348**. It shows a signal in ^{13}P NMR, hence contains either BEMP, its salt or the products of its destruction.

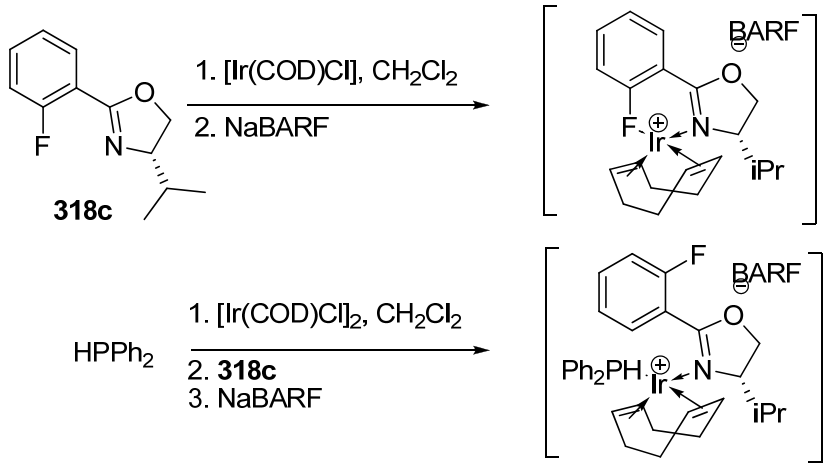
Attempt to synthesize Iridum (1,5-cyclooctadiene) bis(1,3-bis(2,6-diisopropylphenyl)-imidazol-2-ene) tetrakis(3,5-bis(trifluoromethyl)phenyl) borate, 351



50 Mg (0.1287 mmol) of **352** and 81.8 mg (0.0643 mmol) of $[Ir(COD)_2]BARF$ were stirred in 2 ml of absolute THF for 24 h. Column chromatography (according to the **general procedure I)** yilded 65 mg of crystalline orange compound, which was identified as **353** according to its NMR spectra.

Modelling of impurities, possible to exist in 286c, and the test of their activity in nucleophilic hydrogenation.

Modelling of impurities in [Ir(COD)(iPr-Phox)]BARF
The products were not isolates/purified, since it was not possible by column chromatography
They were checked "as is" in nucleophilic hydrogenation, and were found to be inactive



1st test. 50 Mg (0.074 mmol) of $[Ir(COD)Cl]_2$ and 31 mg (0.148 mmol) of **318c** were stirred in 5 ml of absolute CH_2Cl_2 for 4 h. 132 Mg (0.149 mmol) of NaBARF were added, and the mixture was stirred for 2 h. Water was added, aqueous layer was washed 3 times with CH_2Cl_2, and combined organic extracts were dried by Na_2SO_4, evaporated and dried. The yellow crystalline mass was tested in nucleophilic hydrogenation of **281** (**general procedure G**), and found to be inactive (produces metallic iridium).

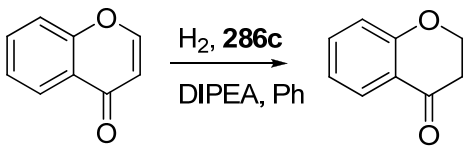
2nd test. 50.7 mg (0.0755 mmol) of $[Ir(COD)Cl]_2$ and 28 mg (0.15 mmol) of Ph_2PH were dissolved in 2 ml of absolute CH_2Cl_2 and stirred 2 h at r.t. in nitrogen filled globebox. The flask with reaction mixture was extracted from the glovebox, but further operations till anion exchange were performed under nitrogen. 31 Mg (0.15 mmol) of **318c** were added and the mixture was stirred overnight. 132 Mg (0.149 mmol) of NaBARF were added, and the mixture was stirred for 2 h. Water was added, aqueous layer was washed 3 times with CH_2Cl_2, and combined organic extracts were dried by Na_2SO_4, evaporated and dried. The yellow crystalline mass was tested in nucleophilic hydrogenation of **281** (**general procedure G**), and found to be inactive (produces metallic iridium).

7.5 Nucleophilic hydrogenation of various substrates

The identity of hydrogenated products was established by ^1H NMR and ^{13}C NMR, and the spectra were in accordance with those published for corresponding reduced compounds.

Benzylidenemalononitrile, 3-nitrobenzylidenmalononitrile and 4-nitrobenzylidenmalononitrile were synthesized from the appropriate aldehydes and malononitrile in water, catalyzed by 1-methylimidazole, according to the published procedure[466]. Ethylidenmalononitrile was syntehsized by the known procedure[467], but the mixture was heated by Microwave owen (Biotage Initiator), and the product was distilled off in vacuum of oil pump. Prop-2-ylidenmalononitril was synthesized by the known procedure[468], the product was distilled off in vacuum of oil pump. 2-(1-Phenylethylidene)malononitrile was synthesized by the known procedure[468], distilled off in vacuum of oil pump and recrystallized from ethanol. 2-Methylcyclohexenone was synthesized by Maria Mesch according to the known procedure[469], purified by fractional distillation in vacuum and then by silica gel column chromatography (pentane/Et_2O 3/1). 2-Phenyl-2-cyclohexenone was synthesized by the known procedure[470] with yield of 10%, after recrystallization from hexane. 2-(1-Ethoxyethylidene)malononitrile[471], 2-iodo-2-cyclohexenone[472], 7-hydroxy-2-trifluoromethylchromone[473], 7-hydroxy-2-trifluoromethylisoflavone[474], 2-bromo-3-methoxycyclohex-2-enone[475], 3-methoxy-2-phenylcyclohex-2-enone[476], 7-hydroxy-3-methylchromone[477] were synthesized according to the known procedures. 2-(Ethoxymethylene)malononitrile, fumaronitrile, ethyl 2-cyano-3-phenylbut-2-enoate and ethyl 2-cyano-3-ethoxyacrylate were found in collection of chemicals by AG Groth. 7-Methoxy-3-(4-chlorophenoxy)chromone **371** was found in collection of chemicals by Khilya V.P. Tetracyanoethylene, maleinic anhydride, p-benzoquinone, 3-methoxycyclohex-2-enone (Merck), cyclohex-2-enone, (Acros) and trifluoromethylmaleinic anhydride (Fluorochem) were purshased and used “as is”. Phenylboronic acid and tetrakis(triphenylphosphine) palladium are obtained as gifts from MCAT. 3-Trifluoroacetylchormone (mixture of ketone and its hydrate) was obtained as a gift from V. Iaroshenko and A. Kotljarov or synthesized by the known procedure[414]. The gifts are kindly acknowledged.

General procedure L (example on chromone)



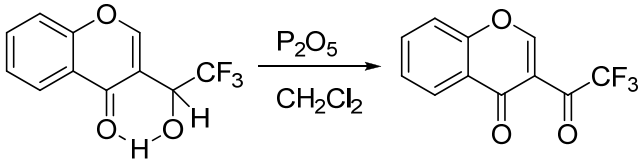
1

50 Mg of chromone and 27.9 mg (5.3 mol-%) of **286c** were placed in teflon vessel, dissolved in 9 ml (6-fold excess, relative to the volume of DIPEA) of absolute toluene. 1.5 Ml

of DIPEA (500 eq relative to the catalyst) were added, followed by 1 drop of thiophene (optionally). The operations were quickly made under air and the teflon vessel was sealed in stainless-steel autoclave. It was purged 3 times with hydrogen, then loaded to a pressure of 100 bar and the mixture was stirred for 8 h. The autoclave was ventilated and the mixture subjected to silica gel column chromatography (Et_2O, *Rf* 0.9) yielding 18 mg (36%) of chroman-4-one. Spectral properties correspond to the published[162].

Analogous procedure applied for coumarin gave an inseparable mixture of unidentified compounds (one of them was chroman-2-one, according to GC/MS and to NMR).

3-Trifluoroacethylchormone 368



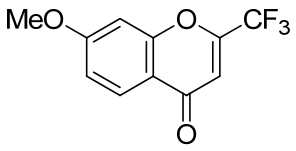
0.8 G of the mixture of 3-trifluoroacetylchromone with its hydrate were stirred with 4.7 g of P_2O_5 in 50 ml of dichloromethane for 30 h (control by ^{19}F NMR), filtrated under nitrogen, filtrate evaporated and dried in a deep vacuum, to give 0.3 g of 3-trifluoroacetylchormone in pure ketonic form. Spectral properties are in accordance with the published[413]. This compound should not be exposed to air/water.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.51-7.54 (m, 1H, 6-H), 7.55-7.58 (m, 1H, 8-H), 7.76-7.81 (m, 1H, 7-H), 8.30 (dd, J 7.9, J 1.6, 1H, 5-H), 8.63 (s, 1H, 2-H)

^{13}C NMR (100 MHz, $CDCl_3$): δ = 115.73 (q, J 289.4, CF_3), 118.34 (8-CH), (119.14, 3-CH), 124.87 (10-C), 126.65 (5-CH), 127.09 (6-CH), 135.04 (7-CH), 155.551 (9-C), 163.07 (q, J 2.2, 2-CH), 172.65 (4-C), 179.38 (q, J 39.2, $\underline{CO}CF_3$)

^{19}F NMR (376 MHz, $CDCl_3$) δ = -74.81

7-Methoxy-2-trifluoromethyl chromone 377



1.01 g (4.4 mmol) of 7-hydroxy-2-trifluoromethylchromone, 5.459 g (40 mmol) of K_2CO_3 (dried) and 1.25 ml (13.2 mmol) of Me_2SO_4 were added to 50 ml of dry acetone. The mixture was refluxed for 4 h in nitrogene atmosphere, poured in 1 L of water, and the precipitate, which represents the 7-methoxy-2-trifluoromethylchromone, was collected by

filtartion and dried. Yield – 0.961 g (89%). The NMR spectra do not correspond to the published[478].

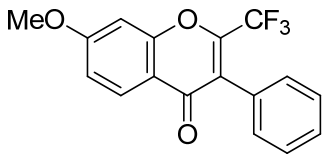
^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.94 (s, 3H, OMe), 6.68 (s, 1H, 3-H), 6.93 (d, J 2.0, 8-H), 7.03 (dd, J 9.0, J 2.0, 6-H), 8.10 (d, J 9.0, 5-H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 55.99 (OMe), 100.40 (8-H), 110.70 (q, J 2.4, 3-CH), 115.78 (6-H), 117.84 (10-C), 118.59 (q, J 274.2, CF_3), 127.28 (5-CH), 151.85 (q, J 39.0, 2-C), 157.50 (9-C), 165.02 (7-C), 176.11 (4-C).

^{19}F NMR (376 MHz, $CDCl_3$): δ = -71.66

HRMS ESI/FT-ICR, observed (calculated): [M+Na^+] 267.0240 (267.0239).

7-Methoxy -2-trifluoromethylisoflavone 367



Synthesized from 7-hydroxy-2-trifluoromethylchromone according to the **general procedure A** with yield of 91%.

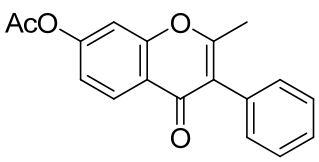
^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.95 (s, 3H, Me), 6.96 (d, J 2.3, 8-H), 7.05 (dd, J 8.6, J 2.3, 1H, 6-H), 7.27 (m, $CHCl_3$ and 2`-H), 7.44 (m, 3H, 3`- and 4`-H), 8.14 (d, J 8.6, 5-H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 56.00 (OMe), 100.06 (8-CH), 115.88 (6-CH), 117.11 (10-C), 119.38 (q, J 276.2, CF_3), 125.57 (3-C), 127.81 (5-CH), 128.11 (3`-CH), 128.71 (4`-CH), 129.08 (1`-C), 129.77 (2`-CH), 147.98 (q, J 36.1, 2-C), 156.91 (9-C), 165.00 (7-C), 176.04 (4-C)

^{19}F NMR (376 MHz, $CDCl_3$): δ = -63.58

HRMS ESI/FT-ICR, observed (calculated): [M+Na^+] 343.0550 (343.0552)

7-Acetoxy-2-methylisoflavone 379



5 G (22 mmol) of crude 1-(2,4-dihydroxyphenyl)-2-phenylethanone and 3.61 g (44 mmol) of AcONa were mixed with 6.71 ml (71.4 mmol) of Ac_2O. The mixture was refluxed

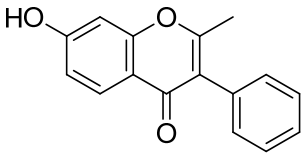
for 14 h, cooled and poured in water. The precipitate was filtrated, dried and recrystallized from methanol. Yield 4.781 g (73.8%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.29 (s, 3H, 2-Me), 2.34 (s, 3H, OAc), 7.11 (dd, J 8.5, J 2.1, 1H, 6-H), 7.25-7.30 (m, 3H, 8-H and 2`-H), 7.36 (tt, J 7.5, J 1.5, 1H, 4`-H), 7.43 (t, J 7.5, 2H, 3`-H), 8.23 (d, J 8.5, 1H, 5-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.35 (2-Me), 21.03 ($\underline{CH_3}CO$), 110.50 (8-CH), 118.90 (6-CH), 121.16 (10-C), 123.56 (3-C), 127.54 (5-CH), 127.71 (4`-CH), 128.27 (3`-CH), 130.25 (2`-CH), 132.71 (1`-C), 154.15 (9-C), 156.14 (7-C), 163.43 (2-C), 168.46 ($CH_3\underline{CO}$), 175.89 (4-C).

HRMS ESI/FT-ICR, observed (calculated): [M+H$^+$] 295.0976 (295.0965); [M+Na$^+$] 317.0760 (317.0784).

2-Methyl-7-methoxychromone



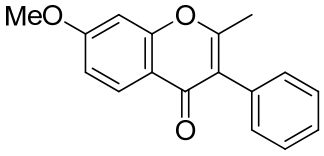
1 G (3.4 mmol) of 7-Acetoxy-2-methylisoflavone was suspended in a mixture of 10 ml of EtOH and 11 ml of H_2O. 3.4 Ml of 5% aqueous NaOH were added, and the mixture was refluxed for 5 min (and not more), poured in water and acidified by 1N HCl to weak acidic reaction. The precipitate, representing 2-methyl-7-methoxychromone, was filtrated and dried. It does not need the further purification. Yield 0.85 g (99%).

^{1}H NMR (400 MHz, DMSO): δ = 2.21 (s, 3H, Me), 6.83 (d, J 2.2, 8-H), 6.90 (dd, J 8.8, J 2.2, 6-H), 7.26 (d, J 8.4, 2H, 2`-H), 7.35 (t, J 7.3, 1H, 4`-H), 7.42 (t, J 7.7, 2H, 3`-H), 7.87 (d, J 8.8, 1H, 5-H), 10.74 (s, 1H, OH).

^{13}C NMR (150 MHz, DMSO): δ = 19.12 (Me), 101.91 (8-CH), 114.79 (6-CH), 115.57 (10-C), 122.12 (3-C), 127.10 (5-CH), 127.38 (4`-CH), 128.00 (3`-CH), 130.54 (2`-CH), 133.42 (1`-C), 157.07 (2-C), 162.48 (9-C), 162.53 (7-C), 174.77 (4-C).

HRMS ESI/FT-ICR, observed (calculated): [M+Na$^+$] 275.0684 (275.0679)

2-Methyl-7-methoxychromone 378



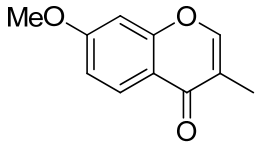
Synthesized from 7-hydroxy-2-methylisoflavone according to the **general procedure A** with quantitative yield.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 2.29 (s, 3H, 2-Me), 3.90 (s, 1H, OMe), 6.85 (d, J 2.2, 1H, 8-H), 6.96 (dd, J 2.2, J 8.8, 1H, 6-H), 7.29 (d, 7.7, 2H, 2`-H), 7.36 (t, J 7.7, 1H, 4`-H), 7.43 (t, J 7.7, 2H, 3`-H), 8.13 (d, J 8.8, 1H, 5-H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 19.30 (2-Me), 55.69 (OMe), 99.81 (8-CH), 113.96 (6-CH), 117.25 (10-C), 123.25 (3-C), 127.52 (5-CH), 127.55 (4`-CH), 128.22 (3`-CH), 130.37 (2`-CH), 133.14 (1`-C), 157.46 (9-C), 162.58 (2-C), 163.75 (7-C), 176.08 (4-C).

HRMS ESI/FT-ICR, observed (calculated): [M+H$^+$] 267.1017 (267.1016); [M+Na$^+$] 289.0831 (289.0835).

7-methoxy-3-methyl-4H-chromen-4-one 373



1 G of 7-hydroxy-3-methyl-chromone was methylated according to the **general procedure A**. Because of its partial solubility in water, it was extracted by dichloromethane (5x50 ml), the extracts were dried by Na_2SO_4, filtered and evaporated. The substance was purified by column chromatography (Et_2O/pentane 1/1) yielding 954 mg (88%) of white crystalline **7-methoxy-3-methyl-4H-chromen-4-one**. Earlier this substance was reported to be coloured[446], evidently because of insufficient purification (the crude compound is red). ^{1}H NMR spectrum corresponds to that, found in literature[446].

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.00 (s, 3H, 3-Me), 3.87 (s, 3H, OMe), 6.77 (d, J 2.3, 8-H), 6.93 (dd, J 9.0, J 2.3, 1H, 6-H), 7.71 (q, J1.3, 1H, 2-H), 8.11 (d, J 9.0, 5-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.13 (3-Me), 55.76 (MeO), 99.96 (8-CH), 114.29 (6-CH), 117.57 (10-C), 120.48 (3-C), 127.09 (5-CH), 151.26 (2-CH), 158.39 (9-C), 163.73 (7-C), 177.65 (4-C).

The method of local softnesses' computation see in section 3.6. Input Gaussian Z-Matrix for **368** (s-trans configuration) see in section 7.6.

The indexes of local softnesses (electrophilic attack) on the atoms of 3-trifluoroacetylchromone **368** (numeration in Figure 8, p. 129, atom-number is simply its number in input Z-Matrix), computed in basis 6-31G, are as following:

Atom	ESP	Mulliken	Hishfeld	NPA

7	0.257106	0.244334	0.259772	0.297562
11	0.575196	0.452379	0.473251	0.642642
13	0.37135	0.302605	0.292015	0.353591
15	0.135648	0.10217	0.088692	0.082553
16	0.066307	0.04622	0.043081	0.034438
17	0.059433	0.064268	0.053029	0.047949

The indexes of local softnesses (electrophilic attack) on the atoms of 3-trifluoroacetylchromone **368** (numeration in Figure 8, p. 129, atom-number is simply its number in input Z-Matrix), computed in basis 6-31G(d,p), are as following:

Atom	ESP	Mulliken	Hishfeld	NPA
7	0.242038	0.189175	0.223301	0.257436
11	0.541675	0.429689	0.448804	0.615553
13	0.40016	0.29838	0.301329	0.377756
15	0.13719	0.083881	0.083319	0.073613
16	0.076336	0.049937	0.052589	0.043541
17	0.068655	0.055373	0.053041	0.045673

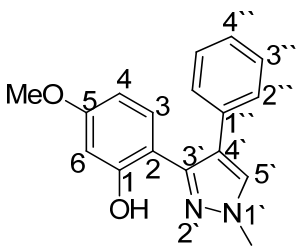
The indexes of local softnesses (electrophilic attack) on the atoms of 3-trifluoroacetylchromone **368** (numeration in Figure 8, p. 129, atom-number is simply its number in input Z-Matrix), computed in basis 6-31++G(d,p), are as following:

Atom	ESP	Mulliken	Hishfeld	NPA
7	0.318768	0.317667	0.242154	0.303915
11	0.565135	0.506538	0.416797	0.584307
13	0.453205	0.359085	0.297607	0.381342
15	0.162894	0.100544	0.083928	0.075696
16	0.072256	0.049999	0.044686	0.034571
17	0.081695	0.079323	0.056151	0.047813

7.6 Proposed mechanism of nucleophilic hydrogenation

Phenylsulphide (Merck) and phenylhydrazine (Merck) were found in collection of chemicals of AG Groth. Methylhydrazine (anhydrous, Fluka) was purshased and used “as is”. PhSNa synthesized with yield of 95% according to the known procedure[479]. (S)-Carvone (Fluka) was found in collection of chemicals by AG Groth, its purity was checked with help of NMR spectra.

5-methoxy-2-(1-methyl-4-phenyl-1H-pyrazol-3-yl)phenol 382



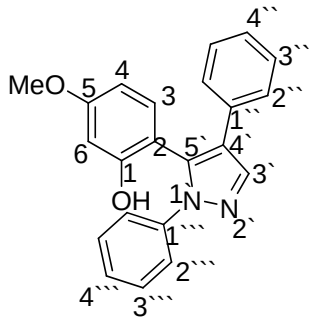
252 Mg (1 mmol) of **7-methoxyisoflavone 281** and 0.16 ml (3 mmol) of methylhydrazine (anhydrous) were refluxed in 20 ml of ethanol (under air, solvent was not absolutized). In 3 h TLC showed no educt, and the reaction mixture was poured into 300 ml of water, then in 24 h brine (100 ml) was added to induce crystallization. In 24 h the white precipitate was filtrated and dried at 100º C directly on the frit. It was washed off from the frit with acetone, the latter was evaporated and the rest was dried in deep vacuum affording **5-methoxy-2-(1-methyl-4-phenyl-1H-pyrazol-3-yl)phenol** as white crystalls. Yield – 250 mg (89%). The structure of this regioisomer is proven by NOESY spectrum, which shows negative correlation between 1`-NMe and 5`-H, and by HMBC spectrum (CNST = 8 Hz), which shows a weak correlation between 1`-NMe and 3`-C. The regioisomer, bearing 2`-NMe-group, should not show the NOE between above mentioned atoms, but show NOE between 2`-NMe and 3-H; also the correlation between 2`-NMe and 3`-C in HMBC spectrum should be strong. This substance form a blue complex with ethanolic $FeCl_3$, while the formation of chelate complex should be impossible in case of 2`-NMe-regioisomer.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 3.75 (s, 3H, OMe), 3.91 (s, 3H, NMe), 6.20 (d, J 8.5, 1H, 4-H), 6.57 (s, 1H, 6-H), 7.08 (d, J 8.5, 1H, 3-H), 7.28-7.47 (br m, 6H, here indirectly detected: 7.31 – 4``-H, 7.32 – 2``-H, 7.33 – 5`-H, 7.35 – 3``-H), 10.76 (br s, OH).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 38.84 (NMe), 55.16 (OMe), 101.71 (6-CH), 105.47 (4-CH), 110.07 (2-C), 120.37 (4`-C), 127.14 (4``-CH), 128.55 (3``-CH), 128.75 (3-C), 129.42 (2``-CH), 131.01 (5`-CH), 133.38 (1``-C), 146.65 (3`-C), 157.35 (1-C), 160.24 (5-C).

HRMS ESI/FT-ICR, observed (calculated): [M+H$^+$] 281.1281 (281.1285); [M+Na$^+$] 303.1119 (303.1104).

2-(1,4-diphenyl-1H-pyrazol-5-yl)-5-methoxyphenol 383



1.008 G (4 mmol) of **7-methoxyisoflavone** and 5.2 ml (52.4 mmol) of phenylhydrazine were refluxed in 20 ml of DMF (not absolute, under air atmosphere) for 24 h. The TLC has shown no educt, and the reaction mixture was poured into 500 ml of water. In one week the

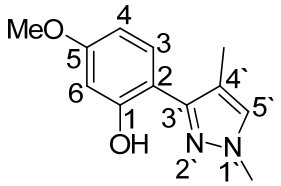
resin has crystallized and was collected by filtration, dried at 100º C directly on the frit. It was washed off from the frit with acetone, the latter was evaporated and the rest was dried in deep vacuum affording **2-(1,4-diphenyl-1H-pyrazol-5-yl)-5-methoxyphenol** as brown crystalls. Yield – 1.3 g (95%). This substance does not form a coloured complex with ethanolic $FeCl_3$, hence the formation of chelate is not possible, that proves the formation of this regioisomer. Another proof is the weak HMBC (CNST = 8 Hz) correlation between 3`-H and 1```-C. For the regioisomer, bearing 2`-Ph group, the above mentioned HMBC-correlation should be strong.

^{1}H NMR (600 MHz, DMSO): δ = 3.68 (s, 3H, OMe), 6.36 (d, J 8.0, 1H, 4-H), 6.44 (s, 1H, 6-H), 6.90 (d, J 8.0, 1H, 3-H), 7.13 (t, J 7.0, 1H, 4``-H), 7.23 (m, 3H, 2``-H and 4```-H), 7.28-7.35 (m, 6H, here indirectly detected: 7.29 – 3``-H; 7.31 – 2```-H; 7.32 – 3```-H), 8.07 (s, 1H, 3`-H), 9.82 (s, 1H, OH).

^{13}C NMR (150 MHz, DMSO): δ = 56.36 (OMe), 102.79 (6-CH), 106.59 (4-CH), 111.35 (2-C), 123.56 (1``-C), 125.37 (2```-CH), 127.46 (4``-CH), 127.94 (3```-CH), 128.41 (4```-CH), 129.87 (2``-CH), 130.09 (3```-CH), 134.03 (4`-C), 134.49 (3-CH), 137.87 (5`-C), 140.30 (3`-CH), 141.72 (1```-C), 158.61 (1-C), 162.53 (5-C).

HRMS ESI/FT-ICR, observed (calculated): [M+H$^+$] 343.1442 (343.1441).

2-(1,4-dimethyl-1H-pyrazol-3-yl)-5-methoxyphenol 384



190 Mg (1 mmol) of **7-methoxy-3-methylchromone** and 0.16 ml (3 mmol) of methylhydrazine (anhydrous) were refluxed in 20 ml of ethanol (under air, solvent was not absolitized). In 24 h TLC showed the presence of educt. 0.16 ml (3 mmol) of methylhydrazine were added, and the mixture was refluxed for 24 h. The TLC showed no educt, and the mixture was poured into 300 ml of water, then in 24 h brine (100 ml) was added to induce crystallization. In 24 h the white precipitate was filtrated and dried at 100º C directly on the frit. During drying it was melted, but was successfully washed off from the frit by acetone. The acetone was evaporated, and the rest was dried in deep vacuum affording 2-(1,4-dimethyl-1H-pyrazol-3-yl)-5-methoxyphenol as yellow oil (was not crystallized by storing at r.t.). Yield – 154 mg (70%). The structure of this regioisomer is proven by NOESY spectrum, which shows negative correlations between 3-H and 4`-Me; between 4`-Me and 5`; between

NMe and 5`. Another regioisomer should not show a correlation between NMe and 5`, but should show one between 2`-NMe and 3-H. This compounds forms the blue complex with ethanolic $FeCl_3$, which is another proof of this structure (formation of chelate-complex is impossible for regioisomer bearing 2`-NMe-group).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.30 (s, 3H, 4`-Me), 3.82 (s, 3H, OMe), 3.86 (s, 3H, NMe), 6.50 (dd, J 8.5, J 2.8, 1H, 4-H), 6.60 (d, J 2.8, 1H, 6-H), 7.19 (s, 1H, 5`-H), 7.54 (d, J 8.5, 1H, 3-H), OH exchanged.

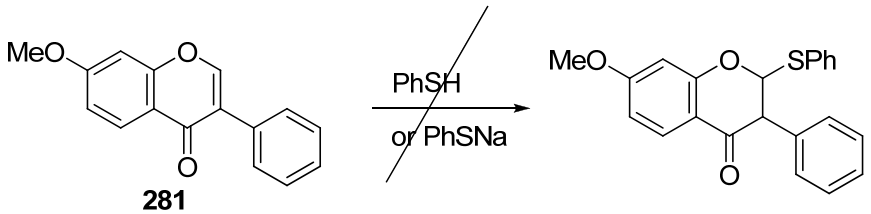
^{1}H NMR (400 MHz, DMSO): δ = 2.18 (s, 3H, 4`-Me), 3.75 (s, 3H, OMe), 3.84 (s, 3H, NMe), 6.47-6.51 (m, 2H, 4-H and 6-H), 7.45 (d, J 9.3, 3-H), 7.61 (s, 1H, 5`-H), 10.89 (s, 1H, OH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.19 (4`-Me), 38.62 (NMe), 55.25 (OMe), 101.79 (6-CH), 105.62 (4-CH), 111.36 (2-C), 113.35 (4`-C), 127.58 (3-CH), 130.95 (5`-CH), 147.91 (3`-C), 157.52 (1`-C), 159.93 (5-C).

^{13}C NMR (100 MHz, DMSO): δ = 10.50 (4`-Me), 38.26 (NMe), 54.99 (OMe), 101.47 (6-CH), 105.20 (4-CH), 111.56 (2-C), 112.66 (4`-C), 128.19 (3-CH), 131.68 (5`-CH), 146.88 (3`-C), 156.70 (1`-C), 159.48 (5-C).

HRMS ESI/FT-ICR, observed (calculated): [M+H$^+$] 219.1132 (219.1128); [M+Na$^+$] 241.0926 (241.0947).

Attempts to prepare 7-methoxy-3-phenyl-2-(phenylthio)chroman-4-one by reaction of 7-methoxyisoflavone 281 with either PhSH or PhSNa



281

1st attempt. 252 Mg (1 mmol) of **281** and 0.12 ml (1.2 mmol) of PhSH were refluxed in absolute THF in nitrogen atmosphere during 24 h. All volatiles (including PhSH) were removed in vacuum, and NMR showed the presence of only **281**.

2nd attempt. To the solution of 147 mg (1.33 mmol) of PhSH in 20 ml of THF 0.83 ml (1.33 mmol) of 1.6M solution of nBuLi were added, this was stirred for 30 min at r.t. 280 Mg (1.1 mmol) of **281** were added, resulting in colour change to red. The mixture was stirred overnight, then poured in water, resulting in precipitation of pure **281** with quantitative recovery.

3rd attempt. 252 Mg (1 mmol) of **281** and 139 mg (1.05 mmol) of PhSNa were dissolved in 5 ml of absolute DMF and stirred under nitrogen atmosphere overnight. Reaction was quenched with 0.12 ml (2 mmol) of iodomethane, and stirred for additional 12 h (under nitrogen). The mixture was poured in water, resulting in precipitation of pure **281** with quantitative recovery.

Quantum-chemical computations.

The computations, their verification and partially interpretation were performed by Prof. Dr. Thomas Exner (University of Konstanz, Germany) and this work is kindly acknowledged.

The initial structures were drawn using HyperChem 8.0.3[480] for Windows (evaluation version by Hypercube, Inc., http://www.hyper.com) or using GaussView 3.0[481] for Linux (full version from Gaussian, Inc., http://www.gaussian.com) and saved in format of Cartesian coordinates. This was fed to Gaussian 03[482] (Revision C.02) for Linux (full version from Gaussian, Inc., http://www.gaussian.com) for geometry optimization by semi-empirical method PM3, using no symmetry restrains. The header for PM3-calculations was as following:

```
%Chk=<Name of file>.chk
# RPM3 FOpt

<Name of the substance>

0  1
<Here goes Gaussian Z-matrix, written in Cartesian coordinates>
```

Output structures (after geometry optimisation by PM3) were fed (with help of program GaussView 3.0[481]) to Gaussian 03[482] for geometry optimisation using DFT (with the empirically parametrized hybrid functional B3LYP[417]). Optimized structures were characterized by the lack of imaginary frequencies (i.e. the optimized stuctures represent stationary points on the potential energy surface). The headers for geometry optimization were as following:

```
%chk=<Name of file>.chk
%mem=30MW
#p opt freq rb3lyp/<Basis>

<Name of the substance>

0 1
<Here goes Gaussian Z-matrix >
```

As <Basis> the corresponding basis was written: "**6-31g"** for 6-31G, "**6-31g****" for 6-31G(d,p) and "**6-31++g****" for 6-31++ G(d,p).

The following optimized structures were obtained (Cartesian coordinates):

In basis 6-31G:

For 2-phenylcyclohex-2-enone **370**:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	6	0	0.000000	0.000000	1.536660
3	6	0	1.444384	0.000000	-0.528450
4	6	0	2.300764	1.021715	0.171611
5	6	0	2.031370	1.577246	1.381809
6	6	0	0.800389	1.158505	2.116049
7	8	0	0.443102	1.694203	3.185010
8	6	0	2.959351	2.570686	1.992704
9	6	0	4.352701	2.385859	1.884949
10	6	0	5.247060	3.323358	2.408241
11	6	0	4.765310	4.464656	3.059015
12	6	0	3.384424	4.654333	3.184953
13	6	0	2.487612	3.718248	2.661807
14	1	0	-0.517169	0.898192	-0.363689
15	1	0	-0.552087	-0.865325	-0.384139
16	1	0	0.450791	-0.935749	1.905718
17	1	0	-1.010726	0.052522	1.952056
18	1	0	1.461501	0.184409	-1.610444
19	1	0	1.891846	-0.999830	-0.390928
20	1	0	3.201145	1.336735	-0.352498
21	1	0	4.735334	1.488744	1.407571
22	1	0	6.316099	3.156889	2.317874
23	1	0	5.457498	5.192569	3.470563
24	1	0	3.001476	5.533666	3.693489
25	1	0	1.422932	3.866871	2.779721

For 7-methoxyisoflavone **281**:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	6	0	0.000000	0.000000	1.414610
3	6	0	1.199718	0.000000	-0.712418
4	6	0	2.393566	0.001280	0.015070
5	6	0	2.433087	0.000779	1.415343
6	6	0	1.198531	-0.000828	2.103648
7	8	0	3.574267	-0.003645	-0.725604
8	6	0	4.781605	0.012232	-0.056419
9	6	0	4.925759	0.040817	1.295094
10	6	0	3.712491	0.000868	2.141491
11	8	0	3.751903	-0.031446	3.398508
12	8	0	-1.249282	0.000000	-0.590385
13	6	0	-1.344959	-0.000439	-2.042175
14	6	0	6.286773	0.112247	1.883850
15	6	0	7.291273	0.875244	1.253547
16	6	0	8.590499	0.915967	1.765699
17	6	0	8.908948	0.203985	2.927530
18	6	0	7.915856	-0.541726	3.573142
19	6	0	6.616157	-0.589019	3.061584
20	1	0	-0.954228	0.000000	1.926672
21	1	0	1.247065	-0.001126	-1.792310
22	1	0	1.227362	-0.002240	3.186954
23	1	0	5.601023	-0.013316	-0.760237
24	1	0	-2.412592	-0.003089	-2.255549
25	1	0	-0.882162	0.897287	-2.467270
26	1	0	-0.877580	-0.895901	-2.466931
27	1	0	7.045310	1.462925	0.374141
28	1	0	9.347255	1.513364	1.266780
29	1	0	9.915928	0.239391	3.331188
30	1	0	8.151723	-1.088788	4.480533
31	1	0	5.848971	-1.150413	3.576805

For 7-methoxy-2-trifluoromethylisoflavone **367**:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	6	0	0.000000	0.000000	1.415970
3	6	0	1.199602	0.000000	-0.713553
4	6	0	2.390975	0.002176	0.016393
5	6	0	2.430803	0.002612	1.414846
6	6	0	1.197146	0.000413	2.105851
7	8	0	3.568949	-0.006498	-0.721782
8	6	0	4.792003	0.006643	-0.071658
9	6	0	4.939543	0.071208	1.279005
10	6	0	3.710609	0.011170	2.126241
11	8	0	3.774077	-0.023612	3.378531
12	8	0	-1.246962	-0.001139	-0.587733
13	6	0	-1.348649	0.001543	-2.040837
14	6	0	6.248641	0.228103	1.964673
15	6	0	7.113030	1.286052	1.624898
16	6	0	8.328150	1.451228	2.294124
17	6	0	8.695475	0.564918	3.312432
18	6	0	7.837249	-0.483913	3.663321
19	6	0	6.618145	-0.648640	3.002091
20	1	0	-0.954593	-0.000466	1.927075
21	1	0	1.247624	-0.004138	-1.793237
22	1	0	1.224996	0.000423	3.189063
23	6	0	5.878240	-0.012858	-1.112035
24	1	0	-2.417186	0.001686	-2.248507
25	1	0	-0.885635	0.899484	-2.464390
26	1	0	-0.885183	-0.894459	-2.468010
27	1	0	6.831478	1.979821	0.840546
28	1	0	8.983525	2.272170	2.021931
29	1	0	9.639363	0.693664	3.832574
30	1	0	8.113521	-1.170876	4.456582
31	1	0	5.948988	-1.448863	3.291135
32	9	0	5.467287	-0.663706	-2.262324
33	9	0	6.248990	1.280463	-1.497601
34	9	0	7.024250	-0.651721	-0.673345

For 7-methoxy-2-trifluoromethylchromone **377**:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	6	0	0.000000	0.000000	1.415000
3	6	0	1.200882	0.000000	-0.713434
4	6	0	2.392044	0.000000	0.014138
5	6	0	2.431532	0.000000	1.417003
6	6	0	1.197751	0.000000	2.104974
7	8	0	3.572487	0.000000	-0.740085
8	6	0	4.778708	0.000000	-0.074706
9	6	0	4.901919	-0.000385	1.266094
10	6	0	3.715652	-0.000844	2.131083
11	8	0	3.807084	-0.001207	3.382377
12	8	0	-1.245809	0.000000	-0.588840
13	6	0	-1.347193	0.000000	-2.042409
14	1	0	-0.954554	0.000000	1.926200
15	1	0	1.247625	0.000000	-1.793233
16	1	0	1.225021	0.000000	3.188441
17	6	0	5.915307	-0.000001	-1.045105
18	1	0	-2.415720	-0.000001	-2.249915
19	1	0	-0.884187	0.897100	-2.467644
20	1	0	-0.884110	-0.897048	-2.467646
21	9	0	5.887251	1.115283	-1.871565
22	9	0	7.130760	-0.000001	-0.378542
23	9	0	5.887241	-1.115288	-1.871562
24	1	0	5.877823	-0.000363	1.730922

For 7-methoxyflavone **282**:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	6	0	0.000000	0.000000	1.413500
3	6	0	1.199527	0.000000	-0.714187
4	6	0	2.396068	0.000000	0.009774

5	6	0	2.431439	-0.000911	1.410307
6	6	0	1.200876	-0.000586	2.100581
7	8	0	3.570729	-0.003618	-0.743493
8	6	0	4.811947	-0.005149	-0.106411
9	6	0	4.894899	0.005643	1.250684
10	6	0	3.722709	0.001423	2.115394
11	8	0	3.809316	0.004435	3.371278
12	8	0	-1.250264	-0.000748	-0.591068
13	6	0	-1.345917	-0.003649	-2.042106
14	1	0	-0.953743	0.000329	1.926487
15	1	0	1.242106	-0.001742	-1.794357
16	1	0	1.232816	-0.000282	3.184080
17	1	0	-2.413624	-0.005361	-2.255633
18	1	0	-0.882354	0.892740	-2.469517
19	1	0	-0.879984	-0.900463	-2.466007
20	1	0	5.858044	0.031251	1.741329
21	6	0	5.926985	-0.007731	-1.067582
22	6	0	5.692768	0.251573	-2.432485
23	6	0	6.752022	0.263176	-3.342646
24	6	0	8.058994	0.013559	-2.909538
25	6	0	8.300403	-0.252821	-1.555684
26	6	0	7.245861	-0.266336	-0.642399
27	1	0	4.682299	0.445616	-2.767993
28	1	0	6.556217	0.468454	-4.390120
29	1	0	8.880674	0.022210	-3.618282
30	1	0	9.309299	-0.456696	-1.212387
31	1	0	7.447698	-0.493471	0.398185

For 7-methoxy-3-phenylcoumarin **283**:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	6	0	0.000000	0.000000	1.411240
3	6	0	1.203280	0.000000	-0.715409
4	6	0	2.397780	0.002019	-0.007155
5	6	0	2.439800	0.005712	1.404845
6	6	0	1.211059	0.001916	2.095542
7	8	0	-1.147181	-0.001534	-0.772493
8	6	0	-2.446999	-0.003272	-0.119842
9	8	0	3.580817	-0.007468	-0.727688
10	6	0	4.871335	-0.015863	-0.123177
11	6	0	4.907457	0.016264	1.346778
12	6	0	3.725337	0.009230	2.041330
13	8	0	5.828977	-0.049312	-0.895606
14	6	0	6.217833	0.061402	2.042965
15	6	0	6.339363	0.765641	3.259727
16	6	0	7.354305	-0.607513	1.542555
17	6	0	8.558847	-0.587521	2.250694
18	6	0	8.660618	0.101883	3.464167
19	6	0	7.544707	0.782738	3.964479
20	1	0	-0.928728	-0.002028	1.966617
21	1	0	1.199416	-0.003200	-1.796747
22	1	0	1.216231	0.001925	3.181160
23	1	0	-3.169959	-0.005128	-0.934041
24	1	0	-2.579592	-0.899857	0.496022
25	1	0	-2.582761	0.893752	0.494673
26	1	0	3.750903	-0.011406	3.126563
27	1	0	5.492742	1.328553	3.640084
28	1	0	7.293056	-1.128594	0.596891
29	1	0	9.420571	-1.111962	1.850114
30	1	0	9.599963	0.118185	4.007667
31	1	0	7.616035	1.338183	4.894420

For 7-methoxyneoflavone **284**:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	6	0	0.000000	0.000000	1.409040
3	6	0	1.205963	0.000000	-0.707088
4	6	0	2.403245	0.012814	-0.001372
5	6	0	2.446516	0.042701	1.415452
6	6	0	1.210657	0.017829	2.094839
7	8	0	-1.144685	-0.012137	-0.775844

8	6	0	-2.445078	-0.031217	-0.124772
9	8	0	3.566788	-0.020547	-0.755429
10	6	0	4.860340	-0.063782	-0.155251
11	6	0	4.881063	-0.008098	1.290929
12	6	0	3.752833	0.057084	2.062175
13	8	0	5.832332	-0.126023	-0.907094
14	6	0	3.886014	0.139636	3.543451
15	6	0	4.680581	-0.797221	4.231204
16	6	0	3.270549	1.173468	4.276906
17	6	0	3.447099	1.264624	5.660684
18	6	0	4.232883	0.322380	6.335054
19	6	0	4.848773	-0.708433	5.616207
20	1	0	-0.927228	-0.021288	1.966709
21	1	0	1.208998	-0.019464	-1.788289
22	1	0	1.204342	0.001782	3.177632
23	1	0	-3.167397	-0.034870	-0.939547
24	1	0	-2.569132	-0.933162	0.485033
25	1	0	-2.590423	0.860060	0.495936
26	1	0	5.865807	0.016037	1.739071
27	1	0	5.152383	-1.601903	3.676653
28	1	0	2.676579	1.918699	3.758053
29	1	0	2.977165	2.074160	6.209987
30	1	0	4.365749	0.392747	7.409769
31	1	0	5.458403	-1.443294	6.131990

For 3-methoxy-2-phenylcyclohex-2-enone **374**:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	6	0	0.000000	0.000000	1.530960
3	6	0	1.441859	0.000000	-0.531527
4	6	0	2.282719	-1.058733	0.140481
5	6	0	1.979549	-1.642633	1.341585
6	6	0	0.812024	-1.154842	2.105971
7	8	0	0.501043	-1.625343	3.223109
8	6	0	2.812044	-2.733110	1.926900
9	6	0	3.165402	-3.863144	1.165077
10	6	0	3.936489	-4.889294	1.717370
11	6	0	4.369843	-4.807204	3.045730
12	6	0	4.021077	-3.692336	3.815865
13	6	0	3.246882	-2.667227	3.264545
14	1	0	-0.541276	0.868406	-0.391923
15	1	0	-0.517974	-0.896067	-0.366236
16	1	0	-1.010362	-0.068104	1.944448
17	1	0	0.435416	0.940369	1.905529
18	1	0	1.898534	0.990152	-0.370000
19	1	0	1.435016	-0.160476	-1.616310
20	8	0	3.456277	-1.453840	-0.478989
21	1	0	2.835772	-3.932672	0.134828
22	1	0	4.195498	-5.752996	1.112226
23	1	0	4.968005	-5.604528	3.476330
24	1	0	4.346885	-3.621267	4.849116
25	1	0	2.964879	-1.818890	3.875242
26	6	0	3.910660	-0.842622	-1.721283
27	1	0	4.899475	-1.268280	-1.886726
28	1	0	3.256783	-1.101535	-2.560497
29	1	0	3.989560	0.245341	-1.632092

For 2-methylcyclohex-2-enone **376**:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	6	0	0.000000	0.000000	1.538120
3	6	0	1.441560	0.000000	-0.541276
4	6	0	2.297015	1.036617	0.142864
5	6	0	2.017594	1.589076	1.346024
6	6	0	0.826702	1.140574	2.112458
7	8	0	0.541408	1.653117	3.215719
8	6	0	2.875155	2.649126	1.989063
9	1	0	-0.517582	0.899012	-0.361432
10	1	0	-0.554680	-0.864441	-0.382820
11	1	0	0.432325	-0.944120	1.908101
12	1	0	-1.010445	0.068937	1.952853

13	1	0	1.444843	0.174755	-1.625225
14	1	0	1.894908	-0.996191	-0.399658
15	1	0	2.295847	3.561784	2.170729
16	1	0	3.239161	2.318407	2.968712
17	1	0	3.734547	2.899231	1.359819
18	1	0	3.199629	1.349673	-0.380886

For 3-trifluoroacetylchromone, *s-cis*-conformation (found more energeticaly reach, as *s-trans*, local softness of *s-trans*-conformation was taken in consideration) **368**:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	6	0	0.000000	0.000000	1.407890
3	6	0	1.201371	0.000000	-0.707737
4	6	0	2.392080	0.001040	0.017832
5	6	0	2.428051	0.001263	1.417690
6	6	0	1.202328	0.000000	2.109169
7	8	0	3.588680	-0.000874	-0.722281
8	6	0	4.781325	0.012068	-0.071579
9	6	0	4.922980	0.024179	1.287234
10	6	0	3.715235	-0.000283	2.150122
11	8	0	3.752613	-0.041783	3.396961
12	6	0	6.263132	0.074737	1.895186
13	8	0	6.508396	0.470050	3.038133
14	6	0	7.453839	-0.426147	1.044622
15	9	0	7.681976	0.426630	-0.047228
16	9	0	8.611344	-0.484906	1.771853
17	9	0	7.206865	-1.688767	0.513809
18	1	0	-0.939469	-0.000324	-0.541712
19	1	0	-0.941142	-0.000860	1.946287
20	1	0	1.234904	-0.000632	-1.790198
21	1	0	1.233268	-0.001230	3.192587
22	1	0	5.598082	0.032896	-0.777507

For 3-trifluoroacetylchromone, *s-trans*-conformation **368**:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	6	0	0.000000	0.000000	1.407760
3	6	0	1.201556	0.000000	-0.707876
4	6	0	2.391409	0.001898	0.018078
5	6	0	2.428058	0.002716	1.418438
6	6	0	1.202270	-0.000586	2.109457
7	8	0	3.590534	0.000289	-0.722229
8	6	0	4.775689	0.015864	-0.066714
9	6	0	4.915192	0.039870	1.294003
10	6	0	3.714744	-0.000304	2.150860
11	8	0	3.752462	-0.055973	3.399230
12	6	0	6.313022	0.074025	1.769729
13	8	0	7.268501	-0.165523	1.012655
14	6	0	6.650362	0.466822	3.221553
15	9	0	7.995469	0.766942	3.323950
16	9	0	5.950334	1.597165	3.613561
17	9	0	6.393309	-0.561512	4.108675
18	1	0	-0.939420	-0.000917	-0.541736
19	1	0	-0.941177	-0.000650	1.946036
20	1	0	1.235250	-0.001673	-1.790300
21	1	0	1.232756	-0.003103	3.192865
22	1	0	5.618912	0.014259	-0.744005

For 7-acetyloxy-2-methylisoflavone **379**:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	6	0	0.000000	0.000000	1.407160
3	6	0	1.182503	0.000000	-0.731539
4	6	0	2.387365	-0.012727	-0.022376
5	6	0	2.430781	-0.028326	1.377494
6	6	0	1.212693	-0.018524	2.084404
7	8	0	3.558844	-0.018840	-0.766989

8	6	0	4.803906	-0.003018	-0.133866
9	6	0	4.930534	0.016508	1.226976
10	6	0	3.726697	-0.043118	2.080704
11	8	0	3.782884	-0.102758	3.334539
12	6	0	6.263117	0.101664	1.886463
13	6	0	6.637660	-0.833423	2.870485
14	6	0	7.163796	1.133225	1.559850
15	6	0	8.414344	1.215899	2.180660
16	6	0	8.781307	0.271476	3.145194
17	6	0	7.887565	-0.750028	3.489336
18	6	0	5.882799	-0.042773	-1.168666
19	8	0	-1.224312	0.085590	-0.691824
20	6	0	-2.023157	-1.038887	-1.003806
21	8	0	-3.086374	-0.836764	-1.570005
22	6	0	-1.479568	-2.389440	-0.615341
23	1	0	-0.943400	0.034464	1.939053
24	1	0	1.178731	0.027782	-1.813185
25	1	0	1.258496	-0.019223	3.167186
26	1	0	5.942818	-1.613470	3.155708
27	1	0	6.873598	1.884577	0.831869
28	1	0	9.093907	2.020574	1.918142
29	1	0	9.750013	0.335437	3.630568
30	1	0	8.161732	-1.480093	4.244173
31	1	0	6.850013	-0.271059	-0.722035
32	1	0	5.639097	-0.802517	-1.918819
33	1	0	5.959290	0.917150	-1.694291
34	1	0	-2.185863	-3.151613	-0.943330
35	1	0	-0.504767	-2.570205	-1.080031
36	1	0	-1.342450	-2.464106	0.468319

For 7-methoxy-2-methylisoflavone **378**:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	6	0	0.000000	0.000000	1.414240
3	6	0	1.199130	0.000000	-0.713720
4	6	0	2.394286	-0.001349	0.013083
5	6	0	2.431535	-0.001979	1.410836
6	6	0	1.199679	0.000414	2.102243
7	8	0	3.572612	0.007154	-0.725869
8	6	0	4.812415	-0.017937	-0.084435
9	6	0	4.929046	-0.055986	1.276145
10	6	0	3.716127	-0.005946	2.122570
11	8	0	3.769491	0.031183	3.379069
12	6	0	6.255968	-0.152125	1.944866
13	6	0	7.167099	-1.168177	1.598499
14	6	0	6.616722	0.756222	2.959026
15	6	0	7.861667	0.662962	3.586410
16	6	0	8.765845	-0.342135	3.221529
17	6	0	8.413051	-1.260624	2.227346
18	6	0	5.898547	0.037097	-1.112225
19	8	0	-1.250544	0.000000	-0.590337
20	6	0	-1.346304	-0.002239	-2.041459
21	1	0	-0.954032	-0.000330	1.926688
22	1	0	1.244751	0.001711	-1.793726
23	1	0	1.230643	0.001139	3.185560
24	1	0	6.888513	-1.901247	0.847598
25	1	0	5.913505	1.522031	3.261087
26	1	0	8.123807	1.372930	4.364517
27	1	0	9.730755	-0.413623	3.713616
28	1	0	9.099836	-2.053605	1.947921
29	1	0	5.658405	0.807615	-1.852679
30	1	0	6.862901	0.260710	-0.657006
31	1	0	5.980046	-0.914929	-1.651492
32	1	0	-2.413989	-0.000750	-2.255046
33	1	0	-0.879728	0.892644	-2.468621
34	1	0	-0.882881	-0.900207	-2.465644

For cyclohex-2-enone **369**:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	6	0	0.000000	0.000000	1.540360

3	6	0	1.437238	0.000000	-0.557676
4	6	0	2.300269	1.033589	0.122977
5	6	0	2.007018	1.565094	1.327456
6	6	0	0.835720	1.136887	2.113639
7	8	0	0.569998	1.654502	3.218263
8	1	0	-0.556674	-0.863997	-0.380607
9	1	0	-0.519581	0.898662	-0.359153
10	1	0	-1.011374	0.074714	1.951762
11	1	0	0.426287	-0.945864	1.912204
12	1	0	1.428261	0.178143	-1.640898
13	1	0	1.894622	-0.994997	-0.423817
14	1	0	3.200569	1.351771	-0.399879
15	1	0	2.635018	2.323248	1.785093

For isoflavone **3**:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	6	0	0.000000	0.000000	1.409530
3	6	0	1.199260	0.000000	-0.707341
4	6	0	2.397530	0.001470	0.012803
5	6	0	2.429968	0.000769	1.415168
6	6	0	1.202377	-0.000719	2.107225
7	8	0	3.582958	-0.003203	-0.722810
8	6	0	4.785395	0.015837	-0.050662
9	6	0	4.926942	0.045676	1.302367
10	6	0	3.714440	0.002375	2.144910
11	8	0	3.747484	-0.030911	3.400984
12	6	0	6.286485	0.123307	1.893782
13	6	0	6.617647	-0.577469	3.071242
14	6	0	7.287337	0.893816	1.266891
15	6	0	8.584801	0.943021	1.782723
16	6	0	8.905065	0.231926	2.944575
17	6	0	7.915579	-0.521791	3.586405
18	1	0	-0.940284	0.000000	-0.541039
19	1	0	-0.941247	-0.000325	1.948268
20	1	0	1.231364	-0.001550	-1.790044
21	1	0	1.235929	-0.001840	3.190635
22	1	0	5.608432	-0.007769	-0.750468
23	1	0	5.853674	-1.145587	3.584006
24	1	0	7.040118	1.481035	0.387541
25	1	0	9.338615	1.546265	1.286480
26	1	0	9.910620	0.273995	3.351056
27	1	0	8.152806	-1.068458	4.493643

For flavone **2**:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	6	0	0.000000	0.000000	1.408570
3	6	0	1.199329	0.000000	-0.709073
4	6	0	2.399994	0.000000	0.007443
5	6	0	2.428337	-0.000411	1.410086
6	6	0	1.204691	0.000000	2.104303
7	8	0	3.579211	-0.002982	-0.740786
8	6	0	4.816447	-0.001474	-0.101650
9	6	0	4.896129	0.009135	1.257104
10	6	0	3.724459	0.003459	2.118211
11	8	0	3.804515	0.006388	3.373678
12	1	0	-0.940253	-0.000325	-0.541253
13	1	0	-0.940853	0.000000	1.948054
14	1	0	1.226737	-0.001345	-1.792015
15	1	0	1.241425	0.000635	3.187911
16	6	0	5.934947	-0.002802	-1.058746
17	6	0	7.259023	-0.213671	-0.623236
18	6	0	5.697801	0.209148	-2.431409
19	6	0	6.758695	0.219232	-3.339553
20	6	0	8.070364	0.016190	-2.896546
21	6	0	8.315063	-0.201772	-1.534612
22	1	0	7.465374	-0.401013	0.424239
23	1	0	4.683728	0.366953	-2.774728
24	1	0	6.560251	0.386789	-4.393143
25	1	0	8.893475	0.024023	-3.603605

26	1	0	9.328025	-0.368111	-1.183208
27	1	0	5.857893	0.033466	1.750276

For 3-phenylcoumarin **293**:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	6	0	0.000000	0.000000	1.408460
3	6	0	1.200232	0.000000	-0.710432
4	6	0	2.400175	0.001844	0.003249
5	6	0	2.433094	0.005289	1.411120
6	6	0	1.203409	0.001904	2.106207
7	8	0	3.586185	-0.007287	-0.715091
8	6	0	4.872109	-0.014030	-0.109108
9	6	0	4.902335	0.018297	1.363487
10	6	0	3.719543	0.009641	2.054004
11	1	0	-0.940917	-0.001299	-0.539613
12	1	0	-0.940478	-0.001624	1.948316
13	1	0	1.229685	-0.002667	-1.792968
14	1	0	1.211809	0.001917	3.191925
15	6	0	6.210735	0.066233	2.062749
16	8	0	5.835207	-0.046353	-0.874675
17	1	0	3.740468	-0.011040	3.139215
18	6	0	6.328990	0.778564	3.275022
19	6	0	7.346982	-0.608136	1.569508
20	6	0	8.549326	-0.585675	2.281201
21	6	0	8.648470	0.112578	3.489799
22	6	0	7.532564	0.799180	3.982462
23	1	0	5.481821	1.344749	3.649078
24	1	0	7.287509	-1.135809	0.627428
25	1	0	9.411248	-1.114560	1.887162
26	1	0	9.586271	0.131272	4.035804
27	1	0	7.602599	1.361130	4.908480

For chromone **1**:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	6	0	0.000000	0.000000	1.408690
3	6	0	1.199362	0.000000	-0.708407
4	6	0	2.399410	0.000000	0.008068
5	6	0	2.429856	0.000000	1.413168
6	6	0	1.203828	0.000416	2.105217
7	8	0	3.581841	0.000000	-0.741691
8	6	0	4.790350	-0.000419	-0.073154
9	6	0	4.899831	-0.000831	1.272008
10	6	0	3.720965	-0.000865	2.134279
11	8	0	3.793152	-0.001759	3.388183
12	1	0	-0.940244	0.000000	-0.541268
13	1	0	-0.941137	0.000000	1.947639
14	1	0	1.229497	-0.000317	-1.791248
15	1	0	1.238698	0.000428	3.188906
16	1	0	5.613838	-0.000367	-0.773152
17	1	0	5.875945	-0.001148	1.739807

For coumarin **137**:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	6	0	0.000000	0.000000	1.407850
3	6	0	1.199384	0.000000	-0.711530
4	6	0	2.402883	0.000000	-0.002795
5	6	0	2.433032	0.000000	1.408303
6	6	0	1.205063	0.000000	2.103460
7	8	0	3.582049	0.000000	-0.737208
8	6	0	4.871101	0.000000	-0.125358
9	6	0	4.874162	0.000001	1.329829
10	6	0	3.724866	-0.000396	2.052705
11	1	0	-0.941081	0.000000	-0.539410
12	1	0	-0.939784	0.000000	1.948695
13	1	0	1.227195	0.000000	-1.794073
14	1	0	1.214834	0.000000	3.189256

15	1	0	5.850884	0.000338	1.795869
16	8	0	5.853037	0.000532	-0.864356
17	1	0	3.761547	-0.000384	3.138205

For 7-methoxychromone **53**:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	6	0	0.000000	0.000000	1.411660
3	6	0	1.202694	0.000000	-0.712967
4	6	0	2.396945	-0.000422	-0.000983
5	6	0	2.436826	-0.001258	1.407613
6	6	0	1.210770	-0.000418	2.094606
7	8	0	3.576773	-0.000406	-0.753566
8	6	0	4.788298	-0.000818	-0.087223
9	6	0	4.902747	-0.001624	1.256772
10	6	0	3.724989	-0.002132	2.124068
11	8	0	3.804761	-0.002885	3.378464
12	8	0	-1.146811	0.000000	-0.773598
13	6	0	-2.446149	-0.000001	-0.119256
14	1	0	-0.929503	0.000000	1.966269
15	1	0	1.199393	0.000000	-1.794482
16	1	0	1.242820	-0.000750	3.178432
17	1	0	5.608490	-0.000754	-0.791080
18	1	0	5.880276	-0.001912	1.721280
19	1	0	-3.170174	-0.000001	-0.932563
20	1	0	-2.579236	-0.896433	0.496493
21	1	0	-2.579463	0.896712	0.496035

For 7-methoxy-3-methylchromone **373**:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	6	0	0.000000	0.000000	1.414560
3	6	0	1.198867	0.000000	-0.713633
4	6	0	2.395278	0.000426	0.010909
5	6	0	2.432741	0.000849	1.413319
6	6	0	1.199211	0.000000	2.102454
7	8	0	3.572690	0.000413	-0.735335
8	6	0	4.787205	0.000826	-0.066856
9	6	0	4.918667	0.001249	1.279099
10	6	0	3.716010	0.001287	2.128309
11	8	0	-1.250318	0.000000	-0.589783
12	6	0	-1.346893	0.000000	-2.040873
13	8	0	3.792684	0.001674	3.384932
14	6	0	6.262914	0.001686	1.951280
15	1	0	-0.954158	-0.000330	1.926774
16	1	0	1.244656	-0.000312	-1.793613
17	1	0	1.228940	0.000000	3.185926
18	1	0	5.606008	0.000761	-0.773108
19	1	0	-2.414712	0.000000	-2.253636
20	1	0	-0.882158	0.896416	-2.466876
21	1	0	-0.882422	-0.896552	-2.466853
22	1	0	6.367587	0.879352	2.599088
23	1	0	6.367619	-0.875211	2.600125
24	1	0	7.080468	0.001263	1.223994

For (S)-carvone **385**:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	6	0	0.000000	0.000000	1.483340
3	6	0	1.343987	0.000000	-0.712030
4	6	0	2.433752	-0.769929	0.079896
5	6	0	2.527187	-0.165669	1.495184
6	6	0	1.174275	-0.058322	2.151830
7	6	0	3.753683	-0.841924	-0.681718
8	6	0	4.867621	-0.194806	-0.304406
9	6	0	3.742877	-1.723894	-1.914206
10	1	0	1.188195	-0.407981	-1.714473
11	1	0	1.669684	1.045093	-0.836224
12	1	0	2.071643	-1.805291	0.196231

13	1	0	3.201232	-0.765276	2.119793
14	1	0	2.978519	0.839015	1.442989
15	1	0	5.785445	-0.277520	-0.879109
16	1	0	4.918819	0.433599	0.577758
17	1	0	4.727419	-1.754789	-2.389912
18	1	0	3.021088	-1.372569	-2.662895
19	1	0	3.455838	-2.753108	-1.657864
20	1	0	1.162110	-0.019967	3.240337
21	6	0	-1.341995	0.082976	2.163872
22	8	0	-1.068587	0.037836	-0.646580
23	1	0	-1.881587	0.986567	1.857213
24	1	0	-1.977024	-0.763776	1.878713
25	1	0	-1.234905	0.089328	3.252689

For 3-formylchromone **372**:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	6	0	0.000000	0.000000	1.391530
3	6	0	1.213950	0.000000	2.103481
4	6	0	2.410656	-0.000428	1.368742
5	6	0	2.433191	-0.000847	-0.026296
6	6	0	1.217179	-0.000838	-0.707897
7	1	0	-0.938678	0.000000	-0.542961
8	1	0	-0.920794	0.000318	1.963747
9	1	0	3.384958	-0.001167	-0.543274
10	1	0	1.212656	-0.001160	-1.792508
11	6	0	3.691799	-0.000876	3.383952
12	1	0	4.701714	-0.001575	3.772471
13	6	0	1.240934	0.000000	3.580724
14	8	0	0.193132	0.000000	4.272328
15	6	0	2.583974	-0.000480	4.174326
16	8	0	3.657544	-0.000869	2.021373
17	6	0	2.744712	-0.000537	5.638962
18	1	0	1.806989	-0.000201	6.209613
19	8	0	3.851111	-0.000932	6.209998

For 7-methoxy-3-(4-chlorophenoxy)chromone **371**:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	6	0	0.000000	0.000000	1.388940
3	6	0	1.202840	0.000000	2.118734
4	6	0	2.408819	0.006083	1.389689
5	6	0	2.441746	0.007029	0.000059
6	6	0	1.229376	0.002927	-0.696074
7	1	0	-0.940217	-0.002202	-0.535960
8	1	0	-0.928332	0.000000	1.948942
9	1	0	3.381855	0.011751	-0.534437
10	6	0	3.663417	0.000773	3.426142
11	1	0	4.667307	0.018479	3.823186
12	6	0	1.200862	0.009368	3.589213
13	8	0	0.152320	0.025327	4.277798
14	6	0	2.543704	-0.001426	4.185378
15	8	0	3.642596	0.012708	2.048181
16	8	0	1.337890	0.001787	-2.073104
17	6	0	0.129714	-0.004003	-2.885405
18	1	0	-0.473447	0.892000	-2.702627
19	1	0	0.484401	-0.006706	-3.914737
20	1	0	-0.468699	-0.901866	-2.696084
21	8	0	2.698659	0.121720	5.566437
22	6	0	2.190804	-0.863665	6.438064
23	6	0	1.919745	-2.173099	6.036532
24	6	0	2.034439	-0.467045	7.768244
25	6	0	1.472365	-3.100761	6.984135
26	1	0	2.051260	-2.474632	5.004410
27	6	0	1.593516	-1.393496	8.715912
28	1	0	2.252753	0.557506	8.042701
29	6	0	1.317769	-2.697930	8.307732
30	1	0	1.251319	-4.119587	6.691210
31	1	0	1.463703	-1.102739	9.750855
32	17	0	0.738327	-3.913641	9.545358

For 3-methoxycyclohexenone **375**:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	6	0	0.000000	0.000000	1.538810
3	6	0	1.436567	0.000000	-0.554364
4	6	0	2.273866	1.058761	0.111792
5	6	0	1.989915	1.584748	1.330910
6	6	0	0.844977	1.130900	2.117456
7	8	0	0.585727	1.622447	3.239017
8	8	0	3.355420	1.402798	-0.664207
9	6	0	4.312785	2.381461	-0.157106
10	1	0	-0.523463	0.894846	-0.362052
11	1	0	-0.548261	-0.867907	-0.382850
12	1	0	0.412798	-0.951008	1.911801
13	1	0	-1.010734	0.088103	1.948493
14	1	0	1.449198	0.174051	-1.635906
15	1	0	1.909011	-0.981105	-0.392198
16	1	0	2.597314	2.356517	1.787504
17	1	0	5.073354	2.461776	-0.931692
18	1	0	3.827932	3.350399	-0.000760
19	1	0	4.759291	2.034691	0.780382

In basis 6-31G(d,p):

For 2-phenylcyclohex-2-enone **370**:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	6	0	0.000000	0.000000	1.530890
3	6	0	1.437794	0.000000	-0.528529
4	6	0	2.297399	1.016666	0.168390
5	6	0	2.034163	1.573198	1.373478
6	6	0	0.798303	1.160468	2.116369
7	8	0	0.453128	1.688376	3.162411
8	6	0	2.963585	2.561267	1.985625
9	6	0	4.352158	2.362590	1.903439
10	6	0	5.244641	3.294561	2.430353
11	6	0	4.764582	4.443953	3.058931
12	6	0	3.387415	4.647853	3.158835
13	6	0	2.493228	3.716621	2.633214
14	1	0	-0.514937	0.898618	-0.362179
15	1	0	-0.554487	-0.861666	-0.386503
16	1	0	0.459864	-0.928700	1.901604
17	1	0	-1.007802	0.046990	1.951701
18	1	0	1.457018	0.184079	-1.609459
19	1	0	1.889260	-0.996547	-0.392952
20	1	0	3.201045	1.326253	-0.354166
21	1	0	4.733480	1.457105	1.439949
22	1	0	6.313878	3.116518	2.358917
23	1	0	5.457175	5.170214	3.474386
24	1	0	3.004221	5.537682	3.650109
25	1	0	1.427117	3.879066	2.725522

For 7-methoxyisoflavone **281**:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	6	0	0.000000	0.000000	1.414170
3	6	0	1.202883	0.000000	-0.704017
4	6	0	2.397022	0.001534	0.024992
5	6	0	2.428067	0.000686	1.422287
6	6	0	1.193398	-0.001165	2.103123
7	8	0	3.553832	-0.003492	-0.708367
8	6	0	4.740275	0.015247	-0.054398
9	6	0	4.908904	0.043866	1.291054
10	6	0	3.706614	-0.000960	2.156991
11	8	0	3.751738	-0.035454	3.386820
12	8	0	-1.226578	-0.000424	-0.580969
13	6	0	-1.304331	-0.002475	-2.001041
14	6	0	6.277234	0.114348	1.858972
15	6	0	7.267499	0.891792	1.233759
16	6	0	8.569411	0.929165	1.729659

17	6	0	8.903715	0.200579	2.871655
18	6	0	7.924156	-0.559167	3.513449
19	6	0	6.622537	-0.603137	3.017488
20	1	0	-0.955437	-0.000330	1.927025
21	1	0	1.252359	-0.001292	-1.784774
22	1	0	1.221134	-0.003187	3.187416
23	1	0	5.562253	-0.007432	-0.759907
24	1	0	-2.367592	-0.005509	-2.242424
25	1	0	-0.837160	0.892675	-2.429377
26	1	0	-0.832357	-0.896250	-2.426847
27	1	0	7.008285	1.492641	0.366536
28	1	0	9.317583	1.539259	1.231722
29	1	0	9.915742	0.233646	3.264518
30	1	0	8.173349	-1.122434	4.408172
31	1	0	5.863787	-1.181994	3.527783

For 7-methoxy-2-trifluoromethylisoflavone **367**:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	6	0	0.000000	0.000000	1.415330
3	6	0	1.202510	0.000000	-0.705147
4	6	0	2.394777	0.002889	0.025980
5	6	0	2.425747	0.003214	1.421086
6	6	0	1.192301	0.000000	2.105003
7	8	0	3.549817	-0.007325	-0.705055
8	6	0	4.752908	0.021300	-0.071918
9	6	0	4.921700	0.077720	1.274329
10	6	0	3.706105	0.009512	2.140717
11	8	0	3.772594	-0.033063	3.366627
12	8	0	-1.225309	-0.000846	-0.578833
13	6	0	-1.307060	0.002577	-2.000000
14	6	0	6.240146	0.232341	1.942931
15	6	0	7.095117	1.294105	1.610205
16	6	0	8.314935	1.454184	2.265132
17	6	0	8.695169	0.559195	3.265451
18	6	0	7.845542	-0.493129	3.611512
19	6	0	6.622628	-0.652008	2.963613
20	1	0	-0.955744	-0.000572	1.927421
21	1	0	1.252798	-0.004058	-1.785720
22	1	0	1.219737	-0.000903	3.189216
23	6	0	5.846566	0.004542	-1.130820
24	1	0	-2.371013	0.004182	-2.237453
25	1	0	-0.837850	0.897886	-2.424996
26	1	0	-0.839628	-0.891519	-2.429534
27	1	0	6.801577	1.995701	0.836480
28	1	0	8.964936	2.281334	1.995552
29	1	0	9.645046	0.684171	3.777066
30	1	0	8.132135	-1.189708	4.393813
31	1	0	5.958390	-1.459168	3.248091
32	9	0	5.427475	-0.640895	-2.233248
33	9	0	6.178683	1.263416	-1.504963
34	9	0	6.959890	-0.605239	-0.701452

For 7-methoxy-2-trifluoromethylchromone **377**:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	6	0	0.000000	0.000000	1.414220
3	6	0	1.203632	0.000000	-0.704974
4	6	0	2.396021	0.000000	0.023410
5	6	0	2.426878	0.000000	1.422600
6	6	0	1.193234	0.000000	2.103457
7	8	0	3.552536	0.000000	-0.722033
8	6	0	4.740099	0.000000	-0.071705
9	6	0	4.886203	0.000000	1.264663
10	6	0	3.710803	0.000000	2.147711
11	8	0	3.798354	0.000000	3.372967
12	8	0	-1.224342	0.000000	-0.580246
13	6	0	-1.305360	0.000000	-2.001449
14	1	0	-0.955549	0.000000	1.926698
15	1	0	1.252527	0.000000	-1.785668
16	1	0	1.220768	0.000000	3.187878

17	6	0	5.880852	0.000000	-1.061939
18	1	0	-2.369214	-0.000001	-2.239308
19	1	0	-0.837068	0.894744	-2.428715
20	1	0	-0.837055	-0.894737	-2.428717
21	9	0	5.828213	1.086279	-1.856610
22	9	0	7.065539	0.000000	-0.428079
23	9	0	5.828329	-1.086394	-1.856460
24	1	0	5.873762	0.000000	1.706442

For 7-methoxyflavone **282**:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	6	0	0.000000	0.000000	1.413080
3	6	0	1.202693	0.000000	-0.705548
4	6	0	2.398996	0.000601	0.020138
5	6	0	2.426760	-0.000627	1.417492
6	6	0	1.195667	0.000000	2.100178
7	8	0	3.550720	-0.005635	-0.725084
8	6	0	4.768067	0.000658	-0.102386
9	6	0	4.879654	0.017407	1.249734
10	6	0	3.716826	0.005040	2.133194
11	8	0	3.803187	0.007288	3.361951
12	8	0	-1.227389	-0.000734	-0.581896
13	6	0	-1.304837	-0.001837	-2.001154
14	1	0	-0.955018	0.000000	1.926736
15	1	0	1.248013	-0.002391	-1.786545
16	1	0	1.226821	0.000845	3.184640
17	1	0	-2.368056	-0.003231	-2.243183
18	1	0	-0.836536	0.892888	-2.429578
19	1	0	-0.834254	-0.895886	-2.428386
20	1	0	5.855742	0.058240	1.715568
21	6	0	5.883423	0.004991	-1.068461
22	6	0	5.672931	0.406445	-2.398278
23	6	0	6.730073	0.429174	-3.305225
24	6	0	8.010881	0.047944	-2.903698
25	6	0	8.227816	-0.362585	-1.586459
26	6	0	7.174622	-0.387934	-0.677034
27	1	0	4.680288	0.706551	-2.712370
28	1	0	6.552267	0.747904	-4.327986
29	1	0	8.833439	0.064792	-3.612348
30	1	0	9.218232	-0.673703	-1.268373
31	1	0	7.351121	-0.734752	0.335436

For 7-methoxy-3-phenylcoumarin **283**:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	6	0	0.000000	0.000000	1.409480
3	6	0	1.207498	0.000000	-0.707277
4	6	0	2.402304	0.001777	-0.000932
5	6	0	2.436076	0.005521	1.408418
6	6	0	1.208319	0.001616	2.091760
7	8	0	-1.122772	-0.001343	-0.764524
8	6	0	-2.389884	-0.002428	-0.119302
9	8	0	3.560271	-0.007176	-0.717791
10	6	0	4.830044	-0.017981	-0.137139
11	6	0	4.888946	0.012168	1.336947
12	6	0	3.720458	0.007312	2.042310
13	8	0	5.768678	-0.049016	-0.898620
14	6	0	6.209663	0.053047	2.009887
15	6	0	6.363050	0.782553	3.202823
16	6	0	7.322781	-0.645904	1.509545
17	6	0	8.535327	-0.630713	2.196029
18	6	0	8.669164	0.085410	3.386447
19	6	0	7.576834	0.796014	3.886032
20	1	0	-0.928751	-0.002003	1.965423
21	1	0	1.206614	-0.003130	-1.790462
22	1	0	1.211671	0.001621	3.178165
23	1	0	-3.130618	-0.003398	-0.919479
24	1	0	-2.526131	-0.896898	0.500606
25	1	0	-2.528082	0.892319	0.499738
26	1	0	3.753271	-0.012213	3.128469

27	1	0	5.530580	1.367133	3.583245
28	1	0	7.233358	-1.194206	0.580834
29	1	0	9.381029	-1.182194	1.795558
30	1	0	9.618165	0.098426	3.914397
31	1	0	7.672217	1.372998	4.801358

For 7-methoxyneoflavone **284**:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	6	0	0.000000	0.000000	1.407210
3	6	0	1.210109	0.000000	-0.699109
4	6	0	2.407570	0.011436	0.004887
5	6	0	2.443132	0.040893	1.418953
6	6	0	1.208147	0.016676	2.090793
7	8	0	-1.120356	-0.010846	-0.768072
8	6	0	-2.387990	-0.027089	-0.124213
9	8	0	3.547872	-0.018729	-0.742282
10	6	0	4.819193	-0.063181	-0.164965
11	6	0	4.862726	-0.011712	1.286440
12	6	0	3.746972	0.052506	2.064490
13	8	0	5.771182	-0.122495	-0.907639
14	6	0	3.885533	0.131912	3.544086
15	6	0	4.671427	-0.809333	4.227028
16	6	0	3.281963	1.166545	4.278183
17	6	0	3.462824	1.255440	5.657700
18	6	0	4.240294	0.308881	6.327356
19	6	0	4.843502	-0.723609	5.608011
20	1	0	-0.927249	-0.019889	1.965518
21	1	0	1.215949	-0.018715	-1.782122
22	1	0	1.200248	0.001856	3.174463
23	1	0	-3.128228	-0.030823	-0.924869
24	1	0	-2.516182	-0.926059	0.490867
25	1	0	-2.534874	0.862761	0.499901
26	1	0	5.855933	0.009666	1.717959
27	1	0	5.135203	-1.617386	3.669617
28	1	0	2.690454	1.915783	3.761185
29	1	0	2.999863	2.068671	6.208847
30	1	0	4.376386	0.377047	7.402525
31	1	0	5.448439	-1.465035	6.121456

For 3-methoxy-2-phenylcyclohex-2-enone **374**:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	6	0	0.000000	0.000000	1.525270
3	6	0	1.435086	0.000000	-0.532110
4	6	0	2.282507	-1.058011	0.131052
5	6	0	1.973173	-1.646954	1.325885
6	6	0	0.812310	-1.155083	2.105532
7	8	0	0.519437	-1.612218	3.203813
8	6	0	2.805217	-2.738930	1.906969
9	6	0	3.132650	-3.876471	1.152486
10	6	0	3.903148	-4.902007	1.697549
11	6	0	4.361576	-4.811353	3.012618
12	6	0	4.037857	-3.689252	3.776335
13	6	0	3.264071	-2.665531	3.231700
14	1	0	-0.542320	0.865537	-0.394747
15	1	0	-0.516185	-0.895904	-0.365745
16	1	0	-1.007559	-0.064285	1.943904
17	1	0	0.441850	0.934911	1.901057
18	1	0	1.897532	0.985838	-0.369486
19	1	0	1.428795	-0.154866	-1.616176
20	8	0	3.441495	-1.433355	-0.469242
21	1	0	2.777437	-3.955829	0.130111
22	1	0	4.142094	-5.774235	1.095292
23	1	0	4.961462	-5.610120	3.439570
24	1	0	4.384799	-3.610866	4.802870
25	1	0	3.003563	-1.806074	3.837941
26	6	0	3.847105	-0.874228	-1.714681
27	1	0	4.846616	-1.271228	-1.895908
28	1	0	3.189683	-1.181877	-2.536118
29	1	0	3.898847	0.219176	-1.680234

30	1	0	-8.329113	15.664864	-13.312205
31	6	0	-8.860615	16.429016	-13.839915
32	1	0	-9.663847	16.789633	-13.231908
33	1	0	-9.254814	16.026159	-14.749428
34	1	0	-8.194684	17.235407	-14.066121

For 2-methylcyclohex-2-enone **376**:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	6	0	0.000000	0.000000	1.532190
3	6	0	1.435395	0.000000	-0.539518
4	6	0	2.293553	1.031018	0.142494
5	6	0	2.020613	1.585438	1.340245
6	6	0	0.824779	1.142886	2.112652
7	8	0	0.546082	1.648631	3.191048
8	6	0	2.880489	2.638331	1.985203
9	1	0	-0.515289	0.899289	-0.360281
10	1	0	-0.556781	-0.860827	-0.385471
11	1	0	0.442227	-0.936872	1.903827
12	1	0	-1.007325	0.062861	1.952928
13	1	0	1.441981	0.174887	-1.622326
14	1	0	1.891773	-0.993440	-0.400159
15	1	0	2.302759	3.549908	2.169579
16	1	0	3.239460	2.302547	2.963611
17	1	0	3.740781	2.887409	1.358472
18	1	0	3.199061	1.338177	-0.380814

For 3-trifluoroacetylchromone, *s-cis*-conformation (found more energeticaly reach, as *s-trans*, local softness of *s-trans*-conformation was taken in consideration) **368**:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	6	0	0.000000	0.000000	1.403970
3	6	0	1.195854	0.000000	-0.707915
4	6	0	2.391715	0.000947	0.010548
5	6	0	2.422733	0.000975	1.408104
6	6	0	1.200627	0.000000	2.099201
7	8	0	3.558493	-0.000499	-0.728750
8	6	0	4.735687	0.010632	-0.094456
9	6	0	4.905629	0.023067	1.256884
10	6	0	3.712818	0.001997	2.145200
11	8	0	3.759654	-0.034123	3.365538
12	6	0	6.268272	0.080230	1.840841
13	8	0	6.520381	0.449792	2.964500
14	6	0	7.459638	-0.387478	0.948393
15	9	0	7.648197	0.475607	-0.085950
16	9	0	8.587066	-0.443962	1.649715
17	9	0	7.221134	-1.604546	0.413596
18	1	0	-0.940370	-0.000325	-0.542230
19	1	0	-0.941368	-0.000650	1.943823
20	1	0	1.224094	-0.000634	-1.791907
21	1	0	1.238329	-0.001144	3.183265
22	1	0	5.551488	0.027284	-0.805592

For 3-trifluoroacetylchromone, *s-trans*-conformation **368**:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	6	0	0.000000	0.000000	1.403840
3	6	0	1.196262	0.000000	-0.707559
4	6	0	2.390878	0.000599	0.011948
5	6	0	2.422871	0.001194	1.409592
6	6	0	1.200347	0.000000	2.099834
7	8	0	3.560375	-0.000159	-0.725819
8	6	0	4.728801	0.003898	-0.085089
9	6	0	4.899932	0.013258	1.268313
10	6	0	3.712053	0.000907	2.149974
11	8	0	3.748217	-0.017188	3.373536
12	6	0	6.326465	0.024796	1.699400

13	8	0	7.240931	-0.081328	0.903561
14	6	0	6.701488	0.200045	3.198071
15	9	0	8.030529	0.320793	3.312944
16	9	0	6.140998	1.310718	3.706193
17	9	0	6.319354	-0.867127	3.917094
18	1	0	-0.940267	-0.000562	-0.542329
19	1	0	-0.941485	-0.000460	1.943489
20	1	0	1.225432	-0.000839	-1.791497
21	1	0	1.236797	-0.000710	3.183891
22	1	0	5.572213	0.001282	-0.766175

For 7-acetyloxy-2-methylisoflavone **379**:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	6	0	0.000000	0.000000	1.404990
3	6	0	1.183092	0.000000	-0.726027
4	6	0	2.389409	-0.013717	-0.018845
5	6	0	2.425633	-0.030179	1.378238
6	6	0	1.208850	-0.020640	2.080542
7	8	0	3.536526	-0.020368	-0.758146
8	6	0	4.760015	-0.002506	-0.144055
9	6	0	4.913831	0.018152	1.210735
10	6	0	3.722714	-0.048294	2.086530
11	8	0	3.786901	-0.113383	3.312788
12	6	0	6.253984	0.103216	1.852237
13	6	0	6.641653	-0.838085	2.819493
14	6	0	7.143955	1.139890	1.531106
15	6	0	8.397824	1.220245	2.137295
16	6	0	8.778151	0.268532	3.083342
17	6	0	7.894527	-0.757781	3.423740
18	6	0	5.834794	-0.042321	-1.185928
19	8	0	-1.203327	0.087253	-0.682599
20	6	0	-1.966877	-1.027532	-0.987688
21	8	0	-3.014239	-0.854336	-1.549047
22	6	0	-1.407092	-2.375439	-0.594879
23	1	0	-0.945923	0.030248	1.935041
24	1	0	1.177044	0.023628	-1.809393
25	1	0	1.256261	-0.024172	3.164190
26	1	0	5.953592	-1.627112	3.099713
27	1	0	6.843094	1.898282	0.814000
28	1	0	9.071411	2.031287	1.876159
29	1	0	9.752715	0.330255	3.558722
30	1	0	8.180190	-1.497138	4.166277
31	1	0	6.808651	-0.239551	-0.741821
32	1	0	5.600730	-0.823365	-1.916345
33	1	0	5.882709	0.906813	-1.731901
34	1	0	-2.105514	-3.140905	-0.929436
35	1	0	-0.427127	-2.540299	-1.051682
36	1	0	-1.274097	-2.444885	0.488381

For 7-methoxy-2-methylisoflavone **378**:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	6	0	0.000000	0.000000	1.413800
3	6	0	1.202207	0.000000	-0.705448
4	6	0	2.397356	-0.001535	0.022885
5	6	0	2.426397	-0.001767	1.417463
6	6	0	1.194568	0.000412	2.101746
7	8	0	3.552134	0.007573	-0.709158
8	6	0	4.770018	-0.021896	-0.085999
9	6	0	4.912286	-0.061805	1.268978
10	6	0	3.710900	-0.003408	2.136086
11	8	0	3.770909	0.040071	3.365114
12	6	0	6.245989	-0.160109	1.920922
13	6	0	7.146554	-1.180751	1.577682
14	6	0	6.619308	0.751401	2.922263
15	6	0	7.866513	0.658994	3.536451
16	6	0	8.760729	-0.350107	3.172753
17	6	0	8.395183	-1.273014	2.193098
18	6	0	5.852864	0.031483	-1.120136
19	8	0	-1.227780	0.000599	-0.580860

20	6	0	-1.305907	-0.000327	-2.000202
21	1	0	-0.955258	0.000000	1.927009
22	1	0	1.249774	0.002056	-1.786310
23	1	0	1.224629	0.002051	3.186048
24	1	0	6.857837	-1.918984	0.834975
25	1	0	5.922925	1.525744	3.221470
26	1	0	8.139485	1.375989	4.305382
27	1	0	9.730923	-0.421089	3.655896
28	1	0	9.075962	-2.071806	1.912963
29	1	0	5.621501	0.819809	-1.843632
30	1	0	6.823303	0.227433	-0.667813
31	1	0	5.908686	-0.911423	-1.676276
32	1	0	-2.369219	0.001460	-2.241822
33	1	0	-0.834704	0.892686	-2.428836
34	1	0	-0.838226	-0.895836	-2.427564

For cyclohex-2-enone **369**:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	6	0	0.000000	0.000000	1.534430
3	6	0	1.431043	0.000000	-0.555976
4	6	0	2.296829	1.027343	0.122483
5	6	0	2.009639	1.561543	1.321550
6	6	0	0.832495	1.139591	2.114476
7	8	0	0.571068	1.649646	3.193898
8	1	0	-0.558662	-0.860411	-0.383332
9	1	0	-0.517291	0.898796	-0.358300
10	1	0	-1.008424	0.067200	1.951722
11	1	0	0.437218	-0.938470	1.907457
12	1	0	1.425647	0.178340	-1.638065
13	1	0	1.891675	-0.992203	-0.424473
14	1	0	3.200758	1.339693	-0.398584
15	1	0	2.643869	2.315674	1.779165

For isoflavone **3**:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	6	0	0.000000	0.000000	1.405600
3	6	0	1.193904	0.000000	-0.707852
4	6	0	2.396004	0.001942	0.006289
5	6	0	2.424213	0.001086	1.406094
6	6	0	1.200472	-0.001097	2.097920
7	8	0	3.554157	-0.002798	-0.726615
8	6	0	4.738207	0.019396	-0.073924
9	6	0	4.909453	0.050100	1.272573
10	6	0	3.711300	0.001923	2.139347
11	8	0	3.754365	-0.033384	3.368156
12	6	0	6.278679	0.126788	1.838015
13	6	0	6.630566	-0.590984	2.994302
14	6	0	7.262707	0.912176	1.212837
15	6	0	8.564977	0.957436	1.707079
16	6	0	8.905911	0.228740	2.847029
17	6	0	7.932639	-0.539345	3.488411
18	1	0	-0.941036	-0.000459	-0.541555
19	1	0	-0.941321	-0.000460	1.945877
20	1	0	1.220737	-0.001679	-1.792039
21	1	0	1.239574	-0.002720	3.181994
22	1	0	5.561133	-0.001850	-0.778497
23	1	0	5.877260	-1.176942	3.504686
24	1	0	6.998674	1.513500	0.347437
25	1	0	9.308080	1.573808	1.209390
26	1	0	9.918196	0.268004	3.238548
27	1	0	8.186989	-1.103023	4.381373

For flavone **2**:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	6	0	0.000000	0.000000	1.404670
3	6	0	1.194097	0.000000	-0.709212

4	6	0	2.398094	0.000733	0.001592
5	6	0	2.422877	-0.000599	1.401492
6	6	0	1.202591	0.000000	2.095214
7	8	0	3.551174	-0.004840	-0.743177
8	6	0	4.766476	0.002623	-0.121939
9	6	0	4.879943	0.018985	1.231465
10	6	0	3.721024	0.005642	2.115606
11	8	0	3.804894	0.008202	3.343582
12	1	0	-0.941001	-0.000796	-0.541797
13	1	0	-0.941153	-0.000459	1.945320
14	1	0	1.217000	-0.002010	-1.793598
15	1	0	1.245290	0.001003	3.179403
16	6	0	5.882741	0.008589	-1.086724
17	6	0	7.174026	-0.382820	-0.693975
18	6	0	5.672254	0.410139	-2.416576
19	6	0	6.730131	0.434734	-3.322477
20	6	0	8.011061	0.054876	-2.919796
21	6	0	8.227705	-0.356138	-1.602661
22	1	0	7.350584	-0.729813	0.318382
23	1	0	4.679359	0.708451	-2.731513
24	1	0	6.552716	0.753412	-4.345248
25	1	0	8.834162	0.073014	-3.627751
26	1	0	9.218268	-0.666152	-1.284092
27	1	0	5.856922	0.060769	1.695226

For 3-phenylcoumarin **293**:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	6	0	0.000000	0.000000	1.403760
3	6	0	1.195680	0.000000	-0.710579
4	6	0	2.398934	0.001740	-0.003876
5	6	0	2.427470	0.005329	1.401370
6	6	0	1.202131	0.001902	2.095983
7	8	0	3.557487	-0.006542	-0.722321
8	6	0	4.824310	-0.016093	-0.144045
9	6	0	4.881787	0.015447	1.332650
10	6	0	3.714963	0.008687	2.037620
11	1	0	-0.941515	-0.001216	-0.540420
12	1	0	-0.939938	-0.001590	1.945977
13	1	0	1.220222	-0.002539	-1.794629
14	1	0	1.214512	0.002245	3.182373
15	6	0	6.202540	0.060954	2.004671
16	8	0	5.766285	-0.046801	-0.901244
17	1	0	3.746957	-0.010163	3.123696
18	6	0	6.354818	0.798376	3.192696
19	6	0	7.314657	-0.642309	1.508500
20	6	0	8.526848	-0.623394	2.195356
21	6	0	8.660497	0.101846	3.380251
22	6	0	7.568851	0.816862	3.875119
23	1	0	5.521898	1.384906	3.569024
24	1	0	7.224899	-1.197348	0.583856
25	1	0	9.372288	-1.178430	1.799512
26	1	0	9.609461	0.118238	3.908111
27	1	0	7.664855	1.400308	4.786167

For chromone **1**:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	6	0	0.000000	0.000000	1.404880
3	6	0	1.193993	0.000000	-0.708760
4	6	0	2.397626	0.000000	0.002306
5	6	0	2.424009	0.000000	1.404658
6	6	0	1.201631	0.000000	2.096231
7	8	0	3.553024	0.000000	-0.742765
8	6	0	4.741276	0.000000	-0.093694
9	6	0	4.883192	0.000001	1.245648
10	6	0	3.717604	0.000001	2.131051
11	8	0	3.793921	-0.000352	3.357529
12	1	0	-0.941021	0.000000	-0.541661
13	1	0	-0.941246	0.000000	1.945348
14	1	0	1.218760	0.000000	-1.793027

15	1	0	1.242070	0.000000	3.180498
16	1	0	5.564499	0.000000	-0.799023
17	1	0	5.872837	0.000001	1.686510

For coumarin **137**:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	6	0	0.000000	0.000000	1.407850
3	6	0	1.199384	0.000000	-0.711530
4	6	0	2.402883	0.000000	-0.002795
5	6	0	2.433032	0.000000	1.408303
6	6	0	1.205063	0.000000	2.103460
7	8	0	3.582049	0.000000	-0.737208
8	6	0	4.871101	0.000000	-0.125358
9	6	0	4.874162	0.000001	1.329829
10	6	0	3.724866	-0.000396	2.052705
11	1	0	-0.941081	0.000000	-0.539410
12	1	0	-0.939784	0.000000	1.948695
13	1	0	1.227195	0.000000	-1.794073
14	1	0	1.214834	0.000000	3.189256
15	1	0	5.850884	0.000338	1.795869
16	8	0	5.853037	0.000532	-0.864356
17	1	0	3.761547	-0.000384	3.138205

For 7-methoxychromone **53**:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	6	0	0.000000	0.000000	1.410640
3	6	0	1.206192	0.000000	-0.704816
4	6	0	2.400896	0.000000	0.006526
5	6	0	2.433140	0.000000	1.412076
6	6	0	1.207403	0.000000	2.091861
7	8	0	3.556648	0.000000	-0.737958
8	6	0	4.745726	0.000000	-0.086376
9	6	0	4.887911	0.000001	1.252213
10	6	0	3.720724	0.000434	2.138356
11	8	0	3.800372	-0.000669	3.365984
12	8	0	-1.123025	0.000000	-0.765485
13	6	0	-2.389919	-0.000431	-0.118757
14	1	0	-0.930152	0.000000	1.964962
15	1	0	1.206036	0.000000	-1.788156
16	1	0	1.239287	0.000000	3.176502
17	1	0	5.568619	-0.000350	-0.791953
18	1	0	5.877779	0.000001	1.692598
19	1	0	-3.131080	-0.000346	-0.918595
20	1	0	-2.526306	-0.895078	0.500671
21	1	0	-2.526663	0.893823	0.501160

For 7-methoxy-3-methylchromone **373**:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	6	0	0.000000	0.000000	1.414200
3	6	0	1.201980	0.000000	-0.705163
4	6	0	2.398700	0.000425	0.021069
5	6	0	2.427711	0.000847	1.420258
6	6	0	1.194068	0.000000	2.102052
7	8	0	3.552288	0.000407	-0.716641
8	6	0	4.745071	0.000398	-0.063352
9	6	0	4.902352	0.000405	1.276448
10	6	0	3.710815	0.001286	2.143520
11	8	0	-1.227585	0.000000	-0.580478
12	6	0	-1.305760	0.000000	-2.000067
13	8	0	3.790678	0.001310	3.373180
14	6	0	6.255025	0.000394	1.927113
15	1	0	-0.955394	0.000000	1.927199
16	1	0	1.249941	-0.000314	-1.786029
17	1	0	1.222934	0.000000	3.186508
18	1	0	5.565819	0.000384	-0.772235
19	1	0	-2.369142	0.000362	-2.241205

20	1	0	-0.836479	0.894358	-2.427904
21	1	0	-0.836504	-0.894372	-2.427904
22	1	0	6.367671	0.876883	2.573215
23	1	0	6.367504	-0.875891	2.573520
24	1	0	7.061284	0.000380	1.188554

For (S)-carvone **385**:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	6	0	0.000000	0.000000	1.488260
3	6	0	1.353170	0.000000	-0.702834
4	6	0	2.437268	-0.764793	0.088455
5	6	0	2.521987	-0.168451	1.500831
6	6	0	1.170222	-0.059072	2.152795
7	6	0	3.756820	-0.839778	-0.665285
8	6	0	4.867225	-0.200589	-0.282338
9	6	0	3.752297	-1.715555	-1.897119
10	1	0	1.198265	-0.400324	-1.707419
11	1	0	1.669352	1.047177	-0.820128
12	1	0	2.075334	-1.799070	0.200898
13	1	0	3.191255	-0.767840	2.128931
14	1	0	2.972005	0.835635	1.459940
15	1	0	5.786419	-0.287026	-0.854507
16	1	0	4.913768	0.424892	0.602281
17	1	0	4.738340	-1.747756	-2.367021
18	1	0	3.035581	-1.362608	-2.647983
19	1	0	3.460301	-2.743295	-1.645956
20	1	0	1.157045	-0.016838	3.241677
21	6	0	-1.342139	0.088177	2.161622
22	8	0	-1.044308	0.036642	-0.635978
23	1	0	-1.874927	0.992583	1.849940
24	1	0	-1.977242	-0.754901	1.870756
25	1	0	-1.241330	0.094094	3.250057

For 3-formylchromone **372**:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	6	0	0.000000	0.000000	1.387110
3	6	0	1.209852	0.000000	2.099186
4	6	0	2.408482	0.000000	1.372883
5	6	0	2.427470	0.000409	-0.022478
6	6	0	1.215723	0.000826	-0.702625
7	1	0	-0.938588	-0.000324	-0.544793
8	1	0	-0.919858	0.000000	1.962341
9	1	0	3.379351	0.000392	-0.541946
10	1	0	1.214139	0.000820	-1.788154
11	6	0	3.673552	0.000000	3.343942
12	1	0	4.686144	0.000341	3.732995
13	6	0	1.229754	0.000000	3.582063
14	8	0	0.206482	0.000001	4.262259
15	6	0	2.584321	0.000000	4.154501
16	8	0	3.636888	0.000000	2.005895
17	6	0	2.786938	0.000000	5.621394
18	1	0	1.850670	0.000000	6.208255
19	8	0	3.884181	-0.000001	6.152655

For 7-methoxy-3-(4-chlorophenoxy)chromone **371**:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	6	0	0.000000	0.000000	1.384990
3	6	0	1.196651	0.000000	2.118288
4	6	0	2.404546	0.006972	1.398154
5	6	0	2.435613	0.008412	0.007821
6	6	0	1.228714	0.003870	-0.695192
7	1	0	-0.940208	-0.003080	-0.536898
8	1	0	-0.929004	-0.000556	1.945427
9	1	0	3.378727	0.013374	-0.525000
10	6	0	3.642296	-0.001956	3.391703
11	1	0	4.650434	0.011828	3.787096

12	6	0	1.186348	0.010757	3.592613
13	8	0	0.163797	0.030474	4.272091
14	6	0	2.540795	-0.003428	4.174129
15	8	0	3.618627	0.013486	2.038188
16	8	0	1.341468	0.003159	-2.047801
17	6	0	0.155234	-0.005536	-2.834084
18	1	0	-0.455173	0.886892	-2.651931
19	1	0	0.488087	-0.008074	-3.872331
20	1	0	-0.446288	-0.902458	-2.644599
21	8	0	2.710711	0.112669	5.532196
22	6	0	2.230109	-0.883112	6.364201
23	6	0	1.992023	-2.190710	5.941482
24	6	0	2.057184	-0.527056	7.702596
25	6	0	1.563527	-3.145155	6.863799
26	1	0	2.139710	-2.468246	4.903978
27	6	0	1.636441	-1.480527	8.624959
28	1	0	2.250433	0.496370	8.004552
29	6	0	1.389846	-2.785483	8.197965
30	1	0	1.370214	-4.163363	6.545612
31	1	0	1.496672	-1.212732	9.666134
32	17	0	0.853995	-3.993966	9.361571

For 3-methoxycyclohexenone **375**:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	6	0	0.000000	0.000000	1.532390
3	6	0	1.431349	0.000000	-0.550106
4	6	0	2.275939	1.059553	0.106603
5	6	0	1.990720	1.586997	1.322622
6	6	0	0.844402	1.131729	2.117057
7	8	0	0.591680	1.610773	3.216207
8	8	0	3.335710	1.387187	-0.662822
9	6	0	4.270835	2.340998	-0.159575
10	1	0	-0.521212	0.894517	-0.362567
11	1	0	-0.548396	-0.865207	-0.386604
12	1	0	0.420226	-0.945495	1.906260
13	1	0	-1.007767	0.083625	1.947824
14	1	0	1.446605	0.166936	-1.632188
15	1	0	1.907269	-0.977228	-0.382711
16	1	0	2.600453	2.356717	1.780489
17	1	0	5.044301	2.432048	-0.922362
18	1	0	3.792790	3.313715	-0.000224
19	1	0	4.714575	1.997304	0.781193

In basis 6-31G++(d,p):

For 2-phenylcyclohex-2-enone **370**:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	6	0	0.000000	0.000000	1.531460
3	6	0	1.437568	0.000000	-0.530415
4	6	0	2.293808	1.024404	0.160107
5	6	0	2.032517	1.579303	1.368165
6	6	0	0.812449	1.145333	2.124329
7	8	0	0.493276	1.646430	3.194427
8	6	0	2.953620	2.581506	1.972410
9	6	0	4.343359	2.372642	1.935555
10	6	0	5.227460	3.319056	2.457210
11	6	0	4.735917	4.492418	3.034218
12	6	0	3.355677	4.706337	3.088406
13	6	0	2.471319	3.759975	2.568621
14	1	0	-0.516274	0.898131	-0.363210
15	1	0	-0.554437	-0.863299	-0.384115
16	1	0	0.448612	-0.934079	1.903779
17	1	0	-1.008394	0.057576	1.950652
18	1	0	1.455700	0.179617	-1.612297
19	1	0	1.892329	-0.994508	-0.388509
20	1	0	3.191909	1.342292	-0.367728
21	1	0	4.733589	1.451408	1.511690
22	1	0	6.297336	3.133538	2.422056
23	1	0	5.420655	5.228906	3.444793

24	1	0	2.963460	5.613194	3.539971
25	1	0	1.403321	3.932419	2.625783

For 7-methoxyisoflavone **281**:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	6	0	0.000000	0.000000	1.415030
3	6	0	1.202663	0.000000	-0.705242
4	6	0	2.398097	0.000426	0.024412
5	6	0	2.431445	-0.001141	1.422594
6	6	0	1.194871	-0.001238	2.104171
7	8	0	3.553969	-0.003392	-0.711772
8	6	0	4.743976	0.009668	-0.062604
9	6	0	4.913565	0.033889	1.283690
10	6	0	3.713202	-0.000623	2.151421
11	8	0	3.766644	-0.023494	3.383371
12	8	0	-1.227041	0.000000	-0.583258
13	6	0	-1.311397	-0.003049	-2.006107
14	6	0	6.284579	0.093169	1.849701
15	6	0	7.259246	0.923653	1.268274
16	6	0	8.564273	0.953640	1.763321
17	6	0	8.915046	0.162856	2.860034
18	6	0	7.949453	-0.652151	3.458033
19	6	0	6.645461	-0.686884	2.962766
20	1	0	-0.953984	0.000466	1.930940
21	1	0	1.252001	-0.000701	-1.786277
22	1	0	1.218162	-0.002168	3.188780
23	1	0	5.563523	-0.013417	-0.770955
24	1	0	-2.376361	-0.006159	-2.238925
25	1	0	-0.846114	0.893861	-2.432273
26	1	0	-0.841400	-0.899225	-2.428499
27	1	0	6.987616	1.569908	0.438090
28	1	0	9.300390	1.605269	1.301125
29	1	0	9.927791	0.189321	3.251714
30	1	0	8.210704	-1.263318	4.317247
31	1	0	5.900053	-1.310770	3.440465

For 7-methoxy-2-trifluoromethylisoflavone **367**:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	6	0	0.000000	0.000000	1.416310
3	6	0	1.202383	0.000000	-0.706451
4	6	0	2.395283	0.001810	0.025711
5	6	0	2.428839	0.001657	1.421828
6	6	0	1.193514	0.000000	2.106463
7	8	0	3.549551	-0.008410	-0.708985
8	6	0	4.753296	0.016243	-0.080115
9	6	0	4.926382	0.070243	1.265656
10	6	0	3.712592	0.011818	2.135115
11	8	0	3.790123	-0.019451	3.362451
12	8	0	-1.225227	-0.000598	-0.581018
13	6	0	-1.313620	0.002346	-2.005095
14	6	0	6.249709	0.211148	1.931333
15	6	0	7.046128	1.343918	1.706719
16	6	0	8.273078	1.487648	2.357664
17	6	0	8.714672	0.503635	3.244674
18	6	0	7.919310	-0.621054	3.484161
19	6	0	6.690607	-0.763224	2.840098
20	1	0	-0.954425	0.000000	1.931215
21	1	0	1.252863	-0.003623	-1.787316
22	1	0	1.216304	0.000000	3.191024
23	6	0	5.847982	-0.003534	-1.141123
24	1	0	-2.379267	0.003402	-2.233832
25	1	0	-0.846833	0.899833	-2.427561
26	1	0	-0.847783	-0.893779	-2.431509
27	1	0	6.702729	2.117083	1.026090
28	1	0	8.879323	2.369606	2.173003
29	1	0	9.669035	0.614374	3.751237
30	1	0	8.252583	-1.386073	4.179272
31	1	0	6.069924	-1.629628	3.041283
32	9	0	5.435696	-0.660703	-2.245513

33	9	0	6.176374	1.257107	-1.530295
34	9	0	6.970627	-0.604118	-0.713409

For 7-methoxy-2-trifluoromethylchromone **377**:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	6	0	0.000000	0.000000	1.415370
3	6	0	1.203406	0.000000	-0.706387
4	6	0	2.396317	0.000000	0.023254
5	6	0	2.429833	0.000000	1.423383
6	6	0	1.194134	0.000412	2.105270
7	8	0	3.552110	0.000429	-0.724523
8	6	0	4.741494	0.000453	-0.080233
9	6	0	4.893002	-0.000295	1.257031
10	6	0	3.717107	-0.000790	2.140103
11	8	0	3.814590	-0.001477	3.367478
12	8	0	-1.224244	0.000000	-0.582016
13	6	0	-1.312938	0.000000	-2.006157
14	1	0	-0.954218	0.000000	1.930637
15	1	0	1.252522	0.000313	-1.787312
16	1	0	1.216492	0.000420	3.189999
17	6	0	5.878784	0.000462	-1.078313
18	1	0	-2.378672	-0.000001	-2.234350
19	1	0	-0.847090	0.896914	-2.430897
20	1	0	-0.847059	-0.896898	-2.430898
21	9	0	5.828254	1.089283	-1.878944
22	9	0	7.073326	0.000487	-0.455230
23	9	0	5.828282	-1.088374	-1.878925
24	1	0	5.880291	-0.000220	1.700515

For 7-methoxyflavone **282**:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	6	0	0.000000	0.000000	1.414040
3	6	0	1.202615	0.000000	-0.706569
4	6	0	2.400262	0.000426	0.020007
5	6	0	2.430136	-0.000504	1.418428
6	6	0	1.196795	-0.000584	2.101664
7	8	0	3.550654	-0.004253	-0.728307
8	6	0	4.770208	0.000597	-0.110991
9	6	0	4.884886	0.013827	1.242525
10	6	0	3.723871	0.002224	2.125771
11	8	0	3.818097	0.002804	3.357883
12	8	0	-1.227688	-0.000948	-0.583994
13	6	0	-1.312449	-0.002737	-2.006339
14	1	0	-0.953485	0.000000	1.930851
15	1	0	1.248046	-0.003396	-1.787769
16	1	0	1.222253	-0.000276	3.186455
17	1	0	-2.377581	-0.003845	-2.238732
18	1	0	-0.846228	0.893921	-2.432268
19	1	0	-0.844512	-0.899402	-2.430264
20	1	0	5.861800	0.053322	1.707045
21	6	0	5.884582	0.006834	-1.079530
22	6	0	5.677648	0.430757	-2.404095
23	6	0	6.736102	0.456615	-3.312484
24	6	0	8.014492	0.055285	-2.917329
25	6	0	8.227323	-0.378096	-1.604913
26	6	0	7.172754	-0.405886	-0.694397
27	1	0	4.688828	0.747266	-2.715063
28	1	0	6.561065	0.793551	-4.329969
29	1	0	8.837079	0.074504	-3.625977
30	1	0	9.214325	-0.704920	-1.291663
31	1	0	7.348215	-0.768194	0.312923

For 7-methoxy-3-phenylcoumarin **283**:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	6	0	0.000000	0.000000	1.410410
3	6	0	1.206807	0.000000	-0.709620

4	6	0	2.401601	0.001259	-0.002212
5	6	0	2.438475	0.005045	1.407290
6	6	0	1.210573	0.001254	2.092766
7	8	0	-1.125993	-0.001100	-0.762879
8	6	0	-2.398397	-0.001289	-0.120621
9	8	0	3.561142	-0.006412	-0.720361
10	6	0	4.830432	-0.015649	-0.141899
11	6	0	4.892645	0.008696	1.331688
12	6	0	3.724554	0.004091	2.039680
13	8	0	5.771102	-0.038402	-0.904290
14	6	0	6.215079	0.043146	2.003908
15	6	0	6.386140	0.814813	3.168497
16	6	0	7.310589	-0.701682	1.530021
17	6	0	8.525373	-0.690865	2.216307
18	6	0	8.678093	0.068782	3.379353
19	6	0	7.602680	0.825677	3.851461
20	1	0	-0.927670	-0.001974	1.968291
21	1	0	1.206057	-0.002775	-1.793177
22	1	0	1.213849	0.000605	3.179271
23	1	0	-3.133152	-0.002222	-0.926036
24	1	0	-2.532901	-0.897743	0.496317
25	1	0	-2.533603	0.895665	0.495401
26	1	0	3.759686	-0.017146	3.126005
27	1	0	5.567684	1.432237	3.527523
28	1	0	7.209455	-1.283847	0.622452
29	1	0	9.357139	-1.277449	1.836888
30	1	0	9.627806	0.079281	3.906203
31	1	0	7.713305	1.435899	4.743335

For 7-methoxyneoflavone **284**:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	6	0	0.000000	0.000000	1.408440
3	6	0	1.209508	0.000000	-0.701545
4	6	0	2.406589	0.010436	0.004039
5	6	0	2.445126	0.038061	1.418234
6	6	0	1.210106	0.016221	2.092267
7	8	0	-1.123361	-0.010010	-0.766117
8	6	0	-2.396500	-0.026591	-0.125421
9	8	0	3.549430	-0.018367	-0.743195
10	6	0	4.818829	-0.061360	-0.167297
11	6	0	4.867045	-0.013718	1.283741
12	6	0	3.749459	0.047517	2.062097
13	8	0	5.772365	-0.118185	-0.913617
14	6	0	3.885662	0.119622	3.543462
15	6	0	4.621531	-0.859136	4.230994
16	6	0	3.325455	1.181901	4.273604
17	6	0	3.501799	1.263243	5.655899
18	6	0	4.229078	0.279200	6.331888
19	6	0	4.787621	-0.782088	5.615440
20	1	0	-0.926207	-0.018603	1.968653
21	1	0	1.215351	-0.017611	-1.784956
22	1	0	1.201182	0.002752	3.176217
23	1	0	-3.130485	-0.030410	-0.931529
24	1	0	-2.522148	-0.927730	0.486503
25	1	0	-2.541399	0.865413	0.495565
26	1	0	5.861046	0.004732	1.714070
27	1	0	5.052523	-1.688124	3.677461
28	1	0	2.772811	1.958691	3.753496
29	1	0	3.074668	2.098220	6.203688
30	1	0	4.361519	0.341288	7.407962
31	1	0	5.353376	-1.551628	6.132430

For 3-methoxy-2-phenylcyclohex-2-enone **374**:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	6	0	0.000000	0.000000	1.526640
3	6	0	1.434182	0.000000	-0.537200
4	6	0	2.288318	-1.048195	0.132357
5	6	0	1.984606	-1.632097	1.332433
6	6	0	0.820503	-1.147038	2.107916

7	8	0	0.529610	-1.609118	3.208149
8	6	0	2.833302	-2.709611	1.919328
9	6	0	3.079669	-3.897210	1.212289
10	6	0	3.867575	-4.909830	1.762220
11	6	0	4.424751	-4.752358	3.034166
12	6	0	4.182165	-3.577282	3.750441
13	6	0	3.390145	-2.567763	3.200185
14	1	0	-0.541811	0.867718	-0.391756
15	1	0	-0.519440	-0.894827	-0.365392
16	1	0	-1.008621	-0.071909	1.942328
17	1	0	0.435730	0.937505	1.904161
18	1	0	1.894892	0.988192	-0.382151
19	1	0	1.424182	-0.163801	-1.619894
20	8	0	3.452529	-1.416379	-0.461781
21	1	0	2.647035	-4.028349	0.224909
22	1	0	4.042614	-5.822400	1.198926
23	1	0	5.036912	-5.539710	3.464954
24	1	0	4.604069	-3.447522	4.743202
25	1	0	3.193089	-1.666775	3.771097
26	6	0	3.841930	-0.896125	-1.733171
27	1	0	4.843943	-1.290186	-1.905891
28	1	0	3.177476	-1.244408	-2.532084
29	1	0	3.880906	0.198081	-1.733081

For 2-methylcyclohex-2-enone **376**:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	6	0	0.000000	0.000000	1.532860
3	6	0	1.435484	0.000000	-0.539763
4	6	0	2.294244	1.029648	0.144023
5	6	0	2.025426	1.583941	1.345776
6	6	0	0.830391	1.135254	2.116690
7	8	0	0.553305	1.632557	3.202875
8	6	0	2.892996	2.634738	1.986214
9	1	0	-0.517132	0.898598	-0.361070
10	1	0	-0.556353	-0.862635	-0.383262
11	1	0	0.437541	-0.939109	1.905639
12	1	0	-1.008044	0.068631	1.951750
13	1	0	1.443002	0.177923	-1.622273
14	1	0	1.892087	-0.993704	-0.400651
15	1	0	2.321614	3.550474	2.171427
16	1	0	3.258358	2.298673	2.962505
17	1	0	3.749909	2.876805	1.351255
18	1	0	3.199789	1.337559	-0.379385

For 3-trifluoroacetylchromone, *s-cis*-conformation (found more energeticaly reach, as *s-trans*, local softness of *s-trans*-conformation was taken in consideration) **368**:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	6	0	0.000000	0.000000	1.405610
3	6	0	1.197394	0.000000	-0.707747
4	6	0	2.393068	0.002034	0.012444
5	6	0	2.425410	0.001508	1.410840
6	6	0	1.201416	-0.000586	2.102352
7	8	0	3.560765	-0.000837	-0.727772
8	6	0	4.739601	0.021965	-0.098547
9	6	0	4.911282	0.044321	1.254290
10	6	0	3.718214	-0.002966	2.143165
11	8	0	3.771034	-0.065661	3.363635
12	6	0	6.272075	0.139760	1.837278
13	8	0	6.516752	0.539436	2.951978
14	6	0	7.487313	-0.310922	0.954105
15	9	0	7.683744	0.562088	-0.075330
16	9	0	8.610738	-0.361256	1.666908
17	9	0	7.279047	-1.533466	0.403626
18	1	0	-0.940255	-0.000459	-0.542589
19	1	0	-0.941219	-0.000459	1.945903
20	1	0	1.224854	-0.001270	-1.792028
21	1	0	1.233930	-0.003047	3.186781
22	1	0	5.551443	0.040370	-0.814687

For 3-trifluoroacetylchromone, *s-trans*-conformation **368**:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	6	0	0.000000	0.000000	1.405600
3	6	0	1.197204	0.000000	-0.708265
4	6	0	2.393037	0.001696	0.011197
5	6	0	2.425128	0.002227	1.410559
6	6	0	1.201391	-0.001097	2.102324
7	8	0	3.561586	-0.000124	-0.729582
8	6	0	4.735007	0.013114	-0.095875
9	6	0	4.901279	0.038885	1.258252
10	6	0	3.717462	-0.001574	2.141363
11	8	0	3.775731	-0.063245	3.364724
12	6	0	6.319373	0.071095	1.708123
13	8	0	7.236109	-0.290660	0.995933
14	6	0	6.690654	0.653565	3.110076
15	9	0	7.980163	1.034574	3.109084
16	9	0	5.947944	1.741431	3.404848
17	9	0	6.536180	-0.265621	4.079233
18	1	0	-0.940368	-0.000795	-0.542374
19	1	0	-0.941214	-0.000727	1.945862
20	1	0	1.224014	-0.001555	-1.792532
21	1	0	1.233928	-0.004129	3.186762
22	1	0	5.571763	0.011971	-0.785252

For 7-acetyloxy-2-methylisoflavone **379**:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	6	0	0.000000	0.000000	1.405460
3	6	0	1.181956	0.000000	-0.727607
4	6	0	2.389442	-0.023080	-0.020469
5	6	0	2.428441	-0.044548	1.377533
6	6	0	1.210289	-0.029174	2.080931
7	8	0	3.535521	-0.029316	-0.763627
8	6	0	4.761611	-0.027700	-0.154417
9	6	0	4.916951	-0.019953	1.200948
10	6	0	3.729518	-0.067239	2.079727
11	8	0	3.801495	-0.119902	3.308525
12	6	0	6.264180	0.035631	1.835627
13	6	0	6.688262	-0.988816	2.697032
14	6	0	7.120469	1.125130	1.612471
15	6	0	8.380054	1.179966	2.214477
16	6	0	8.798274	0.146884	3.056363
17	6	0	7.947052	-0.935815	3.296965
18	6	0	5.837204	-0.059778	-1.195242
19	8	0	-1.204399	0.100036	-0.684217
20	6	0	-1.990104	-1.001026	-0.977398
21	8	0	-3.039315	-0.808490	-1.534773
22	6	0	-1.458113	-2.359139	-0.583391
23	1	0	-0.943934	0.036111	1.939148
24	1	0	1.175349	0.029776	-1.811258
25	1	0	1.253374	-0.032157	3.165031
26	1	0	6.026270	-1.823892	2.900456
27	1	0	6.792473	1.940939	0.973971
28	1	0	9.028218	2.032166	2.031176
29	1	0	9.776044	0.188231	3.527462
30	1	0	8.260845	-1.738366	3.958217
31	1	0	6.811417	-0.257297	-0.750869
32	1	0	5.608134	-0.837445	-1.931318
33	1	0	5.882320	0.894477	-1.733191
34	1	0	-2.169010	-3.112002	-0.921360
35	1	0	-0.479082	-2.543088	-1.035750
36	1	0	-1.333711	-2.432176	0.501006

For 7-methoxy-2-methylisoflavone **378**:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	6	0	0.000000	0.000000	1.414670

3	6	0	1.202128	0.000000	-0.706549
4	6	0	2.398551	0.000000	0.022617
5	6	0	2.429841	0.000703	1.418116
6	6	0	1.195956	0.000715	2.102910
7	8	0	3.552684	0.007564	-0.712658
8	6	0	4.773173	-0.010938	-0.093749
9	6	0	4.916159	-0.042454	1.261887
10	6	0	3.717844	-0.001615	2.131128
11	8	0	3.785361	0.026511	3.362818
12	6	0	6.256338	-0.115735	1.908435
13	6	0	7.122727	-1.190877	1.654879
14	6	0	6.665411	0.877087	2.813620
15	6	0	7.917942	0.808835	3.424956
16	6	0	8.779400	-0.258242	3.152508
17	6	0	8.376586	-1.260868	2.267414
18	6	0	5.857295	0.035853	-1.126417
19	8	0	-1.228211	0.000424	-0.583197
20	6	0	-1.313142	0.002428	-2.005362
21	1	0	-0.953842	-0.000466	1.930884
22	1	0	1.249693	0.001040	-1.787712
23	1	0	1.221253	0.001183	3.187565
24	1	0	6.806243	-1.984903	0.983950
25	1	0	5.995264	1.698846	3.041881
26	1	0	8.218994	1.587265	4.120239
27	1	0	9.752430	-0.311495	3.632376
28	1	0	9.032005	-2.101879	2.059213
29	1	0	5.633585	0.824916	-1.852044
30	1	0	6.828499	0.227274	-0.672618
31	1	0	5.907605	-0.909995	-1.678762
32	1	0	-2.378242	0.005437	-2.237981
33	1	0	-0.843402	0.898186	-2.429289
34	1	0	-0.848157	-0.894671	-2.431763

For cyclohex-2-enone **369**:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	6	0	0.000000	0.000000	1.535420
3	6	0	1.430808	0.000000	-0.557848
4	6	0	2.298825	1.024970	0.121859
5	6	0	2.014679	1.558366	1.325053
6	6	0	0.837394	1.133708	2.115369
7	8	0	0.577692	1.641828	3.199962
8	1	0	-0.558376	-0.862249	-0.380810
9	1	0	-0.519538	0.898045	-0.358619
10	1	0	-1.009033	0.071485	1.951285
11	1	0	0.434837	-0.939465	1.909962
12	1	0	1.424811	0.181985	-1.639509
13	1	0	1.891381	-0.992784	-0.427854
14	1	0	3.203497	1.337952	-0.397976
15	1	0	2.651348	2.310423	1.783052

For isoflavone **3**:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	6	0	0.000000	0.000000	1.407310
3	6	0	1.195579	0.000000	-0.707319
4	6	0	2.398192	0.001199	0.008193
5	6	0	2.427396	-0.000173	1.409108
6	6	0	1.201409	-0.001097	2.100948
7	8	0	3.556344	-0.002169	-0.726403
8	6	0	4.743213	0.013802	-0.077376
9	6	0	4.914255	0.039137	1.270095
10	6	0	3.717440	0.001971	2.137586
11	8	0	3.767692	-0.021465	3.368367
12	6	0	6.285598	0.103855	1.835029
13	6	0	6.651700	-0.677823	2.945140
14	6	0	7.254611	0.942303	1.255780
15	6	0	8.559287	0.979599	1.751255
16	6	0	8.915255	0.187777	2.845531
17	6	0	7.955316	-0.635880	3.440725
18	1	0	-0.940951	0.000000	-0.541923

19	1	0	-0.941280	0.000325	1.947879
20	1	0	1.221513	-0.001146	-1.791798
21	1	0	1.235592	-0.001971	3.185379
22	1	0	5.564581	-0.007141	-0.783896
23	1	0	5.911120	-1.309062	3.420866
24	1	0	6.979063	1.588968	0.427181
25	1	0	9.290981	1.637557	1.291101
26	1	0	9.927750	0.219881	3.237351
27	1	0	8.220685	-1.248225	4.297785

For flavone **2**:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	6	0	0.000000	0.000000	1.406450
3	6	0	1.195737	0.000000	-0.708681
4	6	0	2.400244	0.000598	0.003620
5	6	0	2.425952	-0.000867	1.404873
6	6	0	1.203290	0.000000	2.098587
7	8	0	3.552939	-0.003522	-0.742987
8	6	0	4.769795	0.002086	-0.126081
9	6	0	4.885280	0.014513	1.228919
10	6	0	3.727572	0.001591	2.112066
11	8	0	3.817841	0.001312	3.343171
12	1	0	-0.940908	-0.000860	-0.542098
13	1	0	-0.940961	0.000000	1.947595
14	1	0	1.217736	-0.002865	-1.793294
15	1	0	1.240044	0.000318	3.183174
16	6	0	5.886011	0.011552	-1.092347
17	6	0	7.175317	-0.395179	-0.704331
18	6	0	5.678966	0.433465	-2.417643
19	6	0	6.738910	0.463878	-3.323937
20	6	0	8.018276	0.068155	-2.926151
21	6	0	8.231001	-0.363836	-1.613269
22	1	0	7.351168	-0.755798	0.303474
23	1	0	4.689153	0.744731	-2.730564
24	1	0	6.564093	0.799259	-4.341920
25	1	0	8.842026	0.090641	-3.633352
26	1	0	9.218940	-0.686152	-1.298376
27	1	0	5.862735	0.054584	1.692180

For 3-phenylcoumarin **293**:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	6	0	0.000000	0.000000	1.405510
3	6	0	1.197056	0.000000	-0.711475
4	6	0	2.400049	0.001581	-0.003124
5	6	0	2.430052	0.005227	1.402361
6	6	0	1.203666	0.001498	2.098316
7	8	0	3.560803	-0.005553	-0.721409
8	6	0	4.826821	-0.013183	-0.144063
9	6	0	4.885821	0.013942	1.332340
10	6	0	3.718498	0.006912	2.038567
11	1	0	-0.941613	-0.001078	-0.540471
12	1	0	-0.939978	-0.001590	1.947918
13	1	0	1.219934	-0.002420	-1.795821
14	1	0	1.215407	0.001513	3.184842
15	6	0	6.207382	0.054973	2.005335
16	8	0	5.771446	-0.036923	-0.901181
17	1	0	3.751536	-0.013228	3.124838
18	6	0	6.374518	0.834580	3.165112
19	6	0	7.304089	-0.691443	1.537044
20	6	0	8.517543	-0.674720	2.225479
21	6	0	8.667069	0.093460	3.383275
22	6	0	7.590247	0.852368	3.849066
23	1	0	5.554178	1.452425	3.518985
24	1	0	7.205072	-1.279839	0.633305
25	1	0	9.350673	-1.262878	1.851733
26	1	0	9.615982	0.108908	3.911381
27	1	0	7.699023	1.468790	4.736797

For chromone **1**:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	6	0	0.000000	0.000000	1.406790
3	6	0	1.195503	0.000000	-0.708430
4	6	0	2.399590	0.000000	0.004030
5	6	0	2.427148	0.000000	1.407619
6	6	0	1.202463	0.000000	2.099581
7	8	0	3.555002	0.000425	-0.742753
8	6	0	4.745988	0.000443	-0.098294
9	6	0	4.888948	0.000070	1.243100
10	6	0	3.724451	-0.000398	2.127443
11	8	0	3.806956	-0.000749	3.356777
12	1	0	-0.940901	0.000000	-0.542030
13	1	0	-0.941045	0.000000	1.947688
14	1	0	1.219133	0.000000	-1.792983
15	1	0	1.237371	0.000000	3.184219
16	1	0	5.567705	0.000797	-0.805040
17	1	0	5.879665	0.000113	1.682385

For coumarin **137**:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	6	0	0.000000	0.000000	1.405210
3	6	0	1.195897	0.000000	-0.712855
4	6	0	2.402798	0.000000	-0.009511
5	6	0	2.430102	0.000000	1.398925
6	6	0	1.205451	0.000000	2.095470
7	8	0	3.556822	0.000000	-0.741772
8	6	0	4.825339	0.000000	-0.158042
9	6	0	4.859829	0.000001	1.301490
10	6	0	3.723376	0.000001	2.037132
11	1	0	-0.941865	0.000000	-0.540133
12	1	0	-0.939251	0.000000	1.948719
13	1	0	1.216322	0.000000	-1.797283
14	1	0	1.219254	0.000000	3.182062
15	1	0	5.847214	0.000338	1.747391
16	8	0	5.785589	0.000370	-0.894903
17	1	0	3.770526	0.000001	3.123419

For 7-methoxychromone **53**:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	6	0	0.000000	0.000000	1.411700
3	6	0	1.205869	0.000000	-0.705764
4	6	0	2.401271	0.000000	0.006497
5	6	0	2.436249	0.000000	1.413392
6	6	0	1.208717	0.000000	2.093807
7	8	0	3.556223	0.000000	-0.740537
8	6	0	4.748757	0.000000	-0.095177
9	6	0	4.893244	0.000000	1.245158
10	6	0	3.727831	0.000000	2.131436
11	8	0	3.815533	0.000000	3.361794
12	8	0	-1.125930	0.000000	-0.763221
13	6	0	-2.397965	-0.000001	-0.119124
14	1	0	-0.928953	0.000000	1.968126
15	1	0	1.206458	0.000000	-1.789444
16	1	0	1.235184	0.000322	3.178764
17	1	0	5.569124	-0.000001	-0.803520
18	1	0	5.884301	0.000000	1.683578
19	1	0	-3.133517	-0.000001	-0.923825
20	1	0	-2.531842	-0.896526	0.497562
21	1	0	-2.531901	0.896599	0.497441

For 7-methoxy-3-methylchromone **373**:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	6	0	0.000000	0.000000	1.415150

3	6	0	1.201728	0.000000	-0.706301
4	6	0	2.399538	0.000000	0.020931
5	6	0	2.431253	0.000000	1.420812
6	6	0	1.195366	0.000000	2.103293
7	8	0	3.552487	0.000425	-0.718537
8	6	0	4.748031	0.000448	-0.069455
9	6	0	4.908903	0.000081	1.272013
10	6	0	3.717247	0.000000	2.138615
11	8	0	-1.227969	0.000000	-0.582751
12	6	0	-1.313137	0.000000	-2.004964
13	8	0	3.799239	0.000000	3.371231
14	6	0	6.267815	0.000136	1.912320
15	1	0	-0.953903	0.000329	1.931231
16	1	0	1.249662	0.000314	-1.787429
17	1	0	1.219326	0.000000	3.188029
18	1	0	5.566281	0.000454	-0.780975
19	1	0	-2.378293	0.000000	-2.237202
20	1	0	-0.845918	0.896463	-2.430210
21	1	0	-0.845955	-0.896484	-2.430204
22	1	0	6.387957	0.877334	2.556529
23	1	0	6.388336	-0.877491	2.555873
24	1	0	7.064603	0.000851	1.162808

For (S)-carvone **385**:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	6	0	0.000000	0.000000	1.488590
3	6	0	1.349400	0.000000	-0.707572
4	6	0	2.441373	-0.756366	0.081826
5	6	0	2.527663	-0.157181	1.492892
6	6	0	1.176455	-0.053012	2.147846
7	6	0	3.757538	-0.826653	-0.679921
8	6	0	4.865350	-0.166511	-0.314064
9	6	0	3.754668	-1.722282	-1.898755
10	1	0	1.192244	-0.406946	-1.709208
11	1	0	1.658327	1.049102	-0.830696
12	1	0	2.088160	-1.793691	0.197120
13	1	0	3.198255	-0.754719	2.121832
14	1	0	2.972297	0.849350	1.451855
15	1	0	5.781416	-0.251584	-0.891976
16	1	0	4.909126	0.474235	0.560115
17	1	0	4.739236	-1.752349	-2.372779
18	1	0	3.031210	-1.385809	-2.650919
19	1	0	3.473825	-2.748556	-1.628631
20	1	0	1.166414	-0.008921	3.236978
21	6	0	-1.337389	0.084467	2.174070
22	8	0	-1.046499	0.037179	-0.638099
23	1	0	-1.876459	0.987583	1.868454
24	1	0	-1.972792	-0.762047	1.892872
25	1	0	-1.221788	0.092054	3.261537

For 3-formylchromone **372**:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	6	0	0.000000	0.000000	1.388610
3	6	0	1.211702	0.000000	2.101605
4	6	0	2.409962	0.000000	1.373382
5	6	0	2.429499	0.000000	-0.022992
6	6	0	1.216929	0.000000	-0.704065
7	1	0	-0.939043	0.000000	-0.544187
8	1	0	-0.922125	-0.000319	1.960560
9	1	0	3.380930	0.000000	-0.543906
10	1	0	1.215270	-0.000327	-1.789714
11	6	0	3.682025	0.000001	3.344008
12	1	0	4.697362	0.000001	3.725752
13	6	0	1.237728	0.000000	3.584616
14	8	0	0.214038	0.000000	4.268388
15	6	0	2.592418	0.000001	4.157694
16	8	0	3.639246	0.000239	2.006152
17	6	0	2.791864	0.000001	5.626555
18	1	0	1.860475	0.000348	6.217888

19	8	0	3.889473	0.000002	6.162256

For 7-methoxy-3-(4-chlorophenoxy)chromone **371**:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	6	0	0.000000	0.000000	1.386620
3	6	0	1.198143	0.000000	2.120679
4	6	0	2.405446	0.008495	1.397387
5	6	0	2.437044	0.010576	0.006137
6	6	0	1.229500	0.005127	-0.696061
7	1	0	-0.941522	-0.003440	-0.534731
8	1	0	-0.931566	-0.001542	1.943195
9	1	0	3.380996	0.017172	-0.525995
10	6	0	3.650132	-0.001569	3.389568
11	1	0	4.659785	0.014106	3.781170
12	6	0	1.194511	0.009486	3.595284
13	8	0	0.171860	0.036315	4.279057
14	6	0	2.548941	-0.011499	4.174871
15	8	0	3.621013	0.018043	2.036203
16	8	0	1.339011	0.005103	-2.050391
17	6	0	0.152624	-0.005899	-2.842609
18	1	0	-0.455568	0.887688	-2.660237
19	1	0	0.492851	-0.008193	-3.878242
20	1	0	-0.443603	-0.905828	-2.652152
21	8	0	2.724561	0.103373	5.532568
22	6	0	2.282973	-0.910274	6.368606
23	6	0	2.067626	-2.220511	5.941097
24	6	0	2.119854	-0.564024	7.711495
25	6	0	1.673504	-3.190920	6.865745
26	1	0	2.198956	-2.490968	4.899283
27	6	0	1.733675	-1.532923	8.635299
28	1	0	2.290667	0.462353	8.017897
29	6	0	1.510687	-2.842424	8.204865
30	1	0	1.497051	-4.210894	6.542574
31	1	0	1.601292	-1.272150	9.679509
32	17	0	1.018194	-4.068117	9.369279

For 3-methoxycyclohexenone **375**:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	6	0	0.000000	0.000000	1.533330
3	6	0	1.430906	0.000000	-0.553284
4	6	0	2.280113	1.052666	0.106933
5	6	0	1.999273	1.579656	1.327106
6	6	0	0.853385	1.122002	2.118273
7	8	0	0.605491	1.596862	3.224847
8	8	0	3.342568	1.381979	-0.659032
9	6	0	4.287766	2.331754	-0.157118
10	1	0	-0.523926	0.893432	-0.362723
11	1	0	-0.547525	-0.867421	-0.383945
12	1	0	0.413758	-0.947873	1.909328
13	1	0	-1.008093	0.092006	1.946936
14	1	0	1.442749	0.172809	-1.634690
15	1	0	1.906043	-0.978767	-0.390624
16	1	0	2.612491	2.345310	1.787320
17	1	0	5.055651	2.417149	-0.925818
18	1	0	3.812168	3.305175	0.003666
19	1	0	4.732648	1.978801	0.779430

For every optimized structure the charges (ESP, Mulliken, Hirshfeld and NPA) were computed in the same basis, as single point caculation. For the the same geometry (i.e. without further geometry optimisation) the charges were computed for cation-radical (i.e. one electron is abstracted) and for anion-radical (i.e. one electron is added to the molecule).

The corresponding headers of Gaussian03 input files were as following:

For neutral molecules:

```
%chk=<Name of file>.chk
%mem=30MW
#p rb3lyp/<Basis> pop=(full,npa,mk) IOP(6/79=1)

<Name of the substance>

0 1
<Here goes Gaussian Z-matrix >
```

For cation-radicals:

```
%chk=<Name of file>.chk
%mem=30MW
#p ub3lyp/<Basis> pop=(full,npa,mk) IOP(6/79=1)

<Name of the substance>

1 2
<Here goes Gaussian Z-matrix >
```

For anion-radicals

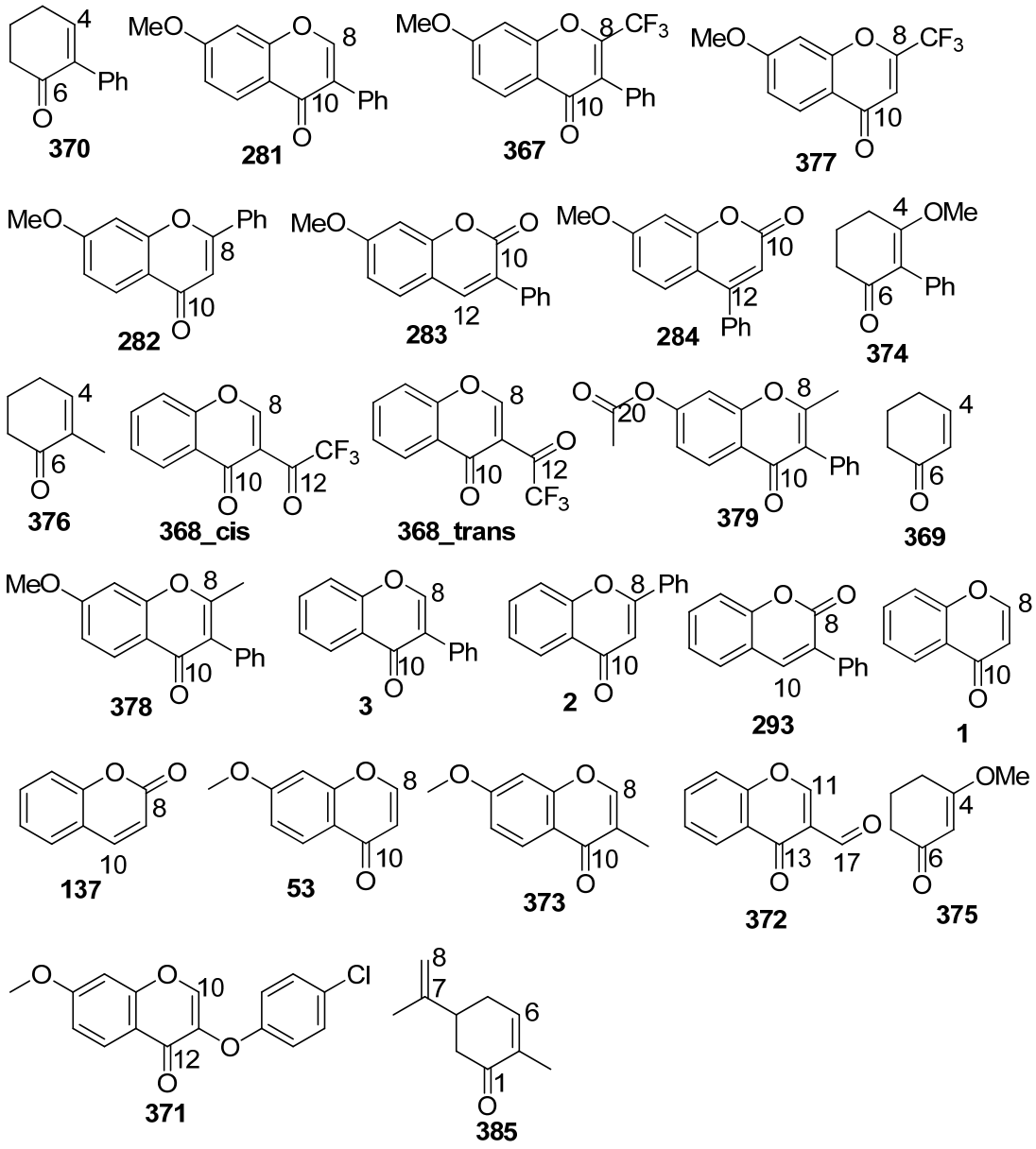
```
%chk=<Name of file>.chk
%mem=30MW
#p ub3lyp/<Basis> pop=(full,npa,mk) IOP(6/79=1)

<Name of the substance>

-1 2
<Here goes Gaussian Z-matrix >
```

As <Basis> the corresponding basis was written: "**6-31g"** for 6-31G, "**6-31g****" for 6-31G(d,p) and "**6-31++g****" for 6-31++ G(d,p).

The charges for neutral molecules, anion- and cation-radicals were extracted from the output-files of Gaussian03, and the indexes of local and global softness and hardness were computed according to the known formulae (for the formulae see section 3.6 and reference therein). For the tables with local softnesses the number of atom in <u>not</u> its number according to IUPAC rule, but the simple index number, which coincide with the index number in the input Z-Matrix (written as "Center number" therein). The computed substances and numeration of atoms, apt to react with nucleophiles, is presented on the scheme 163.



Scheme 163

The indexes of local softnesses (nucleophilic attack) on the atoms, apt to react with nucleophiles, computed in basis 6-31G, are as following:

Substrate	Atom	ESP	Mulliken	Hirshfeld	NPA
2-phenylcyclohex-2-enone, **370**	4	0.665965	0.275158	0.449715	0.668599
	6	0.459266	0.250748	0.332895	0.445138
7-methoxyisoflavone, **281**	8	0.638797	0.312686	0.370658	0.49577
	10	0.489376	0.245992	0.296182	0.412345
7-methoxy-2-trifluoromethylisoflavone, **367**	8	0.690302	0.217736	0.321241	0.429341
	10	0.435421	0.214082	0.279994	0.376185
7-methoxy-2-trifluoromethylchromone, **377**	8	0.655677	0.181734	0.323349	0.426171
	10	0.438154	0.214956	0.31519	0.419836
7-methoxyflavone, **282**	8	0.531543	0.201112	0.258208	0.344139
	10	0.395539	0.159293	0.239399	0.304974
7-methoxy-3-phenylcoumarin, **283**	10	0.121538	0.194525	0.18363	0.130981
	12	0.541061	0.274584	0.373873	0.530228

7-methoxyneoflavone, **284**	10	0.125429	0.192887	0.222704	0.181965
	12	0.664941	0.171544	0.320225	0.512962
3-methoxy-2-phenylcyclohex-2-enone, **374**	4	0.558934	0.328431	0.410038	0.632983
	6	0.428744	0.239981	0.324661	0.436673
2-methylcyclohex-2-enone, **376**	4	0.8816	0.272967	0.435443	0.632109
	6	0.711732	0.280999	0.404559	0.564727
2-trifluoroacetylchromone (*s-cis*), **368**	8	0.817634	0.432876	0.4673	0.652808
	10	0.022394	0.140739	0.100995	0.088485
	12	0.515893	0.278221	0.322879	0.418304
2-trifluoroacetylchromone (*s-trans*), **368**	8	0.760892	0.456386	0.460641	0.67069
	10	0.17049	0.132595	0.086563	0.060201
	12	0.58654	0.260252	0.359558	0.461641
7-acetyloxy-2-methylisoflavone, **379**	8	0.378305	0.148789	0.256158	0.362836
	10	0.535268	0.261634	0.315319	0.45397
	20	-0.085807	0.01532	0.041537	-0.004963
7-methoxy-2-methylisoflavone, **378**	8	0.427603	0.185065	0.29484	0.423519
	10	0.498355	0.251557	0.300706	0.432905
cyclohex-2-enone, **369**	4	0.789294	0.260111	0.474641	0.665664
	6	0.654473	0.24623	0.398129	0.536724
isoflavone, **3**	8	0.607045	0.289358	0.350033	0.458874
	10	0.583328	0.264889	0.320692	0.45231
flavone, **2**	8	0.545516	0.194548	0.259106	0.350367
	10	0.482846	0.176535	0.25398	0.329347
3-phenylcoumarin, **293**	8	0.077715	0.179579	0.171072	0.109103
	10	0.532698	0.259513	0.354233	0.490868
chromone, **1**	8	0.552108	0.232084	0.331011	0.403965
	10	0.506798	0.2413	0.319053	0.432446
coumarin, **137**	8	0.164774	0.17689	0.21921	0.157442
	10	0.315214	0.238839	0.375508	0.473525
7-methoxychromone, **53**	8	0.604989	0.2447	0.342226	0.420629
	10	0.503934	0.229975	0.309512	0.419911
7-methoxy-3-methylchromone, **373**	8	0.66807	0.253143	0.310621	0.395143
	10	0.704549	0.258761	0.317564	0.451107
(S)-Carvone, **385**	1	0.785778	0.349124	0.400017	0.566622
	6	0.938896	0.316565	0.442153	0.665832
	7	-0.086967	-0.03629	0.002594	-0.065715
	8	0.100993	0.045968	0.101934	0.125715
3-formylchromone, **372**	11	0.753857	0.42147	0.458601	0.631817
	13	0.219224	0.203259	0.196009	0.240111
	17	0.102385	0.189418	0.210344	0.166083
7-methoxy-3-(4-chlorophenoxy)chromone, **371**	10	0.771558	0.30624	0.374764	0.48544
	12	0.675915	0.289848	0.351176	0.509452
3-methoxycyclohex-2-enone, **375**	4	0.576391	0.299806	0.388978	0.596378
	6	0.594996	0.246138	0.388704	0.538546

The indexes of local softnesses (nucleophilic attack) on the atoms, apt to react with nucleophiles, computed in basis 6-31G(d,p), are as following:

Substrate	**Atom**	**ESP**	**Mulliken**	**Hirshfeld**	**NPA**
2-phenylcyclohex-2-enone, **370**	4	0.572464	0.2969	0.44384	0.680496
	6	0.326467	0.276179	0.303072	0.398986
7-methoxyisoflavone, **281**	8	0.582273	0.328368	0.367955	0.511283

	10	0.372591	0.271932	0.260721	0.357088
7-methoxy-2-trifluoromethylisoflavone, **367**	8	0.506186	0.280323	0.324154	0.458665
	10	0.342734	0.25474	0.257493	0.344462
7-methoxy-2-trifluoromethylchromone, **377**	8	0.498163	0.220404	0.314628	0.437472
	10	0.353166	0.266305	0.300642	0.40436
7-methoxyflavone, **282**	8	0.461731	0.230793	0.245127	0.330735
	10	0.301787	0.1882	0.217806	0.267234
7-methoxy-3-phenylcoumarin, **283**	10	0.051926	0.222103	0.16834	0.102165
	12	0.441866	0.287373	0.361758	0.527183
7-methoxyneoflavone, **284**	10	0.059604	0.221295	0.208225	0.152613
	12	0.629256	0.229734	0.308056	0.507981
3-methoxy-2-phenylcyclohex-2-enone, **374**	4	0.447773	0.375069	0.40093	0.657794
	6	0.279964	0.262759	0.28959	0.384971
2-methylcyclohex-2-enone, **376**	4	0.822035	0.287839	0.431536	0.641561
	6	0.611895	0.329641	0.387129	0.539616
2-trifluoroacetylchromone (*s-cis*), **368**	8	0.684557	0.447526	0.459524	0.661341
	10	0.023519	0.180048	0.130819	0.128468
	12	0.228993	0.264563	0.250253	0.29928
2-trifluoroacetylchromone (*s-trans*), **368**	8	0.740136	0.479939	0.463104	0.700633
	10	0.171584	0.155618	0.105326	0.082108
	12	0.323898	0.275427	0.300454	0.365062
7-acetyloxy-2-methylisoflavone, **379**	8	0.306366	0.175437	0.250345	0.3684
	10	0.440223	0.297452	0.289742	0.417761
	20	-0.11582	0.020013	0.035937	-0.01319
7-methoxy-2-methylisoflavone, **378**	8	0.358357	0.219758	0.292843	0.441476
	10	0.378197	0.276309	0.266139	0.380733
cyclohex-2-enone, **369**	4	0.709075	0.273322	0.470461	0.677513
	6	0.552366	0.289449	0.382175	0.513008
isoflavone, **3**	8	0.534747	0.298225	0.342299	0.460917
	10	0.473218	0.301747	0.292786	0.41252
flavone, **2**	8	0.44421	0.220057	0.242957	0.334617
	10	0.379409	0.20621	0.23329	0.295839
3-phenylcoumarin, **293**	8	0.011989	0.204058	0.155151	0.077772
	10	0.456418	0.275083	0.344058	0.484215
chromone, **1**	8	0.466311	0.223777	0.311198	0.384748
	10	0.414861	0.277902	0.299174	0.403855
coumarin, **137**	8	0.021248	0.206143	0.203747	0.124153
	10	0.37415	0.241064	0.363789	0.459626
7-methoxychromone, **53**	8	0.531614	0.240668	0.32723	0.40987
	10	0.418149	0.266322	0.289943	0.391169
7-methoxy-3-methylchromone, **373**	8	0.638166	0.255875	0.300521	0.388755
	10	0.645548	0.301997	0.297812	0.423937
(S)-Carvone, **385**	1	0.785778	0.349124	0.400017	0.566622
	6	0.938896	0.316565	0.442153	0.665832
	7	-0.08697	-0.03629	0.002594	-0.06572
	8	0.100993	0.045968	0.101934	0.125715
3-formylchromone, **372**	11	0.708894	0.441339	0.448417	0.641345
	13	0.291536	0.227539	0.187238	0.227958
	17	0.125252	0.191142	0.205451	0.157054
7-methoxy-3-(4-chlorophenoxy)chromone, **371**	10	0.691308	0.307188	0.355592	0.469348
	12	0.538334	0.325552	0.323024	0.471473
3-methoxycyclohex-2-enone, **375**	4	0.481319	0.342532	0.382473	0.622736

	6	0.514925	0.296456	0.376795	0.528391

The indexes of local softnesses (nucleophilic attack) on the atoms, apt to react with nucleophiles, computed in basis 6-31++G(d,p), are as following:

Substrate	**Atom**	**ESP**	**Mulliken**	**Hirshfeld**	**NPA**
2-phenylcyclohex-2-enone, **370**	4	0.969827	0.892026	0.44298	0.774025
	6	0.157301	0.279689	0.311187	0.443713
7-methoxyisoflavone, **281**	8	0.867758	0.980692	0.38107	0.588951
	10	0.218835	0.321718	0.269659	0.377617
7-methoxy-2-trifluoromethylisoflavone, **367**	8	0.563688	0.568022	0.318052	0.447223
	10	0.253057	0.341976	0.2782	0.376453
7-methoxy-2-trifluoromethylchromone, **377**	8	0.494584	0.359423	0.314815	0.432516
	10	0.122374	0.053993	0.314996	0.419796
7-methoxyflavone, **282**	8	0.59699	0.249117	0.242055	0.337745
	10	0.142065	0.029976	0.226949	0.274595
7-methoxy-3-phenylcoumarin, **283**	10	-0.13464	-0.20343	0.185569	0.109707
	12	0.63873	0.585932	0.372452	0.578306
7-methoxyneoflavone, **284**	10	-0.17801	-0.10189	0.230414	0.143448
	12	0.62118	0.016543	0.306757	0.574835
3-methoxy-2-phenylcyclohex-2-enone, **374**	4	0.222585	-2.85791	0.108627	0.123251
	6	0.246076	-0.03065	0.106793	0.110444
2-methylcyclohex-2-enone, **376**	4	0.466592	1.473695	0.302978	0.46251
	6	0.042582	-0.36005	0.262599	0.377741
2-trifluoroacetylchromone (*s-cis*), **368**	8	0.201931	0.218407	0.271001	0.396908
	10	-0.29585	0.044285	0.094982	0.042669
	12	0.404483	0.017973	0.373891	0.540448
2-trifluoroacetylchromone (*s-trans*), **368**	8	0.871439	0.708395	0.464388	0.720826
	10	0.10847	-0.08987	0.105445	0.07736
	12	0.285695	-0.0278	0.323836	0.388961
7-acetyloxy-2-methylisoflavone, **379**	8	0.29988	-0.19324	0.2346	0.326954
	10	0.356201	0.338763	0.296465	0.406636
	20	-0.25231	0.012256	0.041837	-0.01434
7-methoxy-2-methylisoflavone, **378**	8	0.233073	-0.09115	0.245905	0.380187
	10	0.097936	0.116448	0.25663	0.346917
cyclohex-2-enone, **369**	4	0.081746	0.419997	0.332502	0.458171
	6	-0.31108	-0.25507	0.259805	0.341779
isoflavone, **3**	8	0.742006	0.744944	0.34573	0.51148
	10	0.329977	0.353495	0.302823	0.438478
flavone, **2**	8	0.593005	0.288374	0.239296	0.34196
	10	0.280713	0.02121	0.242349	0.307289
3-phenylcoumarin, **293**	8	-0.17636	-0.24647	0.170565	0.08028
	10	0.673712	0.515332	0.349785	0.526849
chromone, **1**	8	0.62773	0.545601	0.327133	0.436078
	10	0.174549	0.232855	0.303564	0.419876
coumarin, **137**	8	-0.12501	-0.06801	0.222069	0.110223
	10	0.208974	-0.13953	0.369754	0.517878
7-methoxychromone, **53**	8	0.76105	0.627112	0.344685	0.46757
	10	0.235831	0.368502	0.295053	0.401096
7-methoxy-3-methylchromone, **373**	8	1.077265	0.783009	0.333282	0.496837
	10	0.618009	0.367536	0.294211	0.424431
(S)-Carvone, **385**	1	0.473385	0.269112	0.27912	0.40244

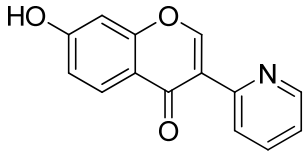
	6	1.887625	0.486424	0.325987	0.558333
	7	0.150785	1.949493	0.01457	-0.04104
	8	-0.20636	0.14897	0.136932	0.113076
3-formylchromone, **372**	11	0.817167	0.622449	0.471718	0.714902
	13	0.072422	0.042085	0.177978	0.202534
	17	0.049725	0.686819	0.231502	0.175286
7-methoxy-3-(4-chlorophenoxy)chromone, **371**	10	1.08634	0.746327	0.379943	0.56289
	12	0.39919	0.25974	0.323737	0.477581
3-methoxycyclohex-2-enone, **375**	4	0.423747	-0.62593	0.092323	0.079916
	6	0.086601	-2.36328	0.111963	0.108423

Additionally from the output-files of Gaussian03 for neutral molecules the energies of HOMO and LUMO were extracted, and the indexes of electrophilicity ω were computed according to the known formula (section 3.6).

7.7 Hydrogenation of 7-methoxy-3-(pyridin-2-yl)chromone

1-(2,4-Dihydroxyphenyl)-2-(pyridin-2-yl)ethanone **389** was synthesized by the known procedure[483] with yield of 53%. Synthesis of most catalysts is described in section 7.4. Crabtree complex ($[Ir(COD)(PCy_3)(Py)]PF_6$) was purshased from ABCR, $Eu(facam)_3$ was purshased from Aldrich. (R)-BINAP was obtained as a gift from MCAT. The gift is kindly acknowledged.

7-Hydroxy-3-(pyridin-2-yl)-chromone 390



3 G (13.1 mmol) of **1-(2,4-dihydroxyphenyl)-2-(pyridin-2-yl)ethanone 389** were placed in a one-neck flask and the flask was closed with septum. The septum was pierced with thermometer and with nitrogen-inlet. 19 Ml of absolute DMF were added and the suspension was dissolved with heating, then cooled to 0º C. The temperature of the synthesis should never exceed 60º C. 6.74 Ml (54 mmol) of $BF_3{\cdot}Et_2O$ were added dropwise *via syringe* with magnetical stirring, the temperature should be not higher than 40º C. Then 2.52 ml (27.5 mmol) of $POCl_3$ were added *via syringe*, keeping the temperature below 40º C. Then the synthesis was exposed to ultrasonic irradiation (35 kHz) for 1.5 h (at 40º C). After completing, the reaction was poured on ice (flask washed with water/acetone/DMF) and left to stay overnight. The yellow precipitate was filtrated and washed by water. It represents the salt of the title compound (**7-hydroxy-3-(pyridin-2-yl)-chromone hydrochloride**, defined

by elemental analysis), which is quite bad soluble in water and in DMSO. Hence, only ^{1}H NMR spectrum was measured. Yield 2.7 g (74.7%).

^{1}H NMR (400 MHz, DMSO): δ = 7.04 (s, 1H, 8-H), 7.07 (br d, J 8.6, 1H, 6-H), 7.80 (br s, 1H, py), 8.05 (d, J 8.6, 1H, 5-H), 8.36 (br s, 2H, py), 8.84 (br d, J 5.1, 1H, 6`-H_{Py}), 9.04 (s, 1H, 2-H), 11.25 (br s, 0.6 H, OH and NH_{Py}, partially exchanged).

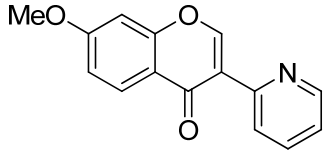
200 Mg of **7-hydroxy-3-(pyridin-2-yl)-chromone hydrochloride** were suspended in 10 ml of pyridine and stirred a few hours untill a clear solution is formed. Then the mixture is poured in 200 ml of water, and in 10 min. brine (ca 50 ml) is added, in order to induce coagulation. The precipitate, representing the free base of 7-hydroxy-3-(pyridin-2-yl)-chromone **390**, is filtrated and throughly washed with water. Yield is quantitative.

^{1}H NMR (400 MHz, DMSO): δ = 6.92 (s, 1H, 8-H), 6.97 (br d, J 9.0, 6-H), 7.37 (dd, J 6.7, J 4.7, 1H, 5`-$H_{Py}$), 7.85 (t, J 6.7, 1H, 4`-H_{Py}), 8.02 (d, J 9.0, 1H, 5-H), 8.26 (d, J 6.7, 3`-$H_{Py}$), 8.61 (br d, J 4.7, 6`-H_{Py}), 8.85 (s, 1H, 2-H), 10.88 (s, 1H, OH)

^{13}C NMR (100 MHz, DMSO): δ = 102.34, 115.59, 116.89, 121.42, 123.06, 123.89, 127.45, 136.52, 149.29, 150.77, 157.09, 157.38, 162.94, 174.54

HRMS ESI/FT-ICR, observed (calculated): [M+H$^+$] 240.0653 (240.0655)

7-Methoxy-3-(pyridin-2-yl)-chromone 388



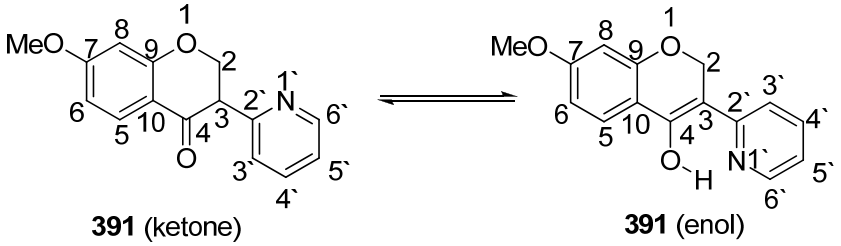
0.75 G (3.14 mmol) of **390** were suspended is 30 ml of absolute THF, 1.3 g (9.4 mmol) of dry K_2CO_3 and 0.3 ml (3.14 mmol) of Me_2SO_4 were added. The mixture was refluxed 24 h (in nitrogen atmosphere). The water was added (in order to hydrolize the rest of highly toxic Me_2SO_4), then resting THF and MeOH were removed *in vacuo*, and the rest was filtrated. The precipitate was washed off by acetone, adsorbed on 2.5 g of silica gel and chromatographed using column with 80 g of silica gel (Et_2O, *Rf* 1.0). Yield 0.7 g (88%), colourless crystalls.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.92 (s, 3H, Me), 6.90 (d, 1H, J 2.3, 8-H), 7.02 (dd, J 9.0, J 2.3, 6-H), 7.27 (m, 5`-$H_{Py}$ and $CHCl_3$), 7.78 (td, J 7.8, J 2.0, 1H, 4`-H_{Py}), 8.24 (d, J 9.0, 5-H), 8.43 (d, J 7.8, 1H, 3`-$H_{Py}$), 8.61 (br d, J 4.7, 6`-H_{Py}), 8.80 (s, 1H, 2-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.80, 100.23, 114.94, 118.69, 122.16, 122.90, 124.53, 127.72, 136.70, 148.93, 150.87, 156.96, 157.79, 164.20, 175.56.

HRMS ESI/FT-ICR, observed (calculated): [M+H$^+$] 254.0809 (254.0812); [M+Na$^+$] 276.0650 (276.0631).

7-Methoxy-3-(pyridin-2-yl)-chroman-4-one 391



391 (ketone) **391** (enol)

The preparation is desrcibed in section 3.7.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.81 (s, 0.12 H, Me_{enol}), 3.84 (s, 3H, Me_{ketone}), 4.12 (dd, J 9.5, J 4.8, 1H, 3-H_{ketone}), 4.75 (dd, J 11.3, J 4.8, 1H, 2-$CH_{2ketone}$), 4.97 (dd, J 11.3, J 9.5, 1H, 2-$CH_{2ketone}$), 5.12 (s, 0.08H, 2-CH_{2enol}), 6.44 (d, J 2.3, 1H, 8-H_{ketone}), 6.61 (dd, J 8.8, J 2.3, 1H, 6-H_{ketone}), 7.21 (dd, J 7.8, J 5.2, 1H, 5`-$H_{ketone}$), 7.27 (d, J 7.8, 1H, 3`-H_{ketone}), 7.66 (td, J 7.8, J 1.8, 1H, 4`-$H_{ketone}$), 7.91 (d, J 8.8, 1H, 5-$H_{ketone}$), 8.59 (br d, J 4.3, 1H, 6`-H_{ketone}), 15.97 (s, partially exchanged, OH_{enol}). The other signals are invisible due to low intensity/low concentration.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 53.43 (3-CH_{ketone}), 55.41 (Me_{enol}), 55.63 (Me_{ketone}), 65.76 (2-CH_{2enol}), 70.84 (2-$CH_{2ketone}$), 93.82 (3-C_{enol}), 100.67 (8-CH_{ketone}), 101.06 (8-CH_{enol}), 107.79 (6-CH_{enol}), 110.21 (6-CH_{ketone}), 114.99 (10-C_{ketone}), 116.20 (3`-$CH_{enol}$), 117.52 (5`-CH_{enol}), 122.50 (5`-$CH_{ketone}$), 124.15 (3`-CH_{ketone}), 125.16 (5-CH_{enol}), 129.39 (5-CH_{ketone}), 136.54 (4`-$CH_{ketone}$), 149.61 (6`-CH_{ketone}), 155.25 (2`-C_{ketone}), 163.79 (9-C_{ketone}), 166.10 (7-C_{ketone}), 190.08 (4-C_{ketone}). The other signals are invisible due to low intensity/low concentration.

^{1}H NMR (400 MHz, THF-D_8): δ = 3.77 (s, 0.6H, Me_{enol}), 3.82 (s, 3H, Me_{ketone}), 4.11 (dd, J 10.0, J 4.8, 1H, 3-H_{ketone}), 4.73 (dd, J 11.3, J 4.8, 1H, 2-$CH_{2ketone}$), 4.95 (dd, J 11.3, J 10.0, 1H, 2-$CH_{2ketone}$) 5.13 (s, 0.4H, 2-CH_{2enol}), 6.42 (d, J 2.3, 0.2H, 8-H_{enol}), 6.49 (d, J 2.3, 1H, 8-H_{ketone}), 6.54 (dd, J 8.8, J 2.3, 0.2H, 6-H_{enol}), 6.60 (dd, J 8.8, J 2.3, 1H, 6-H_{ketone}), 7.05 (dd, J 7.5, J 5.0, 0.2H, 5`-$H_{enol}$), 7.08 (d, J 8.3, 0.2H, 3`-H_{enol}), 7.18 (dd, J 7.8, J 5.0, 1H, 5`-$H_{ketone}$), 7.28 (d, J 7.8, 1H, 3`-H_{ketone}), 7.57 (d, J 8.8, 0.2H, 5-H_{enol}), 7.65 (td, J 7.8, J 1.8, 1H, 4`-$H_{ketone}$), 7.73 (td, J 8.3, J 1.8, 0.2H, 4`-H_{enol}), 7.81 (d, J 8.8, 1H, 5-H_{ketone}), 8.39 (br d, J 4.0, 0.2H, 6`-$H_{enol}$), 8.48 (br d, J 5.0, 1H, 6`-H_{ketone}), 15.45 (s, 0.2H, OH_{enol}).

^{13}C NMR (100 MHz, THF-D_8): δ = 54.11 (3-CH_{ketone}), 55.67 (Me_{enol}), 56.00 (Me_{ketone}), 66.46 (2-CH_{2enol}), 71.73 (2-$CH_{2ketone}$), 95.26 (3-C_{enol}), 101.44 (8-CH_{ketone}), 101.76 (8-CH_{enol}), 108.32 (6-CH_{enol}), 110.56 (6-CH_{ketone}), 114.73 (10-C_{enol}), 116.16 (10-C_{ketone}), 117.35 (3`-

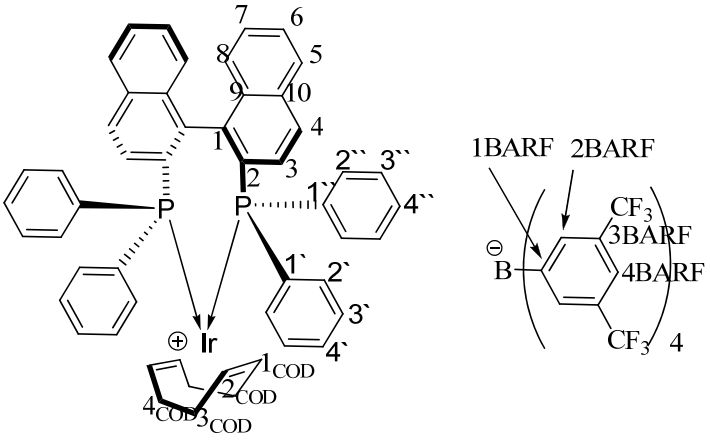
CH_{enol}), 119.17 (5`-$CH_{enol}$), 122.93 (5`-CH_{ketone}), 125.26 (3`-$CH_{ketone}$), 125.65 (5-$CH_{enol}$), 129.68 (5-$CH_{ketone}$), 136.73 (4`-CH_{ketone}), 138.50 (4`-$CH_{enol}$), 146.11 (6`-CH_{enol}), 150.10 (6`-$CH_{ketone}$), 156.87 (2`-C_{ketone}), 157.43 (4-C_{enol} and 2`-C_{enol}), 159.00 (9-C_{enol}), 163.51 (7-C_{enol}), 164.81 (9-C_{ketone}), 166.91 (7-C_{ketone}), 189.71 (4-C_{ketone}).

^{1}H NMR (400 MHz, C_6D_6): δ = 3.08 (s, 3H, Me_{ketone}), 3.22 (s, 0.39H, Me_{enol}), 3.81 (dd, J 9.3, J 4.8, 1H, 3-H_{ketone}), 4.44 (dd, J 11.3, J 4.8, 1H, 2-$CH_{2ketone}$), 4.89 (s, 0.26H, 2-CH_{2enol}), 4.96 (dd, J 11.3, J 9.3, 1H, 2-$CH_{2ketone}$), 6.13 (d, J 7.3, 0.13H, 3`-$H_{enol}$), 6.25 (dd, J 7.3 J 5.0, 0.13H, 5`-H_{enol}), 6.34 (d, J 2.3, 1H, 8-CH_{ketone}), 6.40 (dd, J 8.8, J 2.3, 1H, 6-H_{ketone}), 6.56 (m, 1.13H, 5`-$H_{ketone}$ and 6-$H_{enol}$), 6.65 (d, J 2.3, 0.13H, 8-$H_{enol}$), 6.86 (td, J 7.3, J 1.5, 0.13H, 4`-H_{enol}), 7.00 (br s, 1H, 4`-$H_{ketone}$), 7.01 (br s, 1H, 3`-H_{ketone}), 7.69 (br d, J 5.0, 0.13H, 6`-$H_{enol}$), 8.06 (d, J 8.5, 0.13H, 5-$H_{enol}$), 8.11 (d, J 8.8, 1H, 5-$H_{ketone}$), 8.36 (br d, J 4.5, 1H, 6`-H_{ketone}), 15.93 (s, 0.13H, OH_{enol}).

^{13}C NMR (100 MHz, C_6D_6): δ = 53.40 (3-CH_{ketone}), 54.75 (Me_{enol}), 54.84 (Me_{ketone}), 65.90 (2-CH_{2enol}), 70.84 (2-$CH_{2ketone}$), 94.63 (3-C_{enol}), 100.95 (8-CH_{ketone}), 101.62 (8-CH_{enol}), 108.07 (6-CH_{enol}), 110.17 (6-CH_{ketone}), 114.39 (10-C_{enol}), 115.70 (10-C_{ketone}), 116.09 (3`-$CH_{enol}$), 117.69 (5`-CH_{enol}), 122.06 (5`-$CH_{ketone}$), 124.37 (3`-CH_{ketone}), 125.65 (5-CH_{enol}), 129.55 (5-CH_{ketone}), 135.73 (4`-$CH_{ketone}$), 136.91 (4`-CH_{enol}), 145.04 (6`-$CH_{enol}$), 149.46 (6`-CH_{ketone}), 155.82 (2`-$C_{ketone}$), 156.54 (2`-C_{enol}), 156.69 (4-C_{enol}), 158.47 (9-C_{enol}), 162.88 (7-C_{enol}), 164.07 (9-C_{ketone}), 166.01 (7-C_{ketone}), 189.21 (4-C_{ketone}).

HRMS ESI/TOF, observed (calculated): [M+H^+] 256.0696 (256.0968); [M+Na^+] 278.0778 (278.0778).

Iridium (1,5-cyclooctadiene) ((R)-2,2`-Bis(diphenylphosphino)-1,1`-binaphtyl) tetrakis(3,5-bis(trifluoromethyl)phenyl) borate, [Ir(COD)((R)-BINAP)]BARF, 334



Synthesized from (R)-BINAP, $[Ir(COD)Cl]_2$ and NaBARF with yield of 88%, according to the procedure for racemic complex (see section 7.1). Spectral properties are identical to that of racemic complex (section 7.1).

Because of deep colour, it has shown no rotation at relatively low-intensive α-line of Na. However, the rotation angle was measured using Hg-lamp, at 546 nm.

α_{546}^{19}= -208.3 ($CHCl_3$, c=0.12).

Iridium (1,5-cyclooctadiene) bis(triphenylphosphine) hexafluorophosphate, $[Ir(COD)(PPh_3)_2]PF_6$

200 Mg (0.3 mmol) of $[Ir(COD)Cl]_2$ and 312.2 mg (1.2 mmol) of PPh_3 were refluxed in 5 ml of absolute CH_2Cl_2 for 1 h (nitrogen atmosphere). After cooling a solution of 442 mg (2.4 mmol) of KPF_6 in 5 ml of H_2O was added (under air), the two-phase system was vigorously stirred for 2 h. The layers were separated, aqueous layer washed by CH_2Cl_2 (5x5 ml). The joined organic fractions were dried by Na_2SO_4, filtrated and washed by CH_2Cl_2. The solvent was evaporated to *ca* 1 ml and *ca* 50 ml of absolute Et_2O were added, resulting in precipitation of purposuful complex. It was collected by filtration, throughly washed by Et_2O, and washed off from the frit by CH_2Cl_2. Evaporation of the solvent (at r.t.) followed by drying in a deep vacuum afforded 555 mg (96%) of $[Ir(COD)(PPh_3)_2]PF_6$. Red crystalline substance, insensitive to air, but sensitive to higher temperatures. Should be stored at -20º C.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.95 (q, J 8.6, 4H, a-CH_{2COD}), 2.37 (br d, J 8.6, 4H, e-CH_{2COD}), 4.20 (br s, 4H, CH_{COD}), 7.30 (br t, J 7.0, 12H, 3-H_{Ph}), 7.37 (br t, J 8.5, 12H, 2-H_{Ph}), 7.40 (br t, J 7.0, 6H, 4-H_{Ph}).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 31.01 (CH_{2COD}), 87.12 (t, J 5.5, CH_{COD}), 128.70 (t, J 5.5, 3-CH_{Ph}), 129.71 (dd, J 57.2, J 4.4, 1-C_{Ph}), 131.30 (4-CH_{Ph}), 134.30 (t, J 5.5, 2-CH_{Ph}).

^{31}P{^{1}H} NMR (161 MHz, $CDCl_3$): δ = -143.07 (spt, J 712.5), +18.24 (s).

^{19}F NMR (376 MHz, $CDCl_3$): δ = -73.94 (d, J 712.5).

Quantum-chemical computations of the molecule **388** were performed similarly to the computations of the other molecules (see section 7.6).

The following optimized structures for **388** were obtained (Cartesian coordinates):

In basis 6-31G:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	6	0	0.000000	0.000000	1.414610
3	6	0	1.200282	0.000000	-0.711584

4	6	0	2.392059	0.000000	0.018185
5	6	0	2.432732	0.000000	1.417344
6	6	0	1.197864	0.000414	2.105109
7	8	0	3.576279	0.000000	-0.719101
8	6	0	4.777427	0.000000	-0.055042
9	6	0	4.921186	0.000001	1.300335
10	6	0	3.712609	0.000000	2.144521
11	8	0	3.731859	0.000000	3.405965
12	6	0	6.303444	0.000001	1.844135
13	6	0	6.597583	-0.000403	3.219565
14	7	0	7.297831	0.000425	0.911645
15	6	0	8.579113	0.000861	1.315891
16	6	0	8.951668	0.000904	2.665048
17	6	0	7.936574	0.000470	3.624763
18	8	0	-1.248976	0.000000	-0.590424
19	6	0	-1.344950	0.000000	-2.042335
20	1	0	-0.954487	0.000000	1.926210
21	1	0	1.249331	0.000312	-1.791381
22	1	0	1.225531	0.000423	3.188305
23	1	0	5.617433	0.000000	-0.732790
24	1	0	5.786647	-0.000735	3.933475
25	1	0	9.327391	0.001187	0.529210
26	1	0	9.998725	0.001264	2.946594
27	1	0	8.178548	0.000485	4.682662
28	1	0	-2.412652	0.000000	-2.255278
29	1	0	-0.880156	0.896678	-2.467413
30	1	0	-0.879868	-0.896518	-2.467435

In basis 6-31G(d,p):

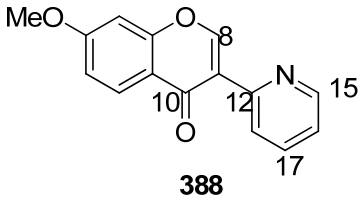
Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	6	0	0.000000	0.000000	1.414150
3	6	0	1.203558	0.000000	-0.702881
4	6	0	2.395418	0.000000	0.028857
5	6	0	2.427930	0.000000	1.424709
6	6	0	1.192666	0.000000	2.104651
7	8	0	3.555625	0.000000	-0.700599
8	6	0	4.736245	0.000407	-0.050028
9	6	0	4.906941	0.000833	1.299418
10	6	0	3.706419	0.000000	2.161919
11	8	0	3.726085	0.000000	3.396093
12	6	0	6.302386	0.001242	1.820581
13	6	0	6.600202	0.001290	3.193010
14	7	0	7.275197	0.001146	0.883909
15	6	0	8.546494	0.001496	1.281671
16	6	0	8.938635	0.001960	2.621900
17	6	0	7.936819	0.002060	3.588280
18	8	0	-1.226229	0.000000	-0.581121
19	6	0	-1.304063	0.000000	-2.001380
20	1	0	-0.955661	0.000000	1.926629
21	1	0	1.255066	0.000313	-1.783514
22	1	0	1.218735	0.000000	3.188857
23	1	0	5.574742	0.000707	-0.733922
24	1	0	5.791340	0.001022	3.910130
25	1	0	9.294005	0.001401	0.489675
26	1	0	9.990410	0.002231	2.888998
27	1	0	8.187251	0.002415	4.645381
28	1	0	-2.367368	-0.000363	-2.242494
29	1	0	-0.834672	0.894496	-2.428551
30	1	0	-0.834628	-0.894472	-2.428555

In basis 6-31G++(d,p):

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000000	0.000000	0.000000
2	6	0	0.000000	0.000000	1.415000
3	6	0	1.203267	0.000000	-0.704232
4	6	0	2.396155	0.000000	0.028505
5	6	0	2.431187	0.000000	1.424796
6	6	0	1.194152	0.000000	2.105668
7	8	0	3.555948	0.000000	-0.702305
8	6	0	4.739749	0.000000	-0.056705

9	6	0	4.913194	0.000000	1.294135
10	6	0	3.712623	-0.000436	2.156348
11	8	0	3.738799	-0.000434	3.392711
12	6	0	6.310847	0.000000	1.814215
13	6	0	6.612925	0.000000	3.187248
14	7	0	7.284522	-0.000001	0.877288
15	6	0	8.558358	-0.000001	1.271198
16	6	0	8.953154	-0.000402	2.612316
17	6	0	7.951715	-0.000824	3.580799
18	8	0	-1.226840	0.000000	-0.583287
19	6	0	-1.311649	0.000000	-2.006212
20	1	0	-0.954163	0.000000	1.930580
21	1	0	1.254636	0.000000	-1.785132
22	1	0	1.215829	0.000000	3.190181
23	1	0	5.572877	-0.000001	-0.746691
24	1	0	5.808510	-0.000324	3.909637
25	1	0	9.302114	-0.000001	0.476401
26	1	0	10.005605	-0.000383	2.877514
27	1	0	8.203002	-0.001147	4.637727
28	1	0	-2.376719	0.000000	-2.238469
29	1	0	-0.844309	0.896563	-2.430803
30	1	0	-0.844288	-0.896552	-2.430802

Atom numeration used for computations:



388

The indexes of local softnesses (nucleophilic attack) on the atoms, apt to react with nucleophiles, computed in basis 6-31G, are as following:

Atom	ESP	Mulliken	Hirshfeld	NPA
8	0.700374	0.384661	0.410875	0.574355
10	0.274268	0.208327	0.216808	0.283112
12	-0.162761	0.127770	0.045615	0.009249
15	0.140359	0.043985	0.108533	0.056504
17	0.116850	0.068227	0.147300	0.147454

The indexes of local softnesses (nucleophilic attack) on the atoms, apt to react with nucleophiles, computed in basis 6-31G(d,p), are as following:

Atom	ESP	Mulliken	Hirshfeld	NPA
8	0.616271	0.409725	0.405077	0.593106
10	0.153294	0.214338	0.181048	0.225988
12	-0.166785	0.120754	0.065007	0.034631
15	0.145176	0.038692	0.112358	0.047414
17	0.107353	0.075296	0.160255	0.169161

The indexes of local softnesses (nucleophilic attack) on the atoms, apt to react with nucleophiles, computed in basis 6-31++G(d,p), are as following:

Atom	ESP	Mulliken	Hirshfeld	NPA
8	0.878343	0.825800	0.422726	0.646018
10	0.156550	0.085759	0.185097	0.231573
12	-0.352645	0.103007	0.068390	0.037126
15	0.043613	0.060405	0.116467	0.053682

17	0.283944	0.107028	0.162983	0.195773

Additionally from the output-files of Gaussian03 for neutral molecules the energies of HOMO and LUMO were extracted, and the indexes of electrophilicity ω were computed according to the known formula (section 3.6).

8 REFERENCES

1. (a) Brahmachari, G.; Gorai, D. *Current Organic Chemistry* **2006,** 10, (8), 873-898; (b) Hendrich, A. B. *Acta Pharmacologica Sinica* **2005,** Volume Date 2006, 27, (1), 27-40; (c) Curini, M.; Cravotto, G.; Epifano, F.; Giannone, G. *Current Medicinal Chemistry* **2006,** 13, (2), 199-222; (d) Grotewold, E., *The Science of Flavonoids*. ed.; Springer: **2006**; (e) Andersen, Ø. M.; Markham, K. R., *Flavonoids: chemistry, biochemistry, and applications*. ed.; CRC, Taylor & Francis: Boca Raton, FL, **2006**; (f) Li, H.; Hu, C. *Zhongguo Yaoxue Zazhi* **2005,** 40, (4), 241-244 [in Chinese]; *Chem. Abstr.* **2006**, 145, 179890.

2. Thakar, G. P.; Janaki, N.; Subba Rao, B. C. *Indian Journal of Chemistry* **1965,** 3, (1), 74-77.

3. Vermes, B.; Antus, S.; Gottsegen, A.; Nogradi, M. *Liebigs Annalen der Chemie* **1983,** 11, 2034-2037..

4. Nogradi, M.; Antus, S.; Gottsegen, A.; Vermes, B. *Studies in Organic Chemistry (Amsterdam)* **1982,** Volume Date 1981, 11(Flavonoids Bioflavonoids), 121.128; *Chem. Abstr*. **1983**, 98, 16440.

5. Salakka, A. K.; Jokela, T. H.; Wahala, K. *Beilstein Journal of Organic Chemistry* **2006,** 2, No. 16. doi:10.1186/1860-5397-2-16 http://bjoc.beilstein-journals.org/content/pdf/1860-5397-2-16.pdf.

6. (a) Ichikawa, K.; Kitaoka, M.; Taki, M.; Takaishi, S.; Iijima, Y.; Boriboon, M.; Akiyama, T. *Planta Medica* **1997,** 63, (6), 540-543; (b) Umehara, K.; Nemoto, K.; Kimijima, K.; Matsushita, A.; Terada, E.; Monthakantirat, O.; De-Eknamkul, W.; Miyase, T.; Warashina, T.; Degawa, M.; Noguchi, H. *Phytochemistry* **2008,** 69, (2), 546-52; (c) Zung, A.; Reifen, R.; Kerem, Z.; Zadik, Z. *Journal of Pediatric Gastroenterology and Nutrition* **2001,** 33, (2), 112-8; (d) Cornwell, T.; Cohick, W.; Raskin, I. *Phytochemistry* **2004,** 65, (8), 995-1016; (e) Cos, P.; De Bruyne, T.; Apers, S.; Vanden Berghe, D.; Pieters, L.; Vlietinck, A. J. *Planta Medica* **2003,** 69, (7), 589-599; (f) Duncan, A. M.; Phipps, W. R.; Kurzer, M. S. *Best Practice & Research Clinical Endocrinology & Metabolism* **2003,** 17, (2), 253-271.

7. Soby, S.; Caldera, S.; Bates, R.; VanEtten, H. *Phytochemistry* **1996,** 41, (3), 759.

8. Tanaka, H.; Sato, M.; Fujiwara, S.; Hirata, M.; Etoh, H.; Takeuchi, H. *Letters in applied microbiology* **2002,** 35, (Part 6), 494-498.

9. Chi, Y. S.; Jong, H. G.; Son, K. H.; Chang, H. W.; Kang, S. S.; Kim, H. P. *Biochemical Pharmacology* **2001,** 62, (9), 1185-91.

10. Bojase, G.; Majinda, R. R.; Gashe, B. A.; Wanjala, C. C. *Planta Medica* **2002,** 68, (7), 615-620.

11. Heller, W.; Tamm, C. *Progress in the Chemistry of Organic Natural Products* **1981,** 40, 105-152.

12. (a) Gazak, R.; Walterova, D.; Kren, V. *Current Medicinal Chemistry* **2007,** 14, (3), 315-38; (b) Saller, R.; Meier, R.; Brignoli, R. *Drugs,* **2001,** 61, (14), 2035-2063.

13. (a) Kaur, M.; Agarwal, R. *Toxicology and Applied Pharmacology* **2007,** 224, (3), 350-359; (b) Singh, R. P.; Agarwal, R. *European Journal of Cancer* **2005,** 41, (13), 1969-1979.

14. (a) Agarwal, C.; Tyagi, A.; Kaur, M.; Agarwal, R. *Carcinogenesis* **2007,** 28, (7), 1463-1470; (b) Kaur, M.; Agarwal, R. *Current Cancer Drug Targets* **2007,** 7, (4), 355-367.

15. Sharma, P. R. *Recent Progress in Medicinal Plants* **2006,** 12, 151-177.

16. Huseini, H. F.; Larijani, B.; Heshmat, R.; Fakhrzadeh, H.; Radjabipour, B.; Toliat, T.; Raza, M. *Phytotherapy Research* **2006,** 20, (12), 1036-1039.

17. Sun, T.; Li, X. *Zhongguo Yaowu Huaxue Zazhi* **2000,** 10, (2), 116-117 [in Chinese]; *Chem. Abstr.* **2000**, 134, 100694.

18. Dann, O.; Volz, G. *Justus Liebigs Annalen der Chemie* **1960,** 631, 102-110.

19. Nussbaumer, P.; Lehr, P.; Billich, A. *Journal of Medicinal Chemistry* **2002,** 45, 4310-4320.

20. Zhang, Z.-B.; Yang, Q.-T. *Asian Journal of Andrology* **2006,** 8, (5), 601-605.

21. Rahman, M.; Riaz, M.; Desai, U. R. *Chemistry & Biodiversity* **2007,** 4, (11), 2495-2527.

22. (a) Lockhart, I. M., Chromanones. In *Chromenes, Chromanones and Chromones*, ed.; Ellis, G. P., Ed.; John Wiley and Sons: **1977**; p. 256-260; (b) Dean, F. M., *Naturally occurring oxygen ring compounds*. ed.; Butterworths: London, **1963**; (c) Harborne, J. B.; Mabry, T. J., *The Flavonoids: advances in research*. ed.; Chapman and Hall: London, **1982**.

23. Geissman, T. A., *The chemistry of flavonoid compounds*. ed.; Pergamon Press: Oxford, New York, **1962**.

24. Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H., *Comprehensive Asymmetric Catalysis*. ed.; Springer: **2000**.

25. de Vries, J. G.; Elsevier, C. J., *The handbook of homogeneous hydrogenation*. ed.; Wiley-VCH: Weinheim, **2007**.

26. (a) Szabo, V.; Antal, E. *Tetrahedron Letters* **1973,** 19, 1659-1662; (b) Szabo, V.; Antal, E. *Acta Chimica Academiae Scientiarum Hungaricae* **1976,** 90 (4), 381-393.

27. Cheng, Y.-h.; Duan, Y.-b.; Qi, Y.; Guo, X.-y.; Tong, Y.-f.; Du, G.-h.; Wu, S. *Huaxue Shiji* **2006,** 28, (7), 437-438 [in Chinese]; *Chem. Abstr.* **2007**, 148, 144537.

28. Cheng, Y.; Duan, Y.; Qi, Y.; Tong, Y.; Guo, X.; du, G.; Wu, S. *Huaxue Yanjilu Yu Yingyong* **2006,** 18, (11), 1334-1335 [in Chinese]; *Chem. Abstr.* **2007**, 148, 517426.

29. Farkas, L.; Nogradi, M.; Antus, S.; Gottsegen, A. *Tetrahedron* **1969,** 25, (5), 1013-1019.

30. Farkas, L.; Gottsegen, A.; Nogradi, M.; Antus, S. *Journal of the Chemical Society C* **1971,** 10, 1994-2000.

31. Farkas, L.; Gottsegen, A.; Nogradi, M.; Antus, S. *Journal of the Chemical Society, Perkin Transactions 1* **1974,** 2, 305-312.

32. Nogradi, M.; Gottsegen, A.; Antus, S.; Strelisky, J.; Vermes, B.; Wolfner, A.; Major, A.; Szuets, T.; Bendeffy, I.; Marmarosi, T. WO9503293, **1995**; *Chem. Abstr.* **1995**, 122, 314354

33. Aneja, R.; Mukerjee, S. K.; Seshadri, T. R. *Chemische Berichte* **1960,** 93, 297-303.

34. Neill, K. G. *Journal of Chemical Society* **1953**, 3454-3455.

35. Visser, F. R.; Lane, G. A. *Australian Journal of Chemistry* **1987,** 40, (10), 1705-1711.

36. Sun, Y. J.; Wu, Q. D.; Van Etten, H. D.; Hrazdina, G. *Archives of Biochemistry and Biophysics* **1991,** 284, (1), 167-173.

37. Cohen, N.; Daniewski, A. R.; Lee, F. K.-C.; Yagaloff, K. A. WO9515956, **1995**; *Chem. Abstr.* **1995**, 123, 339414

38. Woodward, M. D. *Phytochemistry* **1980,** 19, 921-927.

39. Peng, W.-J.; Han, X.-W.; Yu, B. *Chinese Journal of Chemistry* **2006,** 24, (9), 1154 - 1162.

40. Jung, S.-H.; Cho, S.-H.; The, H. D.; Lee, J.-H.; Ju, J.-H.; Kim, M.-K.; Lee, S.-H.; Ryu, J.-C.; Kim, Y. *European Journal of Medicinal Chemistry* **2003,** 38, (5), 537-545.

41. Parmar, V. S.; Singh, S.; Jacobsen, J. P.; Boll, P. M. *Acta Chemica Scandinavica, Series B: Organic Chemistry and Biochemistry* **1987,** B41, (4), 267-270.

42. Briggs, B.; Hansen, M.; Kanter, J.; Mullins, J. J. G.; Ruhter, G.; Udodong, U.; Verral, D., II; Zmijewski, M., Jr. US2000208827, **2001**; *Chem. Abstr.* **2001**, 136, 904149

43. Schmiz, C.; Eiden, F. *Liebigs Annalen der Chemie* **1980**, (12), 2021-2030.

44. Kwak, J.-H.; Kang, H.-E.; Jung, J.-K.; Kim, H.; Cho, J.; Lee, H. *Archives of Pharmacal Research* **2006,** 29, (9), 728-734.

45. Vasquez-Martinez, Y.; Ohri, R. V.; Kenyon, V.; Holman, T. R.; Sepulveda-Boza, S. *Bioorganic & Medicinal Chemistry* **2007,** 15, (23), 7408-7425.

46. Fukushima, S.; Noro, T.; Saiki, Y.; Ueno, A.; Akahori, Y. *Yakugaku Zasshi* **1968,** 88, 1135-1142; *Chem. Abstr.* **1969**, 70, 35079.

47. Heaton, A.; Husband, A. J. WO2006032086, **2006**; *Chem. Abstr.* **2006**, 144, 331171.

48. Ramanujam, S.; Seshadri, T. R. *Proceedings - Indian Academy of Sciences* **1958,** 48A, 175-179.

49. Gottsegen, A.; Antus, S.; Kolonits, P.; Nogradi, M.; Lupi, A.; Delle Monache, G.; Marta, M.; Marini Bettolo, G. B. *Gazzetta Chimica Italiana* **1981,** 111, (5-6), 211-215.

50. Wessely, F.; Prillinger, F. *Monatshefte fuer Chemie* **1938,** 72, 197-199.

51. Prillinger, F.; Schmid, H. *Monatshefte fuer Chemie* **1939,** 72, 427-431.

52. Farkas, L.; Gottsegen, A.; Nogradi, M. *Tetrahedron* **1970,** 26, 2787-2790.

53. Fukushima, S.; Akahori, Y.; Noro, T.; Saiki, Y.; Ueno, A.; Morinaga, K. *Yakugaku Zasshi* **1973,** 93, 896-898; *Chem. Abstr.* **1973**, 79, 91908.

54. Farkas, L.; Gottsegen, A.; Nogradi, M.; Strelisky, J. *Tetrahedron* **1971,** 27, 5049-5054.

55. Davis, F. A.; Chen, B. C. *Journal of Organic Chemistry* **1993,** 58, 1751-1753.

56. Amari, G.; Armani, E.; Ghirardi, S.; Delcanale, M.; Civelli, M.; Caruso, P. L.; Galbiati, E.; Lipreri, M.; Rivara, S.; Lodola, A.; Mor, M. *Bioorganic & Medicinal Chemistry* **2004,** 12, (14), 3763-3782.

57. Kirkiacharian, B. S.; Gomis, M. *Synthetic Communications* **2005,** 35, (4), 563-569.

58. Lipinski, C. A. EP230379, **1987**; *Chem. Abstr*. **1988**, 108, 75224

59. Zilliken, F. W. US4264509, **1981**; *Chem. Abstr.* **1981**, 95:113769

60. Sathyanarayana, S.; Krishnamurty, H. G. *Indian Journal of Chemistry* **1988,** 27B, (10), 899-901.

61. Mouysset, G.; Payard, M.; Tronche, P.; Bastide, J.; Bastide, P. *European Journal of Medicinal Chemistry* **1988,** 23, (2), 199-202.

62. Rehder, K. S.; Kepler, J. A. *Synthetic Communications* **1996,** 26, (21), 4005-4021.

63. (a) Malhotra, S.; Sharma, V. K.; Parmar, V. *Journal of Chemical Research, Synopses* **1988,** 6, 179; (b) Malhotra, S.; Sharma, V. K.; Parmar, V. *Journal of Chemical Research, Miniprint* **1988**, 1570-1582.

64. Bratulescu, G. *Acta Chimica Slovenica* **2002,** 49, (1), 173-180.

65. King, F. E.; King, T. J.; Warwick, A. J. *Journal of Chemical Society* **1952**, 96-100.

66. Davis, F. A.; Chen, B.-C. *Tetrahedron Letters* **1990,** 31, (47), 6823-6826.

67. Krishnamurty, H. G.; Parkash, B.; Seshadri, T. R. *Indian Journal of Chemistry* **1974**, 554-556.

68. Gilbert, A. H.; McGookin, A.; Robertson, A. *Journal of Chemical Society* **1957**, 3740-3745.

69. Crabbe, P.; Leeming, P. R.; Djerassi, C. *Journal of the American Chemical Society* **1958,** 80, 5258-5263.

70. Wang, Q.; Zhu, J.; Li, Y. *Chinese Science Bulletin* **1990,** 35, (9), 744-746; *Chem. Abstr.* **1991**, 114, 6071.

71. Dann, O.; Volz, G. *Annalen der Chemie* **1960,** 631, 111-116.

72. Dann, O.; Volz, G. *Naturwissenschaften* **1961,** 48, 162.

73. Dann, O.; Volz, G. *Annalen der Chemie* **1965,** 685, 167-176.

74. Müller, E.; Wiesemann, W. *Liebig's Annalen der Chemie* **1938,** 537, 86-112.

75. Geissman, T. A.; Armen, A. *Journal of American Chemical Society* **1955,** 77, 1623-1627.

76. Nohara, A.; Ishiguro, T.; Ukawa, K. JP54059279, **1979**; *Chem. Abstr.* **1979**, 91, 175358

77. Heaton, A.; Husband, A. J. WO2006032085, **2006**; *Chem. Abstr.* **2006**, 144, 331172

78. Hanaya, K. A., Yuko; Sasaki, Katsunori; Ishiyama, Junichi. *Nippon Kagaku Kaishi* **1993**, (6), 774-777; *Chem. Abstr.* **1993**, 119, 270956.

79. Pfeiffer, P.; Grimmer, J. *Berichte der Deutschen Chemischen Gesellschaft* **1917,** 50, 911-927.

80. Bradbury, R. B.; White, D. E. *Journal of Chemical Society* **1953**, 871-876.

81. Anderson, E. L.; Marrian, G. F. *Journal of Biological Chemistry* **1939,** 127, 649-656.

82. Suzuki, M.; Mizuno, H.; Nakayama, S. *Nippon Kagaku Zasshi* **1968,** 89, (6), 627-628; *Chem. Abstr.* **1969**, 70, 3755.

83. Suzuki, M.; Oda, T.; Nakayama, S.; Mizuno, H. *Nippon Kagaku Zasshi* **1969,** 90, (4), 401-404; *Chem. Abstr.* **1969**, 71, 21986.

84. Mitsui, S.; Kiseki, N. *Nippon Kagaku Kaishi* **1950,** 71(Pure Chem. Sect.), 203-205; *Chem. Abstr.* **1951**, 45, 38731.

85. Mondon, A.; Callsen, H.; Hartmann, P.; Cuno, G.; Andersen, C. H. *Chemische Berichte* **1975,** 108, (3), 934-943.

86. Miller, C. P.; Collini, M. D.; Morris, R. L.; Singhaus, R. R. US 2006004087, **2006**; *Chem. Abstr.* **2006**, 144, 108195

87. Geissman, T. A.; Clinton, R. O. *Journal of the American Chemical Society* **1946,** 68, 697-700.

88. Pfeiffer, P.; Emmer, H. J. *Berichte der Deutschen Chemischen Gesellschaft* **1920,** 53B, 945-953.

89. (a) Wiley, P. F. *Journal of American Chemical Society* **1951,** 73, 4205-4209; (b) Wiley, P. F. US2621189, **1973**; *Chem. Abstr.* **1953**, 47, 10011

90. Wiley, P. F. *Journal of American Chemical Society* **1952,** 74, 4326-4328.

91. Pfeiffer, P.; Oberlin, H.; Konermann, E. *Berichte der Deutschen Chemischen Gesellschaft* **1925,** 58B, 1947-1958.

92. Ito, Y.; Kitagawa, H.; Hiramori, T.; Suzuki, Y.; Yamagata, M. *Yakugaku Zasshi* **1951,** 71, 686-692; *Chem. Abstr.* **1952**, 46, 48621.

93. Kitagawa, M.; Tanaka, M. EP248420, **1987**; *Chem. Abstr.* **1988**, 108, 94387

94. Koizumi, T. JP03044384, **1991**; *Chem. Abstr.* **1991**, 115, 49411

95. Koizumi, T.; Saito, Y. JP02218674 **1990**; *Chem. Abstr.* **1991**, 114, 122058

96. Koizumi, T. JP03017076, **1991**; *Chem. Abstr.* **1991**, 114, 247144

97. Inoue, N. *The science reports of the Tohoku University / I* **1961,** XLV, 63-67; *Chem. Abstr.* **1963**, 58, 33236.

98. Suginome, H. *Journal of Organic Chemistry* **1959,** 24, 1655-1662.

99. Naylor, P.; Ramage, G. R.; Schofield, F. *Journal of Chemical Society* **1958**, 1190-1193.

100. Ramanathan, V.; Venkataraman, K. *Proceedings - Indian Academy of Sciences* **1953,** 38A, 40-44.

101. Gowan, J. E.; MacGiolla Riogh, S. P.; MacMahon, G. J.; O'Cleirigh, S.; Philbin, E. M.; Wheeler, T. S. *Tetrahedron* **1958,** 2, 116-121.

102. Jarowski, C. I.; Moran, W. J.; Cramer, B. J. *Journal of American Chemical Society* **1949,** 71, 944-946.

103. Tsukayama, M.; Li, H.; Nishiuchi, M.; Takahashi, M.; Kawamura, Y. *Journal of Chemical Research, Synopses* **1998,** 5, 238-239.

104. Tsukayama, M.; Li, H.; Nishiuchi, M.; Takahashi, M.; Kawamura, Y. *Journal of Chemical Research, Miniprint* **1998**, 1181-1196.

105. Talekar, D. G.; Sanghvi, Y. S.; Rao, A. S. *Indian Journal of Chemistry* **1982,** 21B, 710-713.

106. Miyano, M.; Shone, R. L. EP150447, **1985**; *Chem. Abstr.* **1986**, 104, 5775

107. Mozingo, R.; Adkins, H. *Journal of American Chemical Society* **1938,** 60, 669-675.

108. Johnstone, R. A. W.; Wilby, A. H. *Chemical Reviews* **1985,** 85, 129-170.

109. Massicot, J.; Mentzer, C.; Pillon, D. *Comptes Rendus des Seances de l'Academie des Sciences* **1954,** 238, 111-112.

110. Mentzer, C.; Massicot, J. *Bulletin de la Societe Chimique de France* **1956**, 144-148.

111. Cozzi, P.; Pillan, A. *Journal of Heterocyclic Chemistry* **1985,** 22, 441-443.

112. Krishnamurty, H. G.; Sathyanarayana, S. *Synthetic Communications* **1986,** 16, (13), 1657-1663.

113. Wähälä, K.; Hase, T. A. *Heterocycles* **1989,** 28, (1), 183-186.

114. Won, D.; Shin, B.-K.; Han, J. *Journal of Applied Biological Chemistry* **2008,** 51, (1), 17-19; *Chem. Abstr.* **2008**, 610476.

115. Won, D.; Shin, B.-K.; Kang, S.; Hur, H.-G.; Kim, M.; Han, J. *Bioorganic & Medicinal Chemistry Letters* **2008,** 18, (6), 1952-1957.

116. Kim, M.; Shin, B.-K.; Won, D.; Han, J. *Journal of Applied Biological Chemistry* **2007,** 50, (2), 85-87; *Chem. Abstr.* **2007**, 148, 33464.

117. Hong, R.; Feng, J.; Hoen, R.; Lin, G.-q. *Tetrahedron* **2001,** 57, (41), 8685-8689.

118. Sabui, S. K.; Mondal, P.; Venkateswaran, R. V. *Journal of Chemical Research, Synopses* **2002,** 9, 428-429.

119. Sabui, S. K.; Venkateswaran, R. V. *Tetrahedron* **2003,** 59, (42), 8375-8381.

120. Krishnamurty, H. G.; Ghosh, S.; Sathyanarayana, S. *Indian Journal of Chemistry* **1986,** 25B, 1253-1254.

121. Khupse, R. S.; Erhardt, P. W. *Journal of Natural Products* **2008,** 71, (2), 275-277.

122. Goel, S.; Shashi; Makrandi, J. K. *Indian Journal of Chemistry* **2006,** 45B, (2), 535-536.

123. Hyatt, J. A. US2007149788, **2007**; *Chem. Abstr.* **2007**, 147, 95472

124. Setchell, K. D. R.; Sorokin, V. D. US2007027329, **2007**; *Chem. Abstr.* **2007**, *146*, 184287

125. Kim, S.-I.; Wang, X.-L.; Kim, C.-S.; Hur, H.-G.; Kim, K.-T.; Park, S.-W.; Park, H.-J.; Lee, H.-K. WO2006031007, **2006**; *Chem. Abstr.* **2006**, 144,329901

126. Dobrydneva, Y.; Williams, R. L.; Morris, G. Z.; Blackmore, P. F. *Journal of Cardiovascular Pharmacology* **2002,** 40, (3), 399-410.

127. Pihlaja, K.; Taehtinen, P.; Klika, K. D.; Jokela, T.; Salakka, A.; Waehaelae, K. *Journal of Organic Chemistry* **2003,** 68, (18), 6864-6869.

128. Wang, X.-L.; Hur, H.-G.; Lee, J. H.; Kim, K. T.; Kim, S.-I. *Applied and Environmental Microbiology* **2005,** 71, (1), 214-219.

129. (a) Kiyoyuki, Y. *Bulletin of the Chemical Society of Japan* **1962,** 35, 1329-1334; (b) Timar, T.; Jaszberenyi, J. C.; Hosztafi, S. *Acta Chimica Hungarica* **1988,** 125, (3), 457-643; (c) Timar, T.; Hosztafi, S.; Jaszberenyi, J. C. *Acta Chimica Hungarica* **1988,** 125, (4), 617-629; (d) Hanaya, K.; Koga, Y.; Yamagughi, A.; Kudo, H.; Chow, Y. L. *Nouveau Journal de Chimie* **1982,** 6, (3), 149-154; (e) Kashikar, M. D.; Phatak, D. M.; Kulkarni, R. S.; Borkar, A. M.; Kulkarni, A. B. *Indian Journal of Chemistry* **1964,** 2, (12), 485-488; (f) Rebitzer, S.; Annibali, D.; Kopp, S.; Eder, M.; Langer, T.; Chiba, P.; Ecker, G. F.; Noe, C. R. *Farmaco* **2003,** 58, (3), 185-191; (g) Ibrahim, A. R.; Abul-Hajj, Y. J. *Journal of Natural Products* **1990,** 53, (3), 644-656; (h) Miyano, M.; Matsui, M. *Chemische Berichte* **1958,** 91, 2044-2052.

130. Major, A.; Nogradi, M.; Vermes, B.; Kajtar-Peredy, M. *Liebigs Annalen der Chemie* **1988,** 6, 555-558.

131. Toth, E.; Dinya, Z.; Szilagyi, L.; Antus, S. *Heterocyclic Communications* **2001,** 7, (3), 257-262.

132. Eguchi, T.; Hoshino, Y. *Bulletin of the Chemical Society of Japan* **2001,** 74, (5), 967-970.

133. (a) Fukui, K.; Nakayama, M. *Bulletin of the Chemical Society of Japan* **1968,** 41, (6), 1385-1387; (b) Dudley, K. H.; Corley, R. C.; Miller, H. W.; Wall, M. E. *The Journal of organic chemistry* **1967,** 32, (7), 2312-2317.

134. Chambers, R. J.; Marfat, A. *Journal of Heterocyclic Chemistry* **1994,** 31, (6), 1401-1405.

135. Abdel-Rahman, A.-R. H.; Keshk, E. M.; El-Telbani, E. M. *Zeitschrift fuer Naturforschung, B* **2002,** 57, (5), 557-562.

136. Gabutt, C. D.; Hepworth, J. D.; Urquhart, M. W.; Verquez de Miguel, L. M. *Journal of Chemical Society, Perkin Transactions 1* **1997**, 1819-1824.

137. Clarke, D. S.; Gabbutt, C. D.; Hepworth, J. D.; Heron, B. M. *Tetrahedron Letters* **2005,** 46, (33), 5515-5519.

138. Stachulski, A. V.; Berry, N. G.; Low, A. C. L.; Moores, S. L.; Row, E.; Warhurst, D. C.; Adagu, I. S.; Rossignol, J.-F. *Journal of Medicinal Chemistry* **2006,** 49, (4), 1450-1454.

139. Payard, M.; Couquelet, J. *Synthesis* **1979,** 11, 889.

140. Khurana, J. M.; Chauhan, S. *Journal of Chemical Research, Synopses* **2002,** 5, 201-202.

141. Clark-Lewis, J. W.; Della, E. W.; Mahandru, M. M. *Australian Journal of Chemistry* **1969,** 22, (2), 2389-2394.

142. Yamaoka, H.; Hakucho, T.; Akiba, K. *Heterocycles* **1981,** 15, (2), 1159-1162.

143. Kanth, J. V. B.; Brown, H. C. *Tetrahedron* **2002,** 58, (6), 1069-1074.

144. Suesse, M.; Johne, S.; Hesse, M. *Helvetica Chimica Acta* **1992,** 75, (2), 457-470.

145. Ganguly, A. K.; Mahata, P. K.; Biswas, D. *Tetrahedron Letters* **2006,** 47, (8), 1347-1349.

146. Begley, M. J.; Crombie, L.; Hadi, A.; A., H. B.; Josephs, J. L. *Journal of the Chemical Society, Perkin Transactions 1* **1989**, (1), 204-205.

147. Gabbutt, C. D.; Hepworth, J. D.; Heron, B. M.; Thomas, J.-L. *Tetrahedron Letters* **1998,** 39, (8), 881-884.

148. Antus, A.; Gottsegen, A.; Nogradi, M. *Synthesis* **1981**, 574-576.

149. Antus, S.; Gottsegen, A.; Kolonits, P.; Nagy, Z.; Nogradi, M.; Vermes, B. *Journal of the Chemical Society, Perkin Transactions 1* **1982,** 6, 1389-1394.

150. Gottsegen, A.; Antus, S.; Nogradi, M. L., A.; Marini-Bettolo, G. B. *Studies in Organic Chemistry* **1982,** Volume Date 1981, 11(Flavonoids Bioflavonoids), 141-145; *Chem. Abstr.* 1982, 97, 215841.

151. Pew, J. C. *Journal of the American Chemical Society* **1948,** 70, 3031-3034.

152. Hillis, W. E. *Australian Journal of Scientific Research, Ser. B* **1952,** A5, 379-386.

153. Kotake, M.; Kubota, T.; Ichikawa, N. *Journal of the Institute of Polytechnics / C* **1950,** 1, (2), 47-48; *Chem. Abstr.* **1952**, 46, 11475.

154. Shimizu, M.; Yoshikawa, T. *Yakugaku Zasshi* **1952,** 72, 331-333; *Chem. Abstr.* **1953**, 47, 15870.

155. Geissman, T. A.; Lischner, H. *Journal of the American Chemical Society* **1952,** 74, (3001-3004).

156. Carruthers, W. R.; Farmer, R. H.; Laidlaw, R. A. *Journal of the Chemical Society* **1957**, 4440-4444.

157. Jain, A. C.; Kumar, A.; Sharma, N. K. *Indian Journal of Chemistry* **1991,** 30B, (2), 290-291.

158. Ahmad-Junan, S. A. *Malaysian Journal of Science* **2003,** 22, (1), 141-145; *Chem. Abstr.* 2005, 144, 311811.

159. Khurana, J. M.; Sharma, P. *Bulletin of the Chemical Society of Japan* **2004,** 77, (3), 549-552.

160. Khurana, J. M.; Chauhan, S. *Journal of Chemical Research, Miniprint* **2002**, 519-526.

161. (a) Khurana, J.; Ray, A.; Singh, S. *Tetrahedron Letters* **1998,** 39 (22), 3829-3832; (b) Maybury, P. C.; Mitchell, R. W.; Hawthorne, M. F. *Journal of the Chemical Society, Chemical Communications* **1974,** 14, 534-535.

162. Hwu, J. R.; Wein, Y. S.; Leu, Y.-J. *Journal of Organic Chemistry* **1996,** 61, (4), 1493-1499.

163. Bokel, H.-H.; Mackert, P.; Murmann, C.; Schweickert, N. WO2000035901, **2000**; *Chem. Abstr.* **2000**, 133, 58712

164. Gontcharov, A. V.; Nikitenko, A. A.; Raveendranath, P.; Shaw, C.-C.; Wilk, B. K.; Zhou, D. WO2007123941, **2007**; *Chem. Abstr.* **2007**, *147*, 502236

165. Chen, A.-H.; Kuo, W.-B.; Chen, C.-W. *Journal of the Chinese Chemical Society (Taipei, Taiwan)* **2003,** 50, (1), 123-127.

166. Adeleke, B. B.; Weir, D.; Depew, M. C.; Wan, J. K. S. *Canadian Journal of Chemistry* **1984,** 62, (q), 117-120.

167. Boutoute, P.; Mousset, G. *Canadian Journal of Chemistry* **1992,** 70, (8), 2266-2275.

168. Fischer, D.; Ebenau-Jehle, C.; Griesebach, H. *Archives of Biochemistry and Biophysics* **1990,** 276, 390-395.

169. Tiemann, K.; Hinderer, W.; Barz, W. *FEBS Letters* **1987,** 213, (2), 324-328.

170. Flavin, M. T.; Rizzo, J. D.; Khilevich, A.; Kucherenko, A.; Sheinkman, A. K.; Vilaychack, V.; Lin, L.; Chen, W.; Greenwood, E. M.; Pengsuparp, T.; Pezzuto, J. M.; Hughes, S. H.; Flavin, T. M.; Cibulski, M.; Boulanger, W. A.; Shone, R. L.; Xu, Z.-Q. *Journal of Medicinal Chemistry* **1996,** 39, 1303-1313.

171. Saha, S.; Ghosh, T.; Bandyopadhyay, C. *Synthetic Communications* **2008,** 38, (14), 2429-2436.

172. (a) Kim, I. A.; Shin, J. H.; Kim, I. H.; Kim, J. H.; Kim, J. S.; Wu, H. G.; Chie, E. K.; Ha, S. W.; Park, C. I.; Kao, G. D. *Clinical Cancer Research* **2006,** 12, (3), 940-949; (b) Baylin, S.; Pruitt, K. WO2008082646, **2008**; *Chem. Abstr.* **2008**, 829056

173. (a) Niculescu-Duvaz, I.; Roman, E.; Whittaker, S. R.; Friedlos, F.; Kirk, R.; Scanlon, I. J.; Davies, L. C.; Niculescu-Duvaz, D.; Marais, R.; Springer, C. J. *Journal of Medicinal Chemistry* **2008,** 51, (11), 3261-3274; (b) Hirao, M.; Posakony, J.; Nelson, M.; Hruby, H.; Jung, M.; Simon, J. A.; Bedalov, A. *Journal of Biological Chemistry* **2003,** 278, (52), 52773-52782.

174. (a) Tang, W.; Hioki, H.; Harada, K.; Kubo, M.; Fukuyama, Y. *Journal of Natural Products* **2007,** 70, (12), 2010-2013; (b) Li, D.-L.; Li, X.-M.; Peng, Z.-Y.; Wang, B.-G. *Molecules* **2007,** 12, (5), 1163-1169.

175. Takara, K.; Kuniyoshi, A.; Wada, K.; Kinjyo, K.; Iwasaki, H. *Bioscience, Biotechnology, and Biochemistry* **2008,** 72, (8), 2191-2194.

176. Zhang, D.; Li, Y.; Li, Y.; Li, Y.; Li, J.; Chen, H.; Yang, J. CN101058594, **2007**; *Chem. Abstr.* **2007**, 147, 547792

177. (a) Liu, Y.; Wang, H.; Zhang, X.; Tian, Q. CN1730479, **2006**; *Chem. Abstr.* **2006**, 145, 99719; (b) Zhang, X.-f.; Wang, H.-m.; Song, Y.-l.; Nie, L.-h.; Wang, L.-f.; Liu, B.; Shen, P.-p.; Liu, Y. *Bioorganic & Medicinal Chemistry Letters* **2006,** 16, (4), 949-953.

178. Kumar, A.; Singh, B. K.; Tyagi, R.; Jain, S. K.; Sharma, S. K.; Prasad, A. K.; Raj, H. G.; Rastogi, R. C.; Watterson, A. C.; Parmar, V. S. *Bioorganic & medicinal chemistry* **2005,** 13, (13), 4300-4305.

179. (a) Dweck, A. C. *Journal of applied cosmetology* **2006,** 24, (1), 17-32; (b) Roelens, F.; Huvaere, K.; Dhooge, W.; Van Cleemput, M.; Comhaire, F.; De Keukeleire, D. *European Journal of Medicinal Chemistry* **2005,** 40, (10), 1042-1051.

180. Ito, Y.; Kitagawa, H. *Yakugaku Zasshi* **1953,** 73, 107-110; *Chem. Abstr.* **1953**, 47, 65996.

181. Opdyke, D. L. J. *Food and Cosmetics Toxicology* **1974,** 12, (4), 521-522.

182. Yang, Y.; Yu, J.; Ji, R.; Chen, K. CN1810795, **2006**; *Chem. Abstr.* **2006**, 145, 293028

183. Bulawa, C.; Devit, M. WO2007089548, **2007**; *Chem. Abstr.* **2007**, 147, 227229

184. (b) Rathore, D.; Jani, D.; Nagarkatti, R. US2007148185, **2007**; *Chem. Abstr.* **2007**, 147, 110180; (b) Adesanwo, J. K.; Ekundayo, O.; Shode, F. O.; Njar, V. C. O.; van den Berge, A. J. J.; Oludahunsi, O. A. T. *Nigerian Journal of Natural Products and Medicine* **2004,** 8, 69-73; *Chem. Abstr.* **2005**, 144, 66783.

185. Adams, N. D.; Darcy, M. G.; Dhanak, D.; Duffy, K. J.; Fitch, D. M.; Knight, S. D.; Newlander, K. A.; Shaw, A. N. WO2006113432, **2006**; *Chem. Abstr.* **2006**, 145, 438652

186. Lukhtanov, E. A.; Vorobiev, A. V.; Reed, M. W.; Vermeulen, N. M. J. US2006204990, **2006**; *Chem. Abstr.* **2006**, 145, 336042

187. Zhang, Y.; DeWitt, D. L.; Murugesan, S.; Nair, M. G. *Chemistry & Biodiversity* **2004,** 1, (3), 426-441.

188. Yao, C.-S.; Lin, M.; Wang, L. *Chemical & Pharmaceutical Bulletin* **2006,** 54, (7), 1053-1057.

189. Adediran, S. A.; Cabaret, D.; Lohier, J.-F.; Wakselman, M.; Pratt, R. F. *Bioorganic & Medicinal Chemistry Letters* **2004,** 14, (20), 5117-5120.

190. Kontogiorgis, C.; Litinas, K. E.; Makri, A.; Nicolaides, D. N.; Vronteli, A.; Hadjipavlou-Litina, D. J.; Pontiki, E.; Siohou, A. *Journal of Enzyme Inhibition and Medicinal Chemistry* **2008,** 23, (1), 43-49.

191. McGuire, M. A.; Shilcrat, S. C.; Sorenson, E. *Tetrahedron Letters* **1999,** 40, 3293-3296.

192. Ulgheri, F.; Marchetti, M.; Piccolo, O. *Journal of Organic Chemistry* **2007,** 72, (16), 6056-6059.

193. (a) Bussolari, J. C.; Rehborn, D. C.; Combs, D. W. *Tetrahedron Letters* **1999,** 70, (7), 1241-1244; (b) Li, K.; Foresee, L. N.; Tunge, J. A. *Journal of Organic Chemistry* **2005,** 70, (7), 2881-2883.

194. Lee, J. H.; Bang, H. B.; Han, S. Y.; Jun, J.-G. *Tetrahedron Letters* **2007,** 48, (16), 2889-2892.

195. Song, F.; Lu, S.; Gunnet, J.; Xu, J. Z.; Wines, P.; Proost, J.; Liang, Y.; Baumann, C.; Lenhard, J.; Murray, W. V.; Demarest, K. T.; Kuo, G.-H. *Journal of Medicinal Chemistry* **2007,** 50, (12), 2807-2817.

196. Biswas, B.; Sen, P. K.; Venkateswaran, R. V. *Tetrahedron* **2007,** 63, (48), 12026-12036.

197. Murray, R. D. H.; Mendez, J.; Brown, S. A., *The Natural Coumarins. Occurrence, Chemistry and Biochemistry*. ed.; John Wiley and Sons: **1982**; p. 84-88.

198. (a) Estevez, R. R.; Gonzalez, G., A. *Phytochemistry* **1970,** 9, (4), 833-840; (b) Tomimatsu, T.; Hashimoto, M.; Shingu, T.; Tori, K. *Journal of the Chemical Society D, Chemical Communications* **1969,** 4, 168-169; (c) Lahey, F. N.; MacLeod, J. K. *Australian Journal of Chemistry* **1967,** 20, (9), 1943-1955; (d) Joshi, B. S.; Kamat, V. N.; Gawad, D. H. *Journal of the Chemical Society, Perkin Transactions 1* **1974,** 13, 1561-1564; (e) Tomimatsu, T.; Hashimoto, M.; Shingu, T.; Tori, K. *Tetrahedron* **1972,** 28, (7), 2003-2010.

199. Anet, F. A. L.; Hughes, G. K.; Ritchie, E. *Australian journal of scientific research* **1949,** 2A, 608-615.

200. Borsche, W.; Hahn-Weinheimer, P. *Chemische Berichte* **1952,** 85, (3), 198-202.

201. Dean, F. M.; Robertson, A.; Whalley, W. B. *Journal of the Chemical Society* **1950**, 895-902.

202. Mills, F. D. *Journal of Heterocyclic Chemistry* **1980,** 17, 1597-1600.

203. Cube, R. V.; Vernier, J.-M.; Hutchinson, J. H.; Gardner, M. F.; James, J. K.; Rowe, B. A.; Schaffhauser, H.; Daggett, L.; Pinkerton, A. B. *Bioorganic and Medicinal Chemistry Letters* **2005,** 15, 2389-2393.

204. Cohen, N.; Schaer, B.; Saucy, G.; Borer, R.; Todaro, L.; A.-M., C. *Journal of Organic Chemistry* **1989,** 54, 3282-3292.

205. Demyttenaere, J.; Syngel, K. V.; Markusse, A. P.; Vervisch, S.; Debenedetti, S.; Kimpe, N. D. *Tetrahedron* **2002,** 58, 2163-2166.

206. Yates, P.; Macas, T. S. *Canadian Journal of Chemistry* **1988,** 66, 1-10.

207. Crombie, J.; Jones, R. C. F.; Palmer, C. J. *Journal of the Chemical Society, Perkin Transactions 1* **1987**, 345-351.

208. Ahluwalia, V. K.; Nayal, L.; Tehim, A. K. *Indian Journal of Chemistry* **1988,** 27B, 70-71.

209. Tomimatsu, T.; Hasegawa, H.; Tori, K. *Tetrahedron* **1974,** 30, (8), 939-945.

210. Stanjek, V.; Boland, W. *Helvetica Chimica Acta* **1998,** 81, 1596-1607.

211. Nadkarni, K. K.; Kamat, S. P.; Paknikar, S. K. *Indian Journal of Chemistry* **1999,** 33B, 432-435.

212. Lemmich, J.; Pedersen, P. A.; Nielsen, B. E. *Tetrahedron Letters* **1969,** 39, 3365-3366.

213. Seshadri, T. R.; Vishwapaul. *Indian Journal of Chemistry* **1971,** 9, (5), 418-423.

214. Reisch, J.; Voerste, A. A. W. *Journal of the Chemical Society, Perkin Transactions 1* **1994**, 3251-1560.

215. Ying, L.; Gervay-Hague, J. WO2006025983, **2006**; *Chem. Abstr.* **2006**, 144, 274494

216. Miyakado, M.; Ohno, N.; Yoshioka, H.; Mabry, T. J. *Phytochemistry* **1978,** 17, (1), 143-144.

217. Abdel-Megeid, F. M. E.; El-Kaschef, M. A. F.; Ghattas, A. A. G. *Egyptian Journal of Chemistry* **1980,** Volume Date 1977, 20, (5), 453-462; *Chem. Abstr.* **1980**, 93, 239150.

218. Chakraborty, D. P.; Chatterjee, D.; Guha, S.; Das, B. C. *Journal of the Indian Chemical Society* **1985,** 62, (12), 993-998.

219. Crombie, L.; Jones, R. C. F.; Palmer, C. J. *Tetrahedron Letters* **1985,** 26, (24), 2929-2932.

220. Harrowven, D. C.; Wilden, J. D.; Tyte, M. J.; Hursthouse, M. B.; Coles, S. J. *Tetrahedron Letters* **2001,** 42, 1193-1195.

221. Harrowven, D. C.; Tyte, M. J. *Tetrahedron Letters* **2001,** 42, 8709-8711.

222. Antoine, L.; Bouquel, P.; Borghese, A.; Gorissen, H.; Martinelli, M.; Merschaert, A.; Ruhter, G.; Rypens, C.; Scarborough, R.; Schotten, T.; Van Hoeck, J.-P. WO2001094331, **2001**; *Chem. Abstr.* **2002**, 136, 37510

223. Kanter, J.; Mullins, J. J. G.; Pandey, A.; Scarborough, R. WO2001092250, **2001**; *Chem. Abstr.* **2002**, 136, 20016

224. Kuhn, W.; Funk, H.-U.; Senft, G. WO2002018360, **2002**; *Chem. Abstr.* **2002**, 136, 200098

225. Tang, L.; Yu, J.; Leng, Y.; Geng, Y.; Yang, Y.; Ji, R. *Bioorganic & Medicinal Chemistry Letters* **2003,** 13, 3437-3440.

226. Yang, Y.; Tang, L.; Ji, R.; K., C. WO2004076437, **2004**; *Chem. Abstr.* **2004**, 141, 225315

227. Leenders, L. H.; Schoutede, E.; De Schryver, F. C. *Journal of Organic Chemistry* **1973,** 38, (5), 957-966.

228. Lahey, F. N.; Wluka, D. J. *Australian Journal of Chemistry* **1955,** 8, 125-128.

229. Ewing, J.; Hughes, G. K.; Ritchie, E. *Australian journal of scientific research* **1950,** 3A, 342-345.

230. Taugerbeck, A.; Klasen-Memmer, M. WO2006012965, **2006**; *Chem. Abstr.* **2006**, 144, 222646

231. Gaudin, J.-M.; Nikolaenko, O.; de Saint Laumer, J.-Y.; Winter, B.; Blanc, P.-A. *Helvetica Chimica Acta* **2007,** 90, (7), 1245-1265.

232. Kokotos, G.; Tzougraki, C. *Journal of Heterocyclic Chemistry* **1986,** 23, 87-92.

233. Ray, S.; Grover, P. K.; Anand, N. *Indian Journal of Chemistry* **1971,** 9, (7), 619-623.

234. Campbell, W. E.; Cragg, G. M. L. *Phytochemistry* **1979,** 18, (4), 688-689.

235. Paal, C.; Schiedewitz, H. *Berichte* **1930,** 63B, 766-78.

236. Smith, L. I.; Tenenbaum, D. *Journal of the American Chemical Society* **1937,** 59, 667-672.

237. Collins, D. J.; Downes, L. M.; Jhingran, A. G.; Rutschmann, S. B.; Sharp, G. J. *Australian Journal of Chemistry* **1989,** 42, 1235-1248.

238. Csuros, Z.; Zech, K.; Geczy, I. *Hungarica Acta Chimica* **1946,** 1, 1-23.

239. Hata, K.; Kozawa, M.; Baba, K.; Mitsui, M. *Chemical & Pharmaceutical Bulletin* **1973,** 21, (3), 518-522.

240. Nakazaki, M.; Hirose, Y.; Ikematsu, K. *Tetrahedron Letters* **1966,** 39, 4735-4738.

241. Halpern, O.; Waser, P.; Schmid, H. *Helvetica Chimica Acta* **1957,** 40, 758-778.

242. Lemmich, E.; Lemmich, J.; Nielsen, B. E. *Acta Chemica Scandinavica* **1970,** 24, (8), 2893-2900.

243. Lemmich, J.; Lemmich, E.; Nielsen, B. *Acta chemica Scandinavica* **1966,** 20, (9), 2497-2507.

244. Smith, L. I.; Denyes, R. O. *Journal of American Chemical Society* **1936,** 58, 304-309.

245. Amidon, R. W.; Greenfield, H. DE2161847, **1972**; *Chem. Abstr.* **1972**, 77, 114136

246. Xu, Z.-Q.; Pupek, K.; Suling, W. J.; Enache, L.; Flavin, M. T. *Bioorganic & Medicinal Chemistry* **2006,** 14, (13), 4610-4626.

247. Ito, C.; Furukawa, H. *Journal of Chemical Society, Perkin Transactions, 1* **1990**, 2047-2055.

248. Pouliquen, Y. B. M.; Arriaga, A. M. C.; Lima, M. B.; De Sousa, A. L.; Farias, G. M.; Braz-Filho, R. *Revista Latinoamericana de Quimica* **2000,** 28, (2), 80-94.

249. Chatterjee, A.; Bhattacharya, A. *Journal of the Chemical Society* **1959**, 1922-1924.

250. Sano, K.; Yosioka, I.; Kitagawa, I. *Chemical & Pharmaceutical Bulletin* **1975,** 23, (1), 20-28.

251. Sano, K.; Yosioka, I.; Kitagawa, I. *Chemical & Pharmaceutical Bulletin* **1973,** 21, (9), 2095-2097.

252. Gourley, R. N.; Grimshaw, J.; Millar, P. G. *Journal of the Chemical Society C* **1970**, (17), 2318-2323.

253. De Benneville, P. L.; Connor, R. *Journal of the American Chemical Society* **1940,** 62, 283-287.

254. De Benneville, P. L.; Connor, R. *Journal of the American Chemical Society* **1940,** 62, 3067-3070.

255. Armstrong, R. F.; Hilditch, T. P. *Proceedings of the Royal Society of London* **1920,** 98A, 27-40.

256. Palfray, V. L.; Sabetay, S. *Bulletin de la Société Chimique de France* **1938,** 5, 1423-1425.

257. Palfray, L. *Bulletin de la Société Chimique de France* **1940,** 7, 407-430.

258. Sanghvi, Y. S.; Rao, A. S. *Journal of heterocyclic chemistry* **1982,** 19, (6), 1377-1380.

259. Collins, D. J.; Jhingran, A. G.; Rutschmann, S. B. *Australian Journal of Chemistry* **1989,** 42, 1769-1784.

260. Palfray, C. L. *Journal of the American Chemical Society* **1941,** 63, 3540-3541.

261. Onishi, K.; Seiga, K.; Hashiguchi, T.; Katahira, S.; Hashigami, M. JP03232877, **1991**; *Chem. Abstr.* **1992**, 116, 59217

262. Wang, H.; Lian, H.; Chen, J.; Pan, Y.; Shi, Y. *Synthetic communications* **1999,** 29, (1), 129-134.

263. Arora, P. K.; Ray, S. *Journal für praktische Chemie* **1981,** 323, (5), 850-852.

264. Kindler, K.; Lührs, K. *Justus Liebigs Annalen der Chemie* **1965,** 685, 36-48.

265. Akabori, S.; Suzuki, T. *Proceedings of the Imperial Academy / C* **1929,** 5, 255-256; *Chem. Abstr.* **1929**, 23, 40371.

266. Hussey, B. J.; Johnstone, A. W. *Tetrahedron* **1982,** 38, (24), 3775-3781.

267. Elamin, B.; Park, J.-W.; Means, G. E. *Tetrahedron Letters* **1988,** 29, (44), 5599-5600.

268. Berthold; Schotten, H.; T.; Hönig, H. *Synthesis* **2002,** 11, 1607-1610.

269. Ganguly, N. C.; Dutta, S.; Datta, M. *Tetrahedron Letters* **2006,** 47, (32), 5807-5810.

270. Coquerel, Y.; Rodriguez, J. *ARKIVOC (Gainesville, FL, United States)* **2008**, (11), 227-237.

271. Sharma, A.; Kumar, V.; Sinha, A. K. *Advanced Synthesis & Catalysis* **2006,** 348, (3), 354-360.

272. Kumar, V.; Sharma, A.; Sinha, A. K. *Helvetica Chimica Acta* **2006,** 89, (3), 483-495.

273. Grundon, M. F.; McColl, I. S. *Phytochemistry* **1975,** 14, (1), 143-150.

274. Birch, A. J.; Maung, M.; Pelter, A. *Australian Journal of Chemistry* **1969,** 22, (9), 1923-1932.

275. Collins, D. J.; Fallon, G. D.; Staffa, A.; Tope, H. *Australian Journal of Chemistry* **1996,** 49, 719-721.

276. Barrero, A. F.; Alvarez-Manzaneda, E. J.; Chahboun, R.; Meneses, R. *Synlett* **1999,** 10, 1663-1666.

277. Dreiding, A. S.; Tomasewski, A. J. *Journal of the American Chemical Society* **1954,** 46, 540-545.

278. (a) Ranade, A. A.; Joseph, A. R.; Kumbhar, V. B. l.; Paradkar, M. V. *Journal of Chemical Research, Synopses* **2003**, 689-690; (b) Ranade, A. A.; Joseph, A. R.; Kumbhar, V. B. l.; Paradkar, M. V. *Journal of Chemical Research, Miniprint* **2003**, 461-462, 857-868.

279. (a) Asahina, Y.; Fujita, A. *Yakugaku Zasshi* **1919,** 444, 97-109; *Chem. Abstrs.*, **1919**, 13, 7676; (b) Dyson, G. *Journal of the Chemical Society, Transactions* **1887,** 51, 61-72.

280. Gustafsson, B.; Wennström, U.; Holmberg, G.-A. *Acta Chemica Scandinavica* **1975,** B29, 273-280.

281. Eiden, F.; E., B.; Lotter, H. *Liebigs Annalen der Chemie* **1983,** 2, 165-180.

282. Bodnar, B. S.; Vogt, P. F. *Journal of Organic Chemistry* **2009,** 74, (6), 2598-2600.

283. Sondengam, B. L.; Fomum, Z. T.; Charles, G.; Akam, T. M. *Journal of Chemical Society, Perkin Transac-tions 1,* **1983**, 1219-1221.

284. Tyman, J. H. P.; Grundy, J.; Brown, G. R. *Journal of Chemical Society, Perkin Transaction 1* **1981**, 336-343.

285. (a) Karrer, P.; Banerjea, P. *Helvetica Chimica Acta* **1949,** 32, 1692-1693; (b) Yamada, K. *Bulletin of the Chemical Society of Japan* **1962,** 35, (8), 1329-1334; (c) Clark-Lewis, J. W.; Mahandru, M. M. *Australian Journal of Chemistry* **1971,** 34, 563-570; (d) Hochstein, F. A. *Journal of American Chemical Society* **1949,** 71, 305-307; (e) Freeman, J. P.; Hawthorne, M. F. *Journal of American Chemical Society* **1956,** 78, 3366-3369.

286. Kirkiacharian, S.; Brion, J.-D.; Billet, D. *Comptes Rendus des Seances de l'Academie des Sciences, Ser. II* **1982,** 294, 181-184.

287. Jagdale, A. R.; Sudalai, A. *Tetrahedron Letters* **2008,** 49, (23), 3790-3793.

288. (a) Kuznetsova, G. A.; Gashimov, N. F. *Chemistry of Natural Compounds* **1973,** 9, (1), 105-106; (b) Gonzalez, A. G.; Diaz, C. E.; Lopez, D. H.; Luis, J. R.; Rodriguez, L. F. *Anales de Quimica* **1977,** 73, (4), 607-608.

289. Wamhoff, H.; Schorn, G.; Korte, F. *Chemische Berichte* **1967,** 100, 1296-1304.

290. Wamhoff, H.; Korte, F. *Chemische Berichte* **1968,** 101, 772-777.

291. Posakony, J.; Hirao, M.; Stevens, S.; Simon, J. A.; Bedalov, A. *Journal of Medicinal Chemistry* **2004,** 47, 2635-2644.

292. Hutchins, R. O.; Rotstein, D.; Natale, N.; Fanelli, J. *Journal of Organic Chemistry* **1976,** 41, (20), 3328-3329.

293. Lissel, M.; Schmidt, S.; Neumann, B. *Synthesis* **1986**, 383-385.

294. Amantini, D.; Fringuelli, F.; Piermatti, O.; Pizzo, F.; Vaccaro, L. *Journal of Organic Chemistry* **2003,** 68, 9263-9268.

295. Tanaka, H.; Ishihara, M.; Ichino, K.; Ito, K. *Chemical & Pharmaceutical Bulletin* **1988,** 36, (5), 1738-1743.

296. Petkova, N. I.; Nikolova, R. D.; Bojilova, A. G.; Rodios, N. A.; Raptopoulou, C. P. *Synthetic Communications* **2006,** 36, (4), 509-524.

297. Kadin, S. B. *Journal of Organic Chemistry* **1966,** 31, 620-622.

298. Piccolo, O.; Ulgheri, F.; Marchetti, M. WO2005005356, **2005**; *Chem. Abstr.* **2005**, 142, 134324

299. Wood, J. L.; Mcguire, M. A.; Mills, R. J.; Pridgen, L. N.; Yu, M. S.; Su, Q. WO9717330, **1997**; *Chem. Abstr.* **1997**, 127, 34205

300. Xue, D.; Chen, Y.-C.; Cui, X.; Wang, Q.-W.; Zhu, J.; Deng, J.-G. *Journal of Organic Chemistry* **2005,** 70, 3584-3591.

301. Liu, H.-J.; Brahma, R. *Synthetic Communications* **1985,** 15, (11), 965-971.

302. Gourley, R. N.; Grimshaw, J.; Millar, P. G. *Chemical Communications* **1967**, 1278-1279.

303. Schoo, N.; Schäfer, H.-J. *Liebigs Annalen der Chemie* **1993**, 595-600.

304. Nielsen, M. F.; Batanero, B.; Lohl, T.; Schafer, H. J.; Wurthwein, E.-U.; Frohlich, R. *Chemistry--A European Journal* **1997,** 3, (12), 2011-2024.

305. (a) Tabakovic, K.; Tabakovic, I. *Croatica Chemica Acta* **1981,** 54, (4), 451-458; *Chem. Abstr.* **1982**, 96, 217812; (b) Mubarak, M. S.; Peters, D. G. *Journal of the*

Electrochemical Society **2008,** 155, (8), F184-F189; (c) Kumar, A.; Sharma, R. *Bulletin of Electrochemistry* **2002,** 18, (2), 71-74; (d) Jain, R.; Gupta, P.; Bhadauria, A. *Journal of the Indian Chemical Society* **2006,** 83, (2), 195-197; (e) Nematollahi, D.; Azizian, J.; Sargordan-Arani, M.; Hesari, M.; Jameh-Bozorghi, S.; Alizadeh, A.; Fotouhi, L.; Mirza, B. *Chemical & pharmaceutical bulletin* **2008,** 56, (11), 1562-1566.

306. Jadot, J.; Braine, R. *Bulletin de la Societe Royale des Sciences de Liege* **1956,** 25, 62-78; *Chem. Abstr.* **1956**, 50, 88889.

307. Landa, S.; Chuchla, J. *Sbornik Vysoke skoly chemiko-technologicke v Praze, Technologie paliv* **1962,** volume date 1961, (5), 35-44; *Chem. Abstr.* **1966**, 65, 56702

308. Kalechits, I. V.; Polubentseva, M. F.; Lipovich, V. G. *Izvestiya Nauchno-Issledovatelskogo Instituta Nefte- i Uglekhimicheskogo Sinteza pri Irkutskom Universitete* **1967,** 9, (1), 194-206; *Chem. Abstr*. **1970**, 72, 134859.

309. (a) Yamashita, M.; Nishida, M.; Suemitsu, R. *The Science and Engineering Review of Doshisha University* **1986,** 27, (2), 10-15; (b) Yamashita, M.; Tanaka, Y.; Arita, A.; Nishida, M. *Jouranl of Organic Chemistry* **1994,** 59, 3500-3502; (c) Yamashita, M.; Kato, Y.; Suemitsu, R. *Chemistry Letters* **1980**, 847-848.

310. Geethamalika, G.; Sundari, A. S.; Shanmugam, P.; Rajendran, S. P. *Indian Journal of Chemistry* **2004,** 43B, 674-676.

311. (a) Ramesh, M.; Shanmugam, P. *Indian Journal of Chemistry* **1983,** 22B, 617-618; (b) Ramasamy, K.; Kalyanasundaram, S. K.; Shanmugam, P. *Synthesis* **1978**, 545-547.

312. Becker, H.-D.; Lingnert, H. *Journal of Organic Chemistry* **1982,** 47, 1095-1101.

313. Risitano, F.; Grassi, G.; Foti, F.; Bilardo, C. *Heterocycles* **2001,** 55, (7), 1311-1314.

314. Liu, Z.; Liu, Q.; Zhang, W.; Mu, R.; Yang, L.; Liu, Z.-L.; Yu, W. *Synthesis* **2006,** 5, 771-774.

315. Kirkiacharian, B. S. *Comptes rendus des séances de l'Académie des Sciences / C* **1980,** 291, 73-76.

316. Wenk, H. H.; Schwab, W.; Haeser, K. WO2006015811, **2006**; *Chem. Abstr.* **2006**, 144, 190705

317. Haeser, K.; Wenk, H. H.; Schwab, W. *Journal of Agricultural and Food Chemistry* **2006,** 54, (17), 6236-6240.

318. Eckert-Maksic, M.; Rapic, V.; Margetic, D.; Matonickin, V. *Heterocyclic Communications* **2000,** 6, (1), 67-72.

319. Wang, X.; Li, X.; Xue, J.; Zhao, Y.; Zhang, Y. *Tetrahedron Letters* **2009,** 50, (4), 413-415.

320. Silverman, R. B., *The organic chemistry of drug design and drug action*. 2nd ed.; Elsevier Academic Press: Amsterdam, Boston; **2004**.

321. (a) *FDA's policy statement for the development of new stereoisomeric drugs. Chirality* **1992,** 4, (5), 338-340; (b) FDA's policy statement for the development of new stereoisomeric drugs. http://www.fda.gov/cder/guidance/stereo.htm

322. (a) Froimowitz, M.; Cody, V. *Chirality* **1995,** 7, (7), 518-525; (b) Zimmerman, D. M.; Smits, S. E.; Hynes, M. D.; Cantrell, B.; Leander, J.; Mendelsohn, L. G.; Nickander, R. *Drug and Alcohol Dependence* **1985,** 14, 381-402..

323. (a) Hahn, F. E.; Ho, R.; Hopps, H. E.; Smadel, J. E.; Wisseman, C. L., Jr. *The Journal of Bacteriology* **1956,** 72, (4), 561-7; (b) Hahn, F. E.; Wisseman, C. L., Jr.; Hopps, H. E. *The Journal of Bacteriology* **1955,** 69, (2), 215-23; (c) Hahn, F. E.; Wisseman, C. L., Jr.; Hopps, H. E. *The Journal of Bacteriology* **1954,** 67, (6), 674-9; (d) Wisseman, C. L., Jr.; Smadel, J. E.; Hahn, F. E.; Hopps, H. E. *The Journal of Bacteriology* **1954,** 67, (6), 662-673.

324. (a) Legros, J.; Dehli, J.; Bolm, C. *Advanced Synthesis & Catalysis* **2005,** 347, (1), 19-31; (b) Somogyi, A.; Bochner, F.; Foster, D. *Australian Prescriber* **2004,** 27, 47-49.

325. (a) Blaser, H.-U.; Hanreich, R.; Schneider, H.-D.; Spindler, F.; Steinacher, B., The chiral switch of metolachlor: The development of a large-scale enantioselective catalytic process. In *Asymmetric Catalysis on Industrial Scale*, ed.; Blaser, H. U.; Schmidt, E., Eds.; Wiley-VCH: Weinheim, **2004**; p. 55-70; (b) Blaser, H.-U.; Spindler, F., The chiral switch of metolachlor. In *Comprehensive Asymmetric Catalysis I-III*, ed.; Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H., Eds.; Springer: **1999**; Vol. 3, p. 1427-1437; (c) Blaser, H.-U. *Advanced Synthesis & Catalysis* **2002,** 344, (1), 17-31.

326. Suginome, H. *Bulletin of the Chemical Society of Japan* **1966,** 39, (7), 1544-1547.

327. Umehara, K.; Nemoto, K.; Kimijima, K.; Matsushita, A.; Terada, E.; Monthakantirat, O.; De-Eknamkul, W.; Miyase, T.; Warashina, T.; Degawa, M.; Noguchi, H. *Phytochemistry* **2008,** 69, (2), 546-552.

328. (a) DiCenzo, G. L.; VanEtten, H. D. *Phytochemistry* **2006,** 67, (7), 675-683; (b) Kaimoyo, E.; VanEtten, H. D. *Phytochemistry* **2008,** 69, (1), 76-87.

329. Slade, D.; Ferreira, D.; Marais, J. P. *Phytochemistry* **2005,** 66, (18), 2177-2215.

330. (a) Lepri, L.; Del Bubba, M.; Coas, V.; Cincinelli, A. *Journal of Liquid Chromatography and Related Technologies* **1999,** 22, (1), 105-118; (b) Krause, M.; Galensa, R. *Chromatographia* **1991,** 32, (1-2), 69-72; (c) Carbonnier, B. J., Ludovic; Morcellet, Michel. *Journal of Chromatographic Science* **2005,** 43, (7), 358-361; (d) Ficarra, P.; Ficarra, R.; Bertucci, C.; Tommasini, S.; Calabro, M. L.; Costantino, D.; Carulli, M. *Planta Medica* **1995,** 61, (2), 171-176; (e) Ng, S.-C.; Ong, T.-T.; Fu, P.; Ching, C.-B. *Journal of Chromatography A* **2002,** 968, (1), 31-40; (f) Lai, X.-H.; Ng, S.-C. *Journal of Chromatography A* **2004,** 1059, (1), 53-59; (g) Caccamese, S.; Caruso, C.; Parrinello, N.; Savarino, A. *Journal of Chromatography, A* **2005,** 1076, (1-2), 155-162; (h) Antus, S.; Bauer, R.; Gottsegen, A.; Lotter, H.; Seligmann, O.; Wagner, H. *Journal of Chromatography* **1992,** 603, (1-2), 133-137.

331. Andersson, P. G.; Munslow, I. J., *Modern reduction methods*. ed.; Wiley-VCH: Weinheim, 2008.

332. Ugo, R., Aspects of homogeneous catalysis: a series of advances; Manfredi: Milano, 1970.

333. Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H., *Comprehensive asymmetric catalysis. Supplement*. ed.; Springer: Berlin ; New York, **2004**.

334. Oro, L. A.; Carmona, D., Rhodium. In *The Handbook of Homogeneous Hydrogenation*, ed.; de Vries, J. G.; Elsevier, C. J., Eds.; Wiley-VCH: Weinhein, **2007**; Vol. 1, p. 3-30.

335. Krossing, I.; Raabe, I. *Angewandte Chemie International Edition* **2004,** 43, (16), 2066-2090.

336. (a) Gridnev, I. D.; Higashi, N.; Imamoto, T. *Journal of the American Chemical Society* **2001,** 123, (19), 4631-4632; (b) Bykov, A. V.; Sul'man, E. M. *Kataliz v Promyshlennosti* **2006,** 5, 3-11 [in Russian]; *Chem. Abstr.* **2006**, *146*, 69417.

337. (a) Schrock, R. R.; Osborn, J. A. *Journal of American Chemical Society* **1976,** 98, (8), 2134-2143; (b) Schrock, R. R.; Osborn, J. A. *Journal of American Chemical Society* **1976,** 98, (8), 2143 - 2147; (c) Schrock, R. R.; Osborn, J. A. *Journal of American Chemical Society* **1976,** 98, (15), 4450-4455.

338. Crabtree, R. H., Iridium. In *The Handbook of Homogeneous Hydrogenation*, ed.; de Vries, J. G.; Elsevier, C. J., Eds.; Wiley-VCH: Weinhein, **2007**; Vol. 1, p. 31-44.

339. Kallstrom, K.; Munslow, I.; Andersson, P. G. *Chemistry--A European Journal* **2006,** 12, 3194-3200.

340. Crabtree, R. H.; Morehouse, S. M. *Inorganic Chemistry* **1982,** 21, (12), 4210-4213.

341. Blackmond, D. G.; Lightfoot, A.; Pfaltz, A.; Rosner, T.; Schnider, P.; Zimmermann, N. *Chirality* **2000,** 12, 442-449.

342. Crabtree, R. H.; Felkin, H.; Morris, G. E. *Journal of Organometallic Chemistry* **1977,** 141, (2), 205-215.

343. Crabtree, R. *Accounts of Chemical Research* **1979,** 12, (9), 331-337.

344. (a) Chodosh, D. F.; Crabtree, R. H.; Felkin, H.; Morris, G. E. *Journal of Organometallic Chemistry* **1978,** 161, (3), C67-C70; (b) Chodosh, D. F.; Crabtree, R. H.; Felkin, H.; Morehouse, S.; Morris, G. E. *Inorganic Chemistry* **1982,** 21, (4), 1307-1311; (c) Smidt, S. P.; Pfaltz, A.; Martinez-Viviente, E.; Pregosin, P. S.; Albinati, A. *Organometallics* **2003,** 22, (5), 1000-1009.

345. Xu, Y.; Celik, M. A.; Thompson, A. L.; Cai, H.; Yurtsever, M.; Odell, B.; Green, J. C.; Mingos, D. M. P.; Brown, J. M. *Angewandte Chemie International Edition* **2008,** 48, (3), 582 - 585.

346. Nanchen, S.; Pfaltz, A. *Chemistry--A European Journal* **2006,** 12, (17), 4550-4558.

347. Vazquez-Serrano, L. D.; Owens, B. T.; Buriak, J. M. *Inorganica Chimica Acta* **2006,** 359, (9), 2786-2797.

348. Lightfoot, A.; Schnider, P.; Pfaltz, A. *Angewandte Chemie* **1998,** 37, (20), 2897-2899.

349. Morris, R. H., Ruthenium and Osmium. In *The Handbook of Homogeneous Hydrogenation*, ed.; de Vries, J. G.; Elsevier, C. J., Eds.; Wiley-VCH: Weinhein, **2007**; Vol. 1, p. 45-70.

350. Kawano, H.; Ikariya, T.; Ishii, Y.; Saburi, M.; Yoshikawa, S.; Uchida, Y.; Kumobayashi, H. *Journal of the Chemical Society, Perkin Transactions 1* **1989**, 1571-1575.

351. Halterman, R. L., Hydrogenation of Non-Functionalized Carbon-Carbon Double Bonds. In *Comprehensive Asymmetric catalysis I*, ed.; Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H., Eds.; Springer: Berlin, **1999**.

352. (a) Vassylyev, O.; Panarello, A.; Khinast, J. G. *Molecules* **2005,** 10, (6), 587-619; (b) Copéret, C., Hydrogenation with Early Transition Metal, Lanthanide and Actinide Complexes. In *The Handbook of Homogeneous Hydrogenation*, ed.; de Vries, J. G.; Elsevier, C. J., Eds.; Wiley-VCH: Weinhein, **2007**; Vol. 1, p. 111-151.

353. Bullock, R. M., Ionic Hydrogenations. In *The Handbook of Homogeneous Hydrogenation*, ed.; de Vries, A. H. M.; Elsevier, C. J., Eds.; Wiley-VCH: Winheim, **2007**; Vol. 1, p. 153-198.

354. (a) Blaser, H.-U.; Hoge, G.; Lotz, M.; Nettekoven, U.; Schnyder, A.; Spindler, F. *Chimia* **2008,** 62, (6), 476–481; (b) Boussie, T. R.; Diamond, G. M.; Goh, C.; Hall, K. A.; LaPointe, A. M.; Leclerc, M. K.; Murphy, V.; Shoemaker, J. A. W.; Turner, H.; Rosen, R. K.; Stevens, J. C.; Alfano, F.; Busico, V.; Cipullo, R.; Talarico, G. *Angewandte Chemie International Edition* **2006,** 45, (20), 3278-3283; (c) Busico, V. *Macromolecular Chemistry and Physics* **2007,** 208, (1), 26–29.

355. Pugin, B.; Blaser, H.-U., Catalyst Immobilization: Solid Supports. In *Comprehensive Asymmetric Catalysis*, ed.; Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H., Eds. Springer: Berlin, **1999**.

356. Blaser, H. U.; Schmidt, E., *Asymmetric Catalysis on Industrial Scale: Challenges, Approaches and Solutions*. ed.; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, **2004**.

357. Börner, A., *Phosphorus ligands in asymmetric catalysis: synthesis and applications*. ed.; Wiley-VCH: Weinheim, **2008**.

358. (a) Gennari, C.; Monti, C.; Piarulli, U. *Pure and Applied Chemistry* **2006,** 78, (2), 303-310; (b) Pena, D.; Minnaard, A. J.; de Vries, A. H. M.; de Vries, J. G.; Feringa, B. L. *Organic Letters* **2003,** 5, (4), 475-478.

359. Reetz, M. T., Mixtures of monodentate P-ligands in stereo- and regioselective transition metal catalysis. In *Phosphorus Ligands in Asymmetric Catalysis*, ed.; Börner, A., Ed.; Wiley-VCH: Weinheim, **2008**; p. 1133-1171.

360. Frolander, A.; Lutsenko, S.; Privalov, T.; Moberg, C. *Journal of organic chemistry* **2005,** 70, (24), 9882-9891.

361. Nanchen, S.; Pfaltz, A. *Helvetica Chimica Acta* **2006,** 89, (8), 1559-1573.

362. Nanchen, S. N-Heterocyclic Carbene Ligands for Iridium-Catalysed Asymmetric Hydrogenation (Dissertation), Basel (Switzerland), 2005

363. Bedford, R. B.; Chaloner, P. A.; Hitchcock, P. B.; Lopez, G.; Momblona, F.; Serrano, J. L. *Anales de Quimica International Edition* **1996,** 92, (6), 354-357.

364. Takaya, H.; Ohta, T.; Inoue, S.-i.; Tokunaga, M.; Kitamura, M.; Noyori, R. *Organic Syntheses* **1995,** 72, 74-85.

365. Xue, D.; Chen, Y.-C.; Cui, X.; Wang, Q.-W.; Zhu, J.; Deng, J.-G. *Journal of Organic Chemistry* **2005,** 70,, 3584-3591.

366. Merola, J. S.; Husebo, T. L.; Matthews, K. E.; Franks, M. A.; Pafford, R.; Chirik, P. *NATO ASI Series, Series 3: High Technology* **1995,** 5(Aqueous Organometallic Chemistry and Catalysis), 33-45; *Chem. Abstr.* **1996**, 124, 261321.

367. Kazakov, A. L.; Khilya, V. P.; Mezheritskii, V. V.; Yu. Litkei, *Natural and Modified Isoflavonoids [in Russian]*. ed.; Izdat. Rostovsk. Univ.: Rostov na Donu, **1985**; *Chem. Abstr.* **1986**, 105, 97238.

368. Chudgar, N. K.; Mani, N. V.; Sethna, S. *Journal of the Institution of Chemists (India)* **1967,** 39, (5), 203-208; *Chem. Abstr.* **1968**, 69, 77068.

369. (a) Gorbulenko, N. V.; Tkachuk, T. M.; Shokol, T. V.; Semeniuchenko, V. V.; Turov, A. V.; Khilya, V. P. *Chemistry of Heterocyclic Compounds* **2007,** 43, (5), 569-575; (b) Da Re, P.; Verlicchi, L. *Annali di Chimica* **1960,** 50, 1273-1279; *Chem. Abstr.* **1961**, 55, 48658; (c) Setnikar, I.; Murmann, W.; Magistretti, M. J.; Da Re, P.; Verlicchi, L. *Journal of Medicinal and Pharmaceutical Chemistry* **1961,** 3, (3), 471-488.

370. Shokol, T. V.; Semenyuchenko, V. V.; Khilya, V. P. *Ukrainskii Khimicheskii Zhurnal [in Russian]* **2007,** 73, (3-4), 105-107; *Chem. Abstr.* **2007**, 148, 54967.

371. Kim, K.-M.; Park, I.-H. *Synthesis* **2004,** 16, 2641-2644.

372. Zhao, P.-L.; Wu, Q.-Y.; Zhou, Z.-Z.; Yang, G.-F. *Youji Huaxue* **2006,** 26, (5), 694-697; *Chem. Abstr.* **2006**, 146, 295726.

373. Fitzmaurice, R. J.; Etheridge, Z. C.; Jumel, E.; Woolfson, D. N.; Caddick, S. *Chemical Communications* **2006,** 46, 4814-4816.

374. Merle, A.; Descotes, G. *Journal of Heterocyclic Chemistry* **1975,** 12, (5), 981-984.

375. Lisichkin, G. V., *Chemistry of surface grafted compounds [in Russian]*. ed.; Physmatlit: Moscow, **2003**.

376. Hartley, F. R., *Supported metal complexes: a new generation of catalysts*. ed.; Kluwer Academic Publishers: Dordrecht; Boston; Hingham, MA, U.S.A., **1985**.

377. (a) Jamis, J.; Anderson, J. R.; Dickson, R. S.; Campi, E. M.; Jackson, W. R. *Journal of Organometallic Chemistry* **2001,** 627, (1), 37-43; (b) Steiner, I.; Aufdenblatten, R.; Togni, A.; Blaser, H. U.; Pugin, B. *Tetrahedron: Asymmetry* **2004,** 15, (14), 2307-2311; (c) Bayston, D. J.; Fraser, J. L.; Ashton, M. R.; Baxter, A. D.; Polywka, M. E. C.; Moses, E.

Journal of Organic Chemistry **1998,** 63, (9), 3137-3140; (d) Aoki, K.; Shimada, T.; Hayashi, T. *Tetrahedron: Asymmetry* **2004,** 15, (11), 1771-1777; (e) Zsigmond, A.; Undrala, S.; Notheisz, F.; Szollosy, A.; Bakos, J. *Applied Catalysis A: General* **2006,** 303, 29-34; (f) Zsigmond, A.; Undrala, S.; Notheisz, F.; Papp, G.; Joâo, F. *Catalysis Letters* **2007,** 115, (3-4), 163-168; (g) Pugin, B. *Journal of Molecular Catalysis. A, Chemical* **1996,** 107, 273-279; (h) Pugin, B.; Landert, H.; Spindler, F.; Blaser, H.-U. *Advanced Synthesis & Catalysis* **2002,** 344, (9), 974-979.

378. Merckle, C.; Haubrich, S.; Blumel, J. *Journal of Organometallic Chemistry* **2001,** 627, (1), 44-54.

379. Hu, A.; Ngo, H. L.; Lin, W. *Angewandte Chemie* **2004,** 43, (19), 2555-2558.

380. Larsson, P.-O.; Glad, M.; Hansson, L.; Maansson, M.-O.; Ohlson, S.; Mosbach, K. *Advances in Chromatography* **1983,** 21, 41-85.

381. (a) Bayer, E.; Albert, K.; Reiners, J.; Nieder, M.; Müller, D. *Journal of Chromatography* **1983,** 264, 197-213; (b) Tuel, A.; Hommel, H.; Legrand, A. P.; Gonnord, M. F.; Mincsovics, E.; Siouffi, A. M. *Journal de Chimie Physique et de Physico-Chimie Biologique* **1992,** 89, 477-488.

382. Bogart, G. R.; Leyden, D. E.; Wade, T. M.; Schafer, W.; Carr, P. W. *Journal of Chromatography* **1989,** 483, 209-219.

383. Cory, D.; Wong, A.; Ritchey, W. M. *Journal of Organometallic Chemistry* **1982,** 235, (3), 277-285.

384. Sessler, J. L.; Sathiosatham, M.; Doerr, K.; Lynch, V.; Abboud, K. A. *Angewandte Chemie* **2000,** 112, (7), 1356-1359.

385. Rigolet, S.; McCort, I.; Merrer, Y. L. *Tetrahedron Letters* **2002,** 43, 8129-8132.

386. Talalaeva, T. V.; Kocheshkov, K. A. *Bulletin of the Academy of Sciences of the USSR* **1953**, 113-120.

387. (a) Zhang, K.; Schweizer, F. *Synlett* **2005**, (20), 3111-3115; (b) Ueberbacher, B. J.; Osprian, I.; Mayer, S. F.; Faber, K. *European Journal of Organic Chemistry* **2005**, (7), 1266–1270.

388. Farina, V.; Krishnan, B.; Marshall, D. R.; Roth, G. P. *Journal of Organic Chemistry* **1993,** 58, (20), 5434-5444.

389. Frasinyuk, M. S.; Khilya, V. P. *Chemistry of Heterocyclic Compounds* **1999,** 35, (1), 3-22.

390. (a) Shokol, T.; Semenyuchenko, V.; Khilya, V. *Chemistry of Heterocyclic Compounds* **2005,** 41, (5), 673-678; (b) Shokol, T.; Turov, V.; Semeniuchenko, V.; Krivokhizha, N.; Khilya, V. *Chemistry of Heterocyclic Compounds* **2006,** 42, (4), 500-505.

391. (a) Jiang, Z.; Sen, A. *Journal of the American Chemical Society* **1990,** 112, (26), 9655-9657; (b) Jiang, Z.; Sen, A. *Organometallics* **1993,** 12, (4), 1406-1415.

392. Munakata, M.; Yan, S.-G.; Maekawa, M.; Akiyama, M.; Kitagawa, S. *Dalton Transactions* **1997,** 1997, (22), 4257-4262.

393. Barsan, F.; Karam, A. R.; Parent, M. A.; Baird, M. C. *Macromolecules* **1998,** 31, (24), 8439-8447.

394. Jain, A. C.; Mehta, A. *Journal of the Chemical Society, Perkin Transactions 1* **1986,** 2, 215-220.

395. Aguiar, A. M.; Greenberg, H. J.; Rubenstein, K. E. *Journal of Organic Chemistry* **1963,** 28(8), 2091-2093.

396. Peer, M.; De Jong, J. C.; Kiefer, M.; Langer, T.; Rieck, H.; Schell, H.; Sennhenn, P.; Sprinz, J.; Steinhagen, H.; Wiese, B.; Helmchen, G. *Tetrahedron* **1996,** 52, (21), 7547-7583.

397. Sprinz, J.; Helmchen, G. *Tetrahedron letters* **1993,** 34, (11), 1769-1772.

398. Allen, J. V.; Dawson, G. J.; Frost, C. G.; Williams, I. M. J.; Coote, S. J. *Tetrahedron* **1994,** 50, (3), 799-808.

399. (a) Koch, G.; Lloyd-Jones, G. C.; Loiseleur, O.; Pfaltz, A.; Pretot, R.; Schaffner, S.; Schnider, P.; von Matt, P. *Recueil des travaux chimiques des Pays-Bas* **1995,** 114, (4/5), 206-210; (b) Zehnder, M.; Schaffner, S.; Neuburger, M.; Plattner, D. A. *Inorganica Chimica Acta* **2002,** 337, 287-298.

400. Tani, K.; Behenna, D. C.; McFadden, R. M.; Stoltz, B. M. *Organic Letters* **2007,** 9, (13), 2529-2531.

401. Frolander, A.; Lutsenko, S.; Privalov, T.; Moberg, C. *The Journal of Organic Chemistry* **2005,** 70, (24), 9882-9891.

402. Lightfoot, A.; Schnider, P.; Pfaltz, A. *Angewandte Chemie International Edition* **1998,** 37, (20), 2897-2899.

403. Ashby, E. C.; Gurumurthy, R.; Ridlehuber, R. W. *Journal of Organic Chemistry* **1993,** 58, (21), 5832-5837.

404. (a) Ushakov, N. V.; Vdovin, V. M.; Pozdnyakova, M. V.; Pritula, N. A. *Russian chemical bulletin* **1983,** 32, (9), 1920-1923; (b) Garner, A. Y.; Tedeschi, A. A. *Journal of the American Chemical Society* **1962,** 84, 4734-4737; (c) Kirby, A. J.; Warren, S. G., *The organic chemistry of phosphorus*. ed.; Elsevier Pub. Co.: Amsterdam, London, New York; **1967**.

405. Howell, J. A. S.; Fey, N.; Lovatt, J. D.; Yates, P. C.; McArdle, P.; Cunningham, D.; Sadeh, E.; Gottlieb, H. E.; Goldschmidt, Z.; Hursthouse, M. B.; Light, M. E. *Journal of the Chemical Society, Dalton Transactions* **1999,** 17, 3015–3028.

406. van den Broeke, J.; de Wolf, E.; Deelman, B.-J.; van Koten, G. *Advanced Synthesis & Catalysis* **2003,** 345, (5), 625-634.

407. Wang, H. H.; Pignolet, L. H. *Inorganic Chemistry* **1980,** 19, (6), 1470-1480.

408. Vázquez-Serrano, L. D.; Owens, B. T.; Buriak, J. M. *Chemical Communications* **2002,** 2002, (21), 2518–2519.

409. (a) Wolf, J.; Labande, A.; Daran, J.-C.; Poli, R. *Journal of Organometallic Chemistry* **2006,** 691, (3), 433-443; (b) Field, L. D.; Messerle, B. A.; Vuong, K. Q.; Turner, P. *Organometallics* **2005,** 24, (17), 4241-4250; (c) Hahn, F. E.; C., J. M.; Pape, T. *Organometallics* **2006,** 25, (25), 5927-5936; (d) Lee, H. M.; Zeng, J. Y.; Hu, C. H.; Lee, M. T. *Inorganic Chemistry* **2004,** 43, (21), 6822-6829; (e) Lee, H. M.; Chiu, P. L.; Zeng, J. *Inorganica Chimica Acta* **2004,** 357, (14), 4313-4321.

410. Herrmann, W. A.; Goossen, L. J.; Spiegler, M. *Organometallics* **1998,** 17, (11), 2162-2168.

411. (a) Catalano, V. J.; Moore, A. L. *Inorganic Chemistry* **2005,** 44, (19), 6558-6566; (b) Wang, H. M. J. L., Ivan J. B. *Organometallics* **1998,** 17, (5), 972-975.

412. Sosnovskikh, V. Y.; Irgashev, R. A.; Barabanov, M. A. *Synthesis* **2006**, (16), 2707-2718.

413. Sosnovskikh, V. Y.; Irgashev, R. A. *Synlett* **2005**, (7), 1164-1166.

414. Yokoe, I.; Maruyama, K.; Sugita, Y.; Harashida, T.; Shirataki, Y. *Chemical Pharmaceutical Bulletin* **1994,** 42, (8), 1697-1699.

415. Meza, R.; Gordillo, B.; Galvan, M. *International Journal of Quantum Chemistry* **2005,** 104, (1), 29-37.

416. Parr, R. G.; Yang, W., *Density-functional theory of atoms and molecules*. ed.; Oxford University Press; Clarendon Press: New York, Oxford [England]; **1989**.

417. (a) Becke, A. D. *Journal of Chemical Physics* **1993,** 98, 1372-1377; (b) Becke, A. D. *Journal of Chemical Physics* **1993,** 98, 5648-5652; (c) Lee, C.; Yang, W.; Parr, R. G. *Physical Review B* **1988,** 37, 785-789.

418. (a) Staunton, J., α -Pyrones and coumarins. In *Comprehensive organic chemistry: the synthesis and reactions of organic compounds*, ed.; Sammes, P. G., Ed.; Pergamon Press: Oxford [u.a.], **1979**; Vol. 4. Heterocyclic compounds; (b) Castaneda, F.; Marini-Bettolo, G. B. *Rendiconti Istituto Superiore di Sanita (Italian Edition)* **1964,** 27, (1-2), 94-98; *Chem. Abstr.* **1965**, 62, 8924; (c) Chiodoni, V. *Chimica e l'Industria (Milan, Italy)* **1963,** 45, (8), 968-970; *Chem. Abstr.* **1964**, 60, 60622; (d) Magliona, F. C.; Marini-Bettolo, G. B. *Gazzetta Chimica Italiana* **1963,** 93, (4), 345-348; (e) Marini-Bettolo, G. B.; Casinovi, C. G.; d' Alburquerque, I. L. *Gazzetta Chimica Italiana* **1964,** 94, (3-4), 366-371; (f) Papini, P.; Checchi, S.; Ridi, M. *Gazzetta Chimica Italiana* **1954,** 84, 769-780.

419. Nawrot-Modranka, J.; Kostka, K. *Polish Journal of Chemistry* **1988,** 62, (4-6), 417-426; *Chem. Abstr.* **1989**, 111, 194660.

420. Kostka, K.; Nawrot-Modranka, J. *Polish Journal of Chemistry* **1982,** 56, (10-12), 1341-1348; *Chem. Abstr.* 1984, 101, 23276.

421. Nawrot-Modranka, J.; Kostka, K. *Polish Journal of Chemistry* **1989,** 63, (1-3), 103-111; *Chem. Abstr.* **1990**, 112, 178782.

422. Pinto, D. C. G. A.; Silva, A. M. S.; Cavaleiro, J. A. S. *Journal of Heterocyclic Chemistry* **2000,** 37, (6), 1629-1634.

423. Maib, P.; Jerzmanowska, Z. *Polish Journal of Chemistry* **1987,** 61, (1-3), 111-122; *Chem. Abstr.* **1989**, 110, 57563.

424. Iwai, T.; Fujihara, T.; Tsuji, Y. *Chemical Communications* **2008**, 6215 - 6217.

425. (a) Sievers, R. E. US3700410, **1972**; *Chem., Abstr.*, **1973**, 78, 36143; (b) Wenzel, T. J. C., Jessica M., Europium, tris {1,7,7-trimethyl-3-(trifluoroacetyl-kO)bicyclo[2.2.1]heptan-2-onato-kO}. In *e-EROS Encyclopedia of Reagents for Organic Synthesis*, ed.; John Wiley & Sons, Ltd.: Chichester, **2001**; DOI: 10.1002/047084289X.rn00451; *Chem. Abstr.* **2008**, 149, 267255 p.

426. Raj, D. B. A.; Biju, S.; Reddy, M. L. P. *Inorganic Chemistry* **2008,** 47, (18), 8091-8100.

427. Skouta, R.; Li, C.-J. *Angewandte Chemie, International Edition* **2007,** 46, (7), 1117-119.

428. (a) Yanagisawa, A.; Touge, T.; Arai, T. *Angewandte Chemie, International Edition* **2005,** 44, (10), 1546-1548; (b) Yanagisawa, A.; Touge, T.; Arai, T. *Pure and Applied Chemistry* **2006,** 78, (2), 519-523; (c) Asensio, G.; Cuenca, A.; Rodriguez, N.; Medio-Simon, M. *Tetrahedron: Asymmetry* **2003,** 14, (24), 3851-3855; (d) Matsukawa, S.; Imamoto, T. *Journal of the American Chemical Society* **2000,** 122, (51), 12659-12662; (e) Yanagisawa, A.; Yamamoto, H., Protonation of Enolates. In *Comprehensive Asymmetric Catalysis I-III*, ed.; Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H., Eds. Springer: Berlin, **1999**.

429. (a) Nakamura, Y.; Takeuchi, S.; Ohgo, Y.; Yamaoka, M. *Tetrahedron letters* **1997,** 38, (15), 2709-2712; (b) Mikami, K.; Yamaoka, M.; Yoshida, A.; Nakamura, Y.; Takeuchi, S.; Ohgo, Y. *Synlett* **1998**, (6), 607-608.

430. Kandula, S. V.; Puranik, V. G.; Kumar, P. *Tetrahedron Letters* **2003,** 44, (27), 5015-5017.

431. Albrecht, U.; Gordes, D.; Schmidt, E.; Thurow, K.; Lalk, M.; Langer, P. *Bioorganic & Medicinal Chemistry* **2005,** 13, (14), 6.

432. Neugebauer, R. C.; Uchiechowska, U.; Meier, R.; Hruby, H.; Valkov, V.; Verdin, E.; Sippl, W.; Jung, M. *Journal of Medicinal Chemistry* **2008,** 51, (5), 1203-1213.

433. Angloher, S.; Bein, T. *Journal of Materials Chemistry* **2006,** 16, (36), 3623-3634.

434. Bennett, M. A.; Smith, A. K. *Journal of the Chemical Society, Dalton Transactions* **1974,** 2, 233-241.

435. Reger, D. L.; Little, C. A.; Lamba, J. J. S.; Brown, K. J.; Krumper, J. R.; Bergman, R. G.; Irwin, M.; Fackler, J. P. *Inorganic Syntheses* **2004,** 34, 5-8.

436. Rao, P. P.; Srimannarayana, G. *Synthesis* **1981**, (11), 887-888.

437. Hoshino, Y. M., Norio; Suzuki, Akira. *Bulletin of the Chemical Society of Japan* **1988,** 61, (8), 3008-3010.

438. Shokol, T.; Turov, V.; Turov, A.; Krivokhizha, N.; Semenyuchenko, V.; Khilya, V. *Chemistry of Heterocyclic Compounds* **2005,** 41, (11), 1411-1418.

439. Balasubramanian, S.; Nair, M. G. *Synthetic Communications* **2000,** 30, (3), 469-484.

440. Tang, L.; Zhang, S.; Yang, J.; Gao, W.; Cui, J. *Organic Preparations and Procedures International* **2004,** 36, (5), 453-457.

441. Zhou, Z.; Zhao, P.; Huang, W.; Yang, G. *Advanced Synthesis & Catalysis* **2006,** 348, (1-2), 63-67.

442. Kamat, S. P.; Paknikar, S. K.; Beauchamp, P. S. *Journal of Chemical Research, Synopses* **2002**, (5), 242-246.

443. (a) Kotani, M.; Yamamoto, K.; Oyamada, J.; Fujiwara, Y.; Kitamura, T. *Synthesis* **2004,** 9, 1466-1470; (b) Ahluwalia, V. K.; Singh, D.; Singh, R. P. *Monatshefte fuer Chemie* **1985,** 116, (6-7), 869-872.

444. Mineno, T.; Stanford, K. M.; Walker, L. A.; Avery, M. A. *Combinatorial Chemistry and High Throughput Screening* **2002,** 5, (6), 481-487.

445. Fehr, M. J.; Consiglio, G.; Scalone, M.; Schmid, R. *Journal of Organic Chemistry* **1999**, 64, (16), 9.

446. Jain, A. C.; Tyagi, O. D.; Saksena, R. *Indian Journal of Chemistry* **1989,** 28B, (8), 678-679.

447. Kövér, K. E.; Borbély, J. *Magnetic Resonance in Chemistry* **1985,** 23, (2), 90-94.

448. Grdadolnik, J. *Acta Chimica Slovenica* **2002,** 49, 631-642.

449. Benac, B. L.; Burgess, E. M.; Arduengo, A. J., III. *Organic Syntheses* **1986,** 64, 92-95.

450. Saba, S.; Brescia, A.; Kaloustian, M. K. *Tetrahedron Letters* **1991,** 32, (38), 5031-5034.

451. Wittenberg, D.; Gilman, H. *Journal of Organic Chemistry* **1958,** 23, 1063-1065.

452. Busacca, C. A.; Lorenz, J. C.; Grinberg, N.; Haddad, N.; Hrapchak, M.; Latli, B.; Lee, H.; Sabila, P.; Saha, A.; Sarvestani, M.; Shen, S.; Varsolona, R.; Wei, X.; Senanayake, C. H. *Organic Letters* **2005,** 7, (19), 4277-4280.

453. Sudo, A.; Saigo, K. *Tetrahedron: Asymmetry* **1996,** 7, (10), 2939-2956.

454. Cava, M. P.; Litle, R. L.; Napier, D. R. *Journal of American Chemical Society* **1958,** 80, 2257-2263.

455. Sudo, A.; Saigo, K. *Journal of organic chemistry* **1997,** 62, (16), 6.

456. Kainz, S.; Brinkmann, A.; Leitner, W.; Pfaltz, A. *Journal of the American Chemical Society* **1999,** 121, (27), 6421-6429.

457. Schnider, P.; Koch, G.; Pretot, R.; Wang, G.; Bohnen, F. M.; Krüger, C.; Pfaltz, A. *Chemistry--A European Journal* **1997,** 3, (6), 887-892.

458. Langer, J.; Gorls, H.; Gillies, G.; Walther, D. *Zeitschrift für Anorganische und Allgemeine Chemie* **2005,** 631, (13), 2719-2726.

459. Chambers, R. D.; Holling, D.; Sandford, G.; Batsanov, A. S.; Howard, J. A. K. *Journal of Fluorine Chemistry* **2004,** 125, (5), 661-671.

460. Wehman, P.; Donge, H. M. A. V.; Hagos, A.; Kamer, P. C. J.; Leeuwen, P. W. N. M. V. *Journal of Organometallic Chemistry* **1997,** 535, (1-2), 183-193.

461. Kownacki, I.; Kubicki, M.; Marciniec, B. *Inorganica Chimica Acta* **2002,** 334, (1), 301-307.

462. Rifat, A.; Kociok-Kohn, G.; Steed, J. W.; Weller, A. S. *Organometallics* **2004,** 23, (3), 428-432.

463. Gan, X.; Binyamin, I.; Rapko, B. M.; Fox, J.; Duesler, E. N.; Paine, R. T. *Inorganic Chemistry* **2004,** 43, (7), 2443-2448.

464. Tilset, M.; Andell, O.; Dhindsa, A.; Froseth, M. WO2002049758, **2002**; *Chem. Abstr.* **2002**, 137, 63615

465. Mas-Marza, E.; Sanau, M.; Peris, E. *Inorganic Chemistry* **2005,** 44, (26), 9961-9967.

466. Pande, A.; Ganesan, K.; Jain, A. K.; Gupta, P. K.; Malhotra, R. C. *Organic Process Research & Development* **2005,** 9, (2), 133-136.

467. Prajapati, D.; Lekhok, K. C.; Sandhu, J. S.; Ghosh, A. C. *Journal of the Chemical Society, Perkin Transactions 1* **1996**, (9), 959-960.

468. Texier-Boullet, F.; Foucaud, A. *Tetrahedron Letters* **1982,** 23, (47), 4927-4928.

469. Shimazaki, M.; Huang, Z. H.; Goto, M.; Suzuki, N.; Ohta, A. *Synthesis* **1990**, (8), 677-678.

470. Felpin, F. X. *Journal of Organic Chemistry* **2005,** 70, (21), 8575-8578.

471. Ferlin, M. G.; Di Marco, V. B.; Dean, A. *Tetrahedron* **2006,** 62, (26), 6222-6227.

472. Krafft, M. E.; Cran, J. W. *Synlett* **2005**, (8), 1263-1266.

473. Bolos, J.; Gubert, S.; Anglada, L.; Planas, J. M.; Burgarolas, C.; Castello, J. M.; Sacristan, A.; Ortiz, J. A. *Journal of Medicinal Chemistry* **1996,** 39, (15), 2962-2970.

474. Wu, E. S. C.; Loch, J. T., III; Toder, B. H.; Borrelli, A. R.; Gawlak, D. *Journal of Medicinal Chemistry* **1992,** 35, (19), 3519-3525.

475. Shepherd, R. G.; White, A. C. *Journal of the Chemical Society, Perkin Transactions 1* **1987**, (10), 2153-2155.

476. Song, Y. S.; Kim, B. T.; Heo, J. N. *Tetrahedron Letters* **2005,** 46, (36), 5987-5990.

477. Yu, D.; Chen, C. H.; Brossi, A.; Lee, K. H. *Journal of Medicinal Chemistry* **2004,** 47, (16), 4072-4082.

478. Kharrat, S. E.; Kharrat, R. E.; Laurent, P.; Blancou, H. *Synthesis* **2007**, (22), 3542-3552.

479. Kuniyasu, H.; Yamashita, F.; Hirai, T.; Ye, J.-H.; Fujiwara, S.-i.; Kambe, N. *Organometallics* **2006,** 25, (3), 566-570.

480. HyperChem(TM) Professional 7.51, Hypercube, Inc., 1115 NW 4th Street, Gainesville, Florida 32601, USA

481. GaussView, Version 3.0, Dennington II, R.; Keith, T.; Millam, J.; Eppinnett, K.; Hovell, W. L.; Gilliland, R.; Semichem, Inc., Shawnee Mission, KS, 2003.

482. Gaussian 03, Revision C.02, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery, Jr., T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez, and J. A. Pople, Gaussian, Inc., Wallingford CT, 2004.

483. Khilya, V. P.; Kupchevskaya, I. P.; Salikhova, A. I.; Grishko, L. G.; Babichev, F. S.; Kirillova, L. G. *Chemistry of Heterocyclic Compounds* **1977,** 13, (9), 948-953.