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Chromium(II)-Catalyzed Diastereoselective Pinacol Type Cross Coupling between α,β-Unsaturated Carbonyl Compounds and Aliphatic Aldehydes

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Abstract: Using only 10 mol% of $CrCl_2$ as catalyst, acroleins and α,β-unsaturated ketones were coupled with aliphatic aldehydes to obtain substituted 1,2-diols using manganese powder as reducing agent and TMS-Cl as scavenger. Diastereoselectivities depend on the substituents especially on R^1 of the unsaturated carbonyl compound. Formation of the *syn*-diols is preferred with sterically demanding R^1, the *anti*-diols are obtained with smaller substituents.

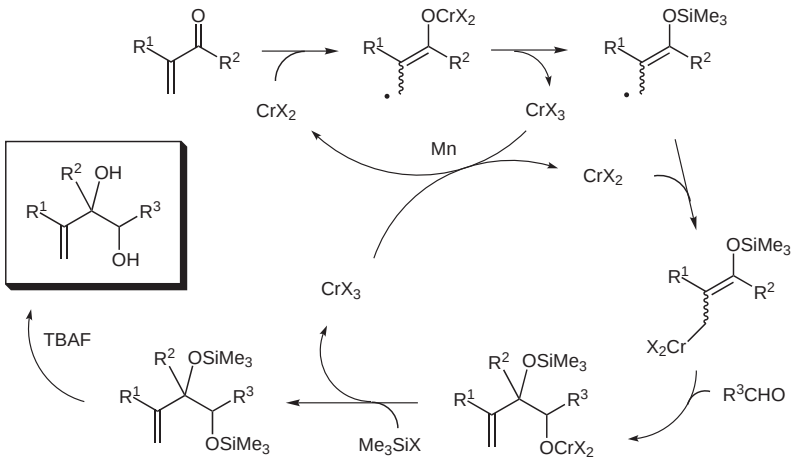
Key words: chromium, catalysis, cross-coupling, pinacols, C–C coupling

The reductive coupling of carbonyl compounds to 1,2-diols plays an important role in natural product synthesis.[1] For economic and ecological reasons catalytic pinacol couplings are of special interest. The catalytic methods described in the literature[2] afford diols in good yields. Unfortunately, most of these methods proceed with low diastereoselectivities or are limited to aromatic or α,β-unsaturated aldehydes. Until now, only cerium-catalyzed pinacol couplings of aliphatic, aromatic and α,β-unsaturated aldehydes furnish *rac*-diols with high diastereoselectivities. All methods reported so far are limited to the homo coupling of aldehydes affording symmetrically substituted 1,2-diols.

In this communication we wish to report the first transition metal-catalyzed cross coupling of aldehydes with α,β-unsaturated carbonyl compounds. Recently, Takai and coworkers[3] reported the pinacol type cross coupling between α,β-unsaturated ketones and aliphatic aldehydes using an excess of 4 equivalents of chromium(II) chloride.[4] A catalytic reaction[5] in the presence of manganese powder was also attempted. Thus, with 40 mol% of chromium(II) chloride and an excess of manganese powder the product of the cross coupling of nonanal with 5-phenyl-1-penten-3-one afforded a mixture of diastereomeric diols in 42% yield with a diastereoselectivity of 40% d.e.[3]

We have now observed, that the couplings of vinyl ketones with aliphatic aldehydes proceed with only 10 mol% of chromium(II) chloride affording the desired pinacols in up to 80% yield and with up to > 95% d.e. diastereoselectivity (Scheme 2) when reaction times were extended and the aldehydes were added very slowly to the reaction mixture containing the α,β-unsaturated ketones, manganese powder and trimethylsilyl chloride in DMF.[5] Shorter reaction times lead to a decrease in yields but same diastereoselectivities.

A postulated catalytic cycle, based on the work of Fürstner[5] and Takai[3] is shown in Scheme 1.

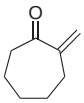
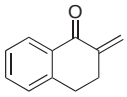
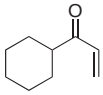


Scheme 1 Postulated catalytic cycle.

Instead of the air and moisture sensitive chromium(II) chloride the more stable chromium(III) chloride can be used as well without any decrease in yield and diastereoselectivity.

The results of the reductive cross couplings are summarized in Table 1.

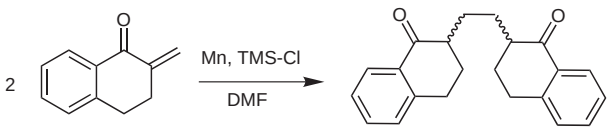
Table 1 Results of the Cr-Catalyzed Pinacol Cross Coupling Between α,β-Unsaturated Ketones and Aldehydes

Entry	Enone	R^3	Yield [%][a]	*syn*/*anti*[b]
1		$Ph(CH_2)_2$	80	> 98:2
2		$PhCH_2$	58	> 98:2
3		Et	66	> 98:2
4		Et	51	> 98:2
5		$Ph(CH_2)_2$	56	77:23

[a] Yields refer to isolated products.
[b] Diastereomeric ratios were determined by isolation and/or NMR-spectroscopy.

The cyclic vinyl ketones (Table 1, entries 1–4) could be coupled in satisfactory yields, which depend on the substituent R^3 of the aldehyde. Diastereoselectivities were generally very high for the reactions, which proceed via 6-membered transition states.[6] For the cross coupling of 2-methylene-1-tetralone with propionaldehyde (Table 1, entry 4) the procedure had to be inverted in order to prevent the side reaction shown in Scheme 2. So, the tetralone was added slowly to the reaction. Corresponding side reactions were observed for most vinyl ketones. However, except for 2-methylene-1-tetralone, these homo couplings never exceeded 5%. On the other hand, in the absence of chromium chloride the homo coupling (Scheme 3) became the main reaction.

We observed that the substitution pattern of the C=C double bond is crucial for the outcome of the cross coupling reaction. β-Substituted vinyl ketones gave low yields or did not react at all. For example, 2-cyclopentenone and 3-phenylpropanal were coupled to the corresponding pinacol in only 15% yield but still with a diastereoselectivity of > 95% d.e. No reaction was observed for the β,β-disubstituted vinyl ketone pulegone.



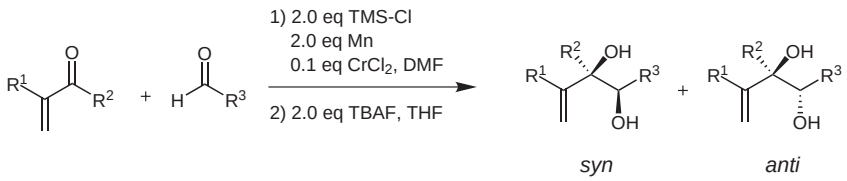
Scheme 3 Homo coupling of a vinyl ketone as side reaction.

Aromatic aldehydes could also be coupled with vinyl ketones but under the reaction conditions homo pinacol coupling gained in importance[2d] and yields of the cross coupling products decreased to 25%.

The pinacols obtained by couplings of vinyl ketones with aldehydes contain one tertiary alcohol function. Although there are only few methods known for the diastereoselective preparation of such compounds, pinacols with two secondary alcoholic groups would be more useful for the syntheses of natural products. We have now found that our chromium-catalyzed pinacol cross coupling proceeds equally well with vinyl ketones as with substituted acroleins.[7]

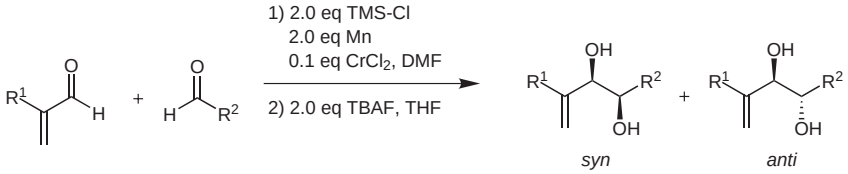
Cr(II)-catalyzed couplings of acrolein acetals and 2-methylacrolein acetals with aldehydes have been reported by Boeckman and coworkers[8] while Takai and coworkers[9] used stoichiometric amounts of Cr(II). In both cases only acrolein acetal and 2-methylacrolein acetal were coupled with different aldehydes to obtain the corresponding diol-monoalkylethers. Under our conditions acroleins with different sterically demanding substituted and free carbonyl groups are tolerated (Table 2) to obtain the free pinacols after treatment with TBAF.

For those substrates the procedure[10] had to be altered. We were able to couple different acroleins with aliphatic aldehydes in good yields when the acroleins were added slowly to the reaction mixture in order to prevent homo pinacol coupling. The diastereomeric excess seems to depend on the substituents especially of the acrolein. Acroleins with bulky substituents R^1 furnished mainly *syn*-diols with high diastereomeric excess (Table 2, entries 1–3), while smaller substituents R^1 gave mixtures of *syn* and *anti* products (Table 2, entries 4–7). For R^1 = ethyl (Table 2, entry 5) no diastereoselectivity was observed while the *anti* products prevailed for the small substituents R^1 = CH_3 and H (Table 2, entries 6 and 7). This change of product configuration from *syn* to *anti* is likely to be a consequence of the preferred conformation of the 6-membered transition state of the cross coupling reaction.[6]



Scheme 2 Cr-catalyzed pinacol cross coupling between α,β-unsaturated ketones and aldehydes.

Table 2 Results of the Cr-Catalyzed Pinacol Cross Coupling Between 2-Substituted Acroleins and Aliphatic Aldehydes.



Entry	R^1	R^2	Yield (%)[a]	*syn*/*anti*[b]
1	*t*-Bu	*t*-Bu	61	> 98:2
2	*t*-Bu	Et	69	93:7
3	*t*-Bu	$Ph(CH_2)_2$	73	86:14
4	*i*-Pr	*t*-Bu	68	92:8
5	Et	*t*-Bu	75	50:50
6	Me	*t*-Bu	54	28:72
7	H	*t*-Bu	52	22:78

[a] Yields refer to isolated products.
[b] Diastereomeric ratios were determined by isolation and/or NMR-spectroscopy.

Cozzi, Umani-Ronchi and coworkers reported the use of Cr(salen) to catalyze an asymmetric Nozaki–Hiyama reaction.[11] We have also tried Cr(salen)Cl[12] as catalyst for our cross coupling reaction but yields were not satisfactory. Now, we are testing other chelating ligand systems to achieve an enantioselective catalytic reaction.

Asymmetric pinacol cross couplings using chiral chromium complexes as catalysts as well as intramolecular ring closure pinacol couplings aiming at the total syntheses of a variety of natural products as well as the introduction of heteroatoms are presently under investigation in our group.

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(10) **Typical Procedure**: Reactions were carried out under an argon atmosphere using Schlenk techniques. The chromium catalysts and the manganese powder were stored in a glove box under nitrogen atmosphere. In a Schlenk tube 8 mL of DMF and 0.51 mL of TMS-Cl (4 mmol) were added to 220 mg (4 mmol) of Mn powder and 25 mg (0.2 mmol) of $CrCl_2$. The resulting suspension was stirred at room temperature for 15 min, 2 mmol of the less reactive coupling component [the vinylketones for reactions as shown in Table 1 except for 2-methylene-1-tetralone (Table 1, entry 4); the aliphatic aldehydes in the cases of coupling reactions with acroleins

(Table 2) or 2-methylidene-1-tetralone (Table 1, entry 4)] was added in one portion. 2 mL of a 0.5 M solution of the second coupling component (1 mmol) was added slowly over a period of 40 hours by use of a syringe pump. 20 mL of ether and 20 mL of water were added. After separation of the organic layer, the aqueous layer was extracted with diethyl ether (3 × 20 mL), the combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. To the residue 10 mL of THF and 1.4 g (4 mmol, 2 equiv) of TBAF were added and stirred for 45 min at room temperature. After adding 10 mL of water and 20 mL of ether the aqueous layer was extracted with ether (4 × 20 mL), the combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash chromatography on 25 g of silica gel (petroleum ether–ethyl acetate, 9:1). The relative configuration was determined by either NOE spectroscopy of the corresponding acetonides or by Corey–Winter-reaction followed by NMR examination of the resulting olefins.

Table 1, entry 1: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.14 (m, 5 H), 5.11 (s, 1 H), 5.04 (s, 1 H), 3.34 (m, 1 H), 2.87 (m, 1 H), 2.55 (m, 1 H), 2.28 (m, 2 H), 1.84–1.11 (m, 12 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 155.3, 142.2, 128.4, 128.3, 125.7, 113.8, 80.1, 75.7, 34.8, 34.5, 32.5, 31.5, 30.9, 23.0; Anal. calcd for $C_{17}H_{24}O_2$: C, 78.42; H, 9.29; O, 12.29. Found: C, 78.22; H, 9.15.

Table 2, entry 1: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.32 (s, 1 H), 5.12 (s, 1 H), 4.48 (s, 1 H), 3.20 (s, 1 H), 2.55 (br s, 1 H), 2.06 (bs, 1 H), 1.12 (s, 9 H), 1.00 (s, 9 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 160.8, 109.0, 79.2, 67.0, 35.8, 35.7, 29.4, 26.6. Anal. calcd for $C_{12}H_{24}O_2$: C, 71.95; H, 12.08; O, 15.97. Found: C, 72.03; H, 11.98.

Table 2, entry 2, *syn*-diol: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.14 (s, 1 H), 5.11 (s, 1 H), 3.98 (d, *J* = 6.6 Hz, 1 H), 3.56 (m, 1 H), 2.66 (bs, 2 H), 1.55 (m, 1 H), 1.37 (m, 1 H), 1.10 (s, 9 H), 1.00 (t, *J* = 7.4 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 158.6, 109.6, 75.4, 72.3, 35.7, 29.0, 26.0, 10.6. Anal. calcd for $C_{10}H_{20}O_2$ (mixture of *syn* and *anti*, not separable by column chromatography): C, 69.72; H, 11.70; O, 18.58. Found: C, 69.60, H, 11.76. ***anti*-diol**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.27 (s, 1 H), 5.21 (s, 1 H), 4.14 (d, *J* = 6.2 Hz, 1 H), 3.61 (m, 1 H), 2.66 (br s, 2 H), 1.81 (m, 1 H), 1.22 (m, 1 H), 1.11 (s, 9 H), 1.02 (t, *J* = 7.4 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.1, 109.7, 75.1, 72.6, 35.7, 29.1, 24.3, 10.3.

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