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Catalytic Regioselective Benzoylation of 1,2-*trans*-Diols in Carbohydrates with Benzoyl Cyanide: The Axial Oxy Group Effect and the Action of Achiral and Chiral Amine Catalysts

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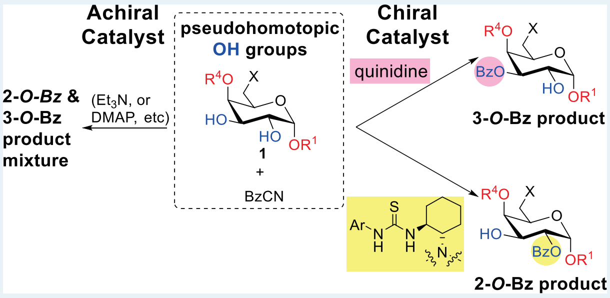


ABSTRACT: Regioselective protection of the polyfunctional carbohydrates with acyl groups under catalytic conditions is a prerequisite for efficient structural modification and chain extension via glycosidation. A general and also strong "axial oxy group effect" was now observed with benzoyl cyanide as the acylating agent and 4-dimethylaminopyridine as the catalyst, permitting the preferred *O*-acylation of equatorial hydroxy groups next to axial oxy groups. This effect is substantiated with 2,3-*O*-unprotected *β*-D-galacto- and *α*-D-glucopyranosides and 3,4-*O*-unprotected mannopyranosides possessing vicinal *trans*-diol moieties. Moreover, vicinal *trans*-diols with axial oxy groups next to each hydroxy group, possessing expectedly comparable reactivity, could be differentiated with chiral tertiary amine catalysts. Particularly interesting in this regard is the action of bifunctional (*S*,*S*)-*N*-(*N*,*N*-dialkylaminocyclohexyl)-thioureas as catalysts; they favor 2-*O*-benzoylation of 2,3-*O*-unprotected *α*-galactopyranosides, as is also supported by density functional theory calculations. This directing effect can be reversed with quinidine as the catalyst or with bulky substituents at the anomeric position.

KEYWORDS: *chiral catalyst, bifunctional thiourea catalysis, regioselective acylation, carbohydrates, vicinal trans-diols*

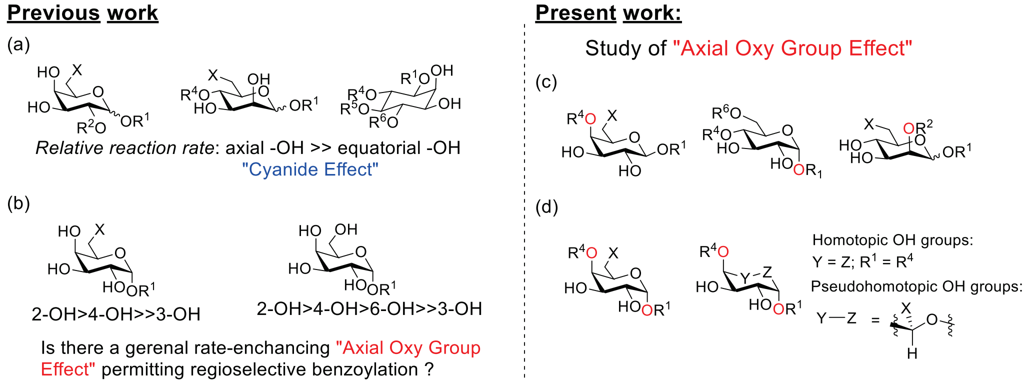
■ INTRODUCTION

Site-selective reactions at multifunctional substrates require masking of undesired reaction sites. In enzyme-catalyzed reactions, this masking is provided by suitable placement of the substrate in the active site and in chemical reactions generally by the attachment of protecting groups. When the protection can be reached regioselectively through an efficient catalytic procedure in a minimum of synthetic steps, the chemical procedure is at least competitive or even superior, as enzyme catalysis requires the availability of complex, mostly precious proteins that often possess a narrow substrate scope.

Regioselective *O*-acylation of the hydroxy groups of the polyfunctional carbohydrates plays an important role as it could directly afford desired intermediates for structural modification as well as building blocks for oligosaccharide assembly in glycosylation reactions.[1−6] To simplify this task, numerous efforts have been undertaken in the past decades.[2,7−9] Yet, understanding the distinctness of each hydroxy group of carbohydrates and of the different acylating agents should permit the development of desirable efficient methods for direct regioselective functional group modification. This way, reliable general rules for regioselective protection applicable to any structurally related substrate should become available.

As 6-*O*-protected and 4,6-*O*-protected glycopyranosides are commonly available from the parent compounds in convenient one- or two-step procedures, the regioselectivity issue necessitates, above all, the differentiation of diols with 1,2-*cis* or 1,2-*trans* stereostructures and of triols with corresponding consecutive diol stereostructures (Scheme 1). For acylation, common acyl halides or anhydrides and equivalent amounts of a base for the neutralization of the leaving group are employed.[10] However, such procedures are neither sustainable nor applicable to expensive chiral bases. Therefore, we studied benzoyl cyanide (**BzCN**) that is a strong acylating agent, and it reacts even at temperatures as low as −78 °C, thus permitting eventually kinetic reaction control (and avoiding the catalysis of acyl migration during the reaction course). These properties

Scheme 1. ***cis*-Diol, *trans*-Diol, *cis*–*trans*-Triol, and -Tetrol Moieties in Glycopyranosides and Their Regioselective Benzoylation with BzCN; (a) Vicinal *cis*-Diols ($R^n \neq H$, $n = 1–6$; X = OR^6, H); (b) *cis*–*trans*-Triols, *cis*–*trans*-Tetrols (R^1, $R^6 \neq H$; X = OR^6, H); (c) Vicinal *trans*-Diols with One Axial Oxy Group; (d) Vicinal *trans*-Diols with Two Axial Oxy Groups**



are due to the fact that the cyanide leaving group is a sterically nondemanding and quite strong base in organic solvents (dimethyl sulfoxide: pK_a about 12.9,[11] which is in the range of ammonium salts). Yet, the cyanide group is also a strong hydrogen-bond acceptor and the resulting hydrogen cyanide is a hydrogen-bond donor. Thus, benzoylation is catalyzed in a dual way: (i) via hydrogen bonding of hydrogen cyanide to the **BzCN** nitrogen and (ii) via hydrogen bonding of the released cyanide to the hydroxy group of the substrate (or to a proton of the catalyst with following substrate deprotonation; see below), this way regenerating the hydrogen cyanide and providing a reactive oxide species as the acyl group acceptor. Hence, only catalytic amounts of the amine base for the generation of a presumed reactive *N*-acyl-ammonium intermediate are required for this process.

Though **BzCN** has been already used for partial acylation of carbohydrates,[12−17] the role of the released cyanide and regenerated hydrogen cyanide on regioselective *O*-benzoylation and particularly of 1,2-*cis*-diols did not attract any attention. Recently, we found that **BzCN** in the presence of catalytic amounts of 4-dimethylaminopyridine (DMAP) gives at low temperatures preferentially axial hydroxy group benzoylation of 1,2-*cis*-diols.[18] This valuable result is due to a "cyanide effect" that is based on dual hydrogen bonding to the axial oxygen, thus supporting the formation of the thermodynamically less favored product in 1,2-*cis*-diol moieties of galacto-, fuco-, manno-, and rhamnopyranosides and inositols (Scheme 1a). Extension of these studies to *cis*–*trans*-triols and -tetrols, as present in *α*-galactopyranosides (see Scheme 1b), led to the observation that the equatorial hydroxy group vicinal to an axial oxy group is by far the most reactive hydroxy group.[19] This "axial oxy group effect" is caused by the accumulation of lone pair orbitals of the *cis*-oriented oxygens, thus leading to increased nucleophilicity of the vicinal hydroxy group. This effect should be operative in all structurally related systems. Thus, through the cooperation of the cyanide effect and the axial oxy group effect, we were even able to regioselectively transform 2,3,4-*O*-unprotected as well as completely unprotected *α*-D-galatopyranosides into their valuable 3-*O*-unprotected derivatives in one-pot reactions.[19] The study indicated an unexpected relative reaction rate of *α*-D-galactopyranosides of 2-O > 4-O > 6-O ≫ 3-O (Scheme 1b); commonly the 6- and the 3-hydroxy groups are regarded as the most reactive hydroxy groups.[10]

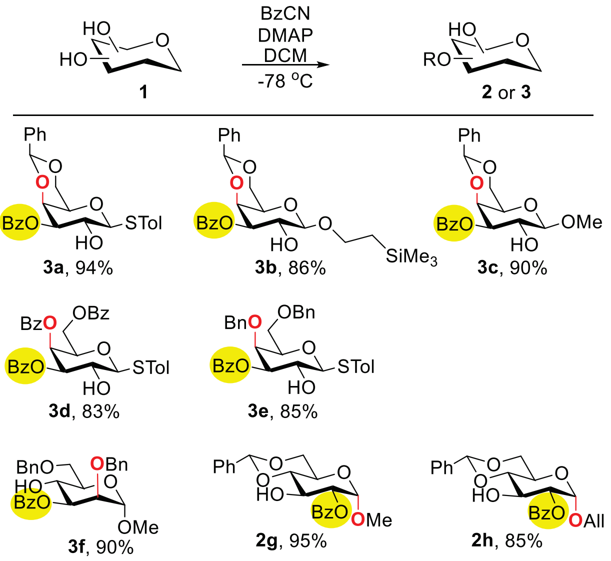
The axial oxy group effect was more or less alluded to in a previous work.[20−23] However, as the action of this effect was not found to be very efficient and, hence, not obvious with commonly used benzoylating agents (as for instance, Bz_2O and BzCl), its importance was not recognized. In these studies, metal salts as additives[20−24] or less reactive bulky acylating agents[25] were indispensable to gain reasonable regioselectivity. Yet, the high reactivity of **BzCN** even at very low temperatures assists, as discussed above, kinetic product formation that is often required for high regioselectivity. Hence, with **BzCN** as the acylating agent and catalytic amounts of a base, the axial oxy group effect seems to be particularly strong. Thus, this effect should in general permit highly regioselective benzoylations without requiring any further additive.

Studies on the generality of the axial oxy group effect coincide with an important missing part in our regioselectivity studies, that is, the regioselective protection of equatorial 1,2-*trans*-diol moieties that are present in the most important sugars, for instance, at the 2,3-position of galacto-, fuco- and glucopyranosides and the 3,4-position of manno- and rhamnopyraosides (Scheme 1c). Highly regioselective access to these positions is frequently needed for chain extension and structural modification. Hence, the aim of the present work is (i) to study the generality of the axial oxy group effect with **BzCN** as the acylating agent and catalytic amounts of a base (Scheme 1c) and (ii) to investigate the differentiation of 1,2-*trans*-diol hydroxy groups, where the reactivity of each hydroxy group is supported by an axial oxy group effect (Scheme 1d). Important in this context are the readily accessible and frequently employed 2,3-*O*-unprotected *α*-galactopyranosides and *α*-fucopyranosides with axial oxy groups at C-1 and C-4 and particularly those derivatives with identical R^1 and R^4 groups. This pseudo-dissymmetric structural motif results in pseudo-homotopic hydroxy groups at C-2 and C-3 that can be hardly differentiated.

■ RESULTS

Regioselective *O*-Benzoylation of Equatorial 1,2-*trans*-Diols with One Axial Oxy Group Effect. The first studies were performed with 4,6-*O*-protected *β*-D-galactopyranosides for which, due to the axial oxy group effect, 3-*O*-benzoylation was expected (Table 1). Indeed, under the applied reaction conditions (1.1 equiv of **BzCN**, 0.1 equiv of DMAP as the catalyst in dry dichloromethane (DCM) as the

Table 1. DMAP-Catalyzed Regioselectivity of 1,2-*trans*-Diols with Axial Oxy Group Effects[a]



[a] All reactions were performed with **BzCN** (1.1 equiv) and DMAP (0.1 equiv) and 4 Å molecular sieves at −78 °C in dry DCM. The products were reported with isolation yield.

solvent at −78 °C), the 2,3-*O*-unprotected *β*-D-galactopyranosides **1a**−**1e**, having different 4,6-*O*-protection (PhCH, Bn and Bz) and different anomeric aglycones [TolS, MeO, $Me_3Si(CH_2)_2O$], furnished, with the assistance of the axial oxy group at C-4, exclusively the 3-*O*-benzoylated products **3a**−**3e** in very good yields. To further demonstrate the generality and usefulness of this effect, different substrates were investigated under these reaction conditions. 3,4-*O*-Unprotected *α*-D-mannopyranoside **1f** and 2,3-*O*-unprotected *α*-D-glucopyranosides **1g** and **1h** led also in excellent yields to 3-*O*-benzoylated mannopyranoside **3f** and to 2-*O*-benzoylated glucopyranosides **2g** and **2h**, respectively. Hence, as a rule, under the above described reaction conditions, the axial oxy group-mediated effect leads in 1,2-*trans*-diols reliably to regioselective benzoylation of the equatorial hydroxy group next to the axial oxy group.

Regioselective *O*-Benzoylation of Equatorial 1,2-*trans*-Diols with Two Axial Oxy Group Effects. With the foregoing results, connotating a very efficient action of the axial oxy group effect, the anticipations for regioselective benzoylations of 4,6-*O*-protected 2,3-*O*-unprotected *α*-galactopyranosides, with an axial oxy group effect supporting the reactivity at each of the two pseudo-homotopic hydroxy groups, were quite confined. Indeed, such a situation was encountered with 2,3-*O*-unprotected *α*-D-galactopyranosides: the regioselectivity was more or less lost under the general reaction conditions (see Table S1). Apparently, the differentiation of the two pseudo-homotopic hydroxy groups in 2- and 3-positions of *α*-D-galactopyranosides is only possible with the help of different substituents at C-1 (essentially the ring oxygen) and at C-4 (the C-5 to C-6 moiety). A direct proof of this notion was the pronounced effect of 4,6-*O*-benzylidene protection (**1n**, Table 2, entry 1) that, for steric and stereoelectronic reasons, favors 3-*O*-benzoylation, leading to a **2n**/**3n** ratio of 1:3.4.

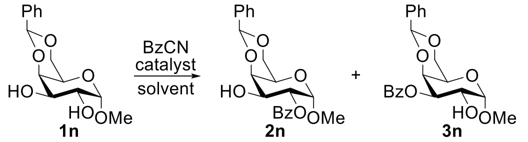
Yet, as these substituents at C-1 and C-4 point away from the reaction centers, for regioselective acylations, sterically demanding (chiral!) tertiary amine bases with functional groups for hydrogen bonding were regarded as promising candidates. 4,6-*O*-Benzylidene-protected *α*-D-galactopyranoside **1n**, a frequently employed substrate, was selected for these studies (Tables 2 and 4). For practically useful regioselectivities for **3n** formation, an improvement factor of 3 or better (→**2n**/**3n** < 1:10), and for **2n** formation, an improvement factor of 10 or better (→**2n**/**3n** > 3:1) over the results in Table 2, entry 1 were desirable. In order to gain a standard for these studies, at first, achiral trialkylamine bases Et_3N and *N*,*N*-diisopropylethylamine (DIPEA) were used in catalytic amounts. These bases furnished regioselectivities comparable to those obtained with DMAP (Table 2, entries 2 and 3: Et_3N, **2n**/**3n** = 1:3; DIPEA, **2n**/**3n** = 1:2.8).

Besides acid−base catalysis via hydrogen-bonding effects,[26] dual hydrogen bonding, especially caused by chiral catalysts,[26−34] gained considerable interest for the regioselective activation of hydroxy groups. Cinchona alkaloid derivatives commonly perform as efficient catalysts via hydrogen bonding.[35] Therefore, at first, quinine-type catalysts were employed in the regioselectivity studies of **1n** with **BzCN**. The quinine-type catalysts **C1**−**C5** showed some increase in favor of **2n** formation (Table 2, entries 4−8). However, with quinidine-type catalysts, **C6**−**C10** formation of the 3-*O*-benzoylated product **3n** was strongly increased (entries 9−13). The best results were obtained with the dihydroquinidine **C7** as the catalyst (entry 10, 87%, **2n**/**3n** = 1:10.8); the natural quinidine also performed with good yield and regioselectivity (entry 9, 85%, **2n**/**3n** = 1:10.4), thus fulfilling our primary goal with improved regioselectivity in favor of 3-*O*-benzoylation. Solvent optimization studies with **1n** as the substrate and **C6** as the catalyst led to a further increase of the regioselectivity in favor of **3n** formation (see, Table S2). It is worth mentioning that nonpolar solvents such as $CHCl_3$, contributed to a further increase of regioselectivity (Table 2, entries 18, 19), where $CHCl_3$ as the sole solvent afforded almost exclusive 3-*O*-benzoylation of **3n** (entry 19). Thus, an efficient method for the highly regioselective 3-*O*-benzoylation of 1,2-*trans*-diols having axial oxy groups next to each of the hydroxy groups could be established.

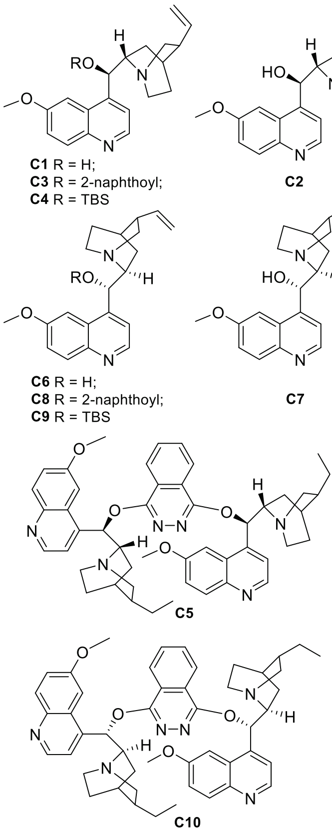
The studies with quinines, quinidines, and dihydroquinidines (Table 2, entries 4−13) exhibit that the configuration of the oxygen of the dialkylaminoethanol moiety in these catalysts plays some role in the regioselective acylation, but the influence of hydrogen-bonding is—if at all—only marginal, as catalyst **C9** with *O*-silyl protection led almost to the same increase of **3n** formation (entry 12) as the parent quinidine (**C6**, entry 9). Also with (*R*)-3-hydroxy-1-azabicyclo [2.2.2]-octane ((*R*)-(−)-quinuclidinol) or achiral 1-azabicyclo[2.2.2]-octane (quinuclidine) and 1,4-diazabicyclo[2.2.2]octane (DABCO), a preference for 3-*O*-benzoylation of **1n** was observed (entries 14−16). It was also shown that the 6-methoxyquinoline moiety of quinine and quinidine and its derivatives had practically no or only little influence on product formation (entry 17). Hence, strong basicity, steric bulk, and (*S*)-configuration of the *N*-oxyethyl moiety of these tertiary amine catalysts favor the regioselective 3-*O*-benzoylation that is modulated by the employed solvent. Thus, a rule for highly regioselective 3-*O*-benzoylation of *α*-D-galactopyranosides is gained.

The regioselective 3-*O*-benzoylation of 2,3-*O*-unprotected *α*-D-galactopyranosides with quinidine as the catalyst was further investigated with different substrates (Table 3). Replacement

Table 2. Different Base-Catalyzed Regioselective Benzoylation of **1n** with BzCN as Benzoylating Agents[a]



entry	catalyst	temp	solvent	yield (%)[b] (**2n**/**3n**)[c]
1	DMAP	−78 °C	DCM	83 (1/3.4)
2	Et_3N	−78 °C	DCM	83 (1/3.0)
3	DIPEA	−78 °C	DCM	80 (1/2.8)
4	**C1**	−78 °C	DCM	75 (1.1/1)
5	**C2**	−78 °C	DCM	70 (1.2/1)
6	**C3**	−78 °C to r.t.	DCM	55 (1.5/1)
7	**C4**	−78 °C to r.t.	DCM	68 (1/2.6)
8	**C5**	−78 °C to r.t.	DCM	73 (1.3/1)
9	**C6**	−78 °C	DCM	85 (1/10.4)
10	**C7**	−78 °C	DCM	87 (1/10.8)
11	**C8**	−78 °C to r.t.	DCM	67 (1/5.5)
12	**C9**	−78 °C to r.t.	DCM	73 (1/9.3)
13	**C10**	−78 °C to r.t.	DCM	71 (1/3.2)
14	(*R*)-(−)-quinuclidinol	−78 °C	DCM	79 (1/5.9)
15	DABCO	−78 °C	DCM	83 (1/4.5)
16	quinuclidine	−78 °C	DCM	76 (1/6.1)
17	6-methoxy quinoline	−78 °C to r.t.	DCM	55 (1/2.6)
18	**C6**	−70 °C	DCM/$CHCl_3$	87 (1/15.1)
19	**C6**	−60 °C	$CHCl_3$	90 (1/18.6)



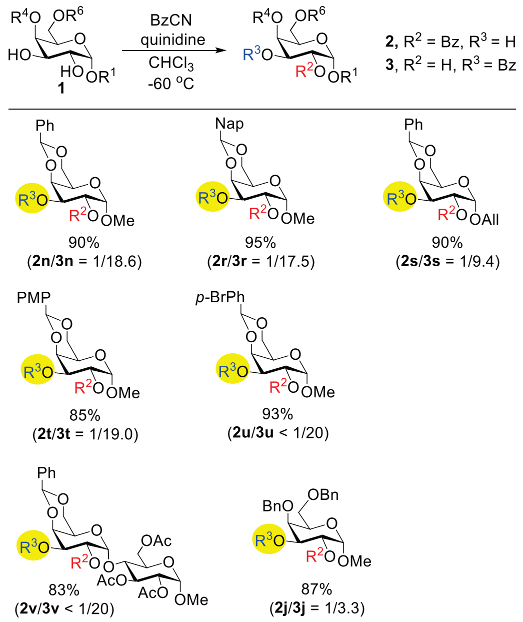
[a]All reactions were performed with **BzCN** (1.1 equiv) and catalyst (0.1 equiv) and 4 Å molecular sieves in dry solvent. [b]Isolation yield. [c]The ratio was determined by ^1H NMR.

of the 4,6-*O*-benzylidene group, as in **1n**, by the 4,6-*O*-(2-naphthylidene) group, as in **1r**, or variation of the methoxy group to an allyloxy group at the anomeric center, as in **1s**, did not change the regioselectivity, thus leading to high yields of **3r** and **3s**, respectively. Also, either electron-donating or -withdrawing substrates at the benzylidene protecting group, as in **1t** and **1u**, had no negative influence on the regioselective benzoylation of **3t** and **3u**. Moreover, even the disaccharide **1v** led to exclusive formation of the corresponding 3-*O*-benzoylation derivative **3v**. This excellent result was also supported by the steric demand at C-4, as with 4,6-di-*O*-benzyl protected substrate **1j**, the regioselective 3-*O*-benzoylation was diminished (**2j**:**3j** = 1:3.3); however, quinidine as the catalyst still showed better regioselectivity than DMAP (Table S1, entry 2, **2j**:**3j** = 1:1.5).

Having successfully accomplished the highly regioselective 3-*O*-benzoylation of *α*-D-galactopyranoside substrate **1n**, the next goal was to reverse the regioselectivity in favor of 2-*O*-benzoylation. The factors favoring 3-*O*-benzoylation were reason to search for alternatively functioning catalysts, as for instance, catalysts with strong hydrogen-bonding capacity. Of particular interest were thioureas as they are excellent bishydrogen-bond donors[36] that should increase the differentiation between the two pseudo-homotopic hydroxy groups of the substrate **1n**. In addition, they could be loaded with a chiral tertiary amine base, thus providing a bifunctional catalyst that combines activation of the benzoylating agent and the increase of the substrate oxygen nucleophilicity with the potential for site-selectivity due to the chirality that should be able to distinguish between the different substituents at C-1 and C-4. Such bifunctional catalysts have been already studied for some other problems of carbohydrate chemistry[37−46] and as well as in the acyl transfer area.[47]

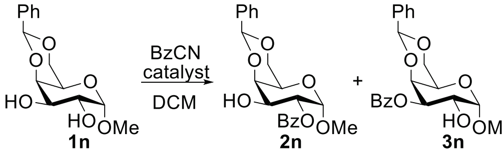
First, the commercially available Takemoto catalyst (**C11**) was investigated under the standard reaction conditions. With the (*S*,*S*)-isomer of **C11**, for the first time, preferred 2-*O*-benzoylation was observed (Table 4, entry 2, **2n**/**3n** = 2.3:1). Encouraged by this promising result, a series of bifunctional catalysts [(*S*,*S*)-**C12**−(*S*,*S*)-**C15**, entries 3−6] were synthesized and screened for their capacity to promote regioselective 2-*O*-benzoylation of **1n** with **BzCN** under the standard reaction conditions. Replacement of the dimethylamino group in (*S*,*S*)-**C11** by a pyrrolidino group as in (*S*,*S*)-**C12** further increased 2-*O*-benzoylation (entry 3, **2n**/**3n** = 2.6:1). The corresponding piperidino derivative (*S*,*S*)-**C13** furnished the best result (entry 4, **2n**/**3n** = 3.9:1) corresponding to a 12-fold increase in **2n** formation over the standard reaction with triethylamine as the catalyst (entry 1). This ratio could be further improved by carrying out the reaction at higher concentration (entries 8 and 9): for instance, with an 0.57 molar solution of **1n**, a 5.5:1 ratio of **2n**/**3n** was obtained (entry 9), thus providing a 17-fold increase of 2-*O*-

Table 3. Quinidine-Catalyzed Regioselective Benzoylation of 2,3-*O*-Unprotected *α*-D-Galactopyranoside[a]

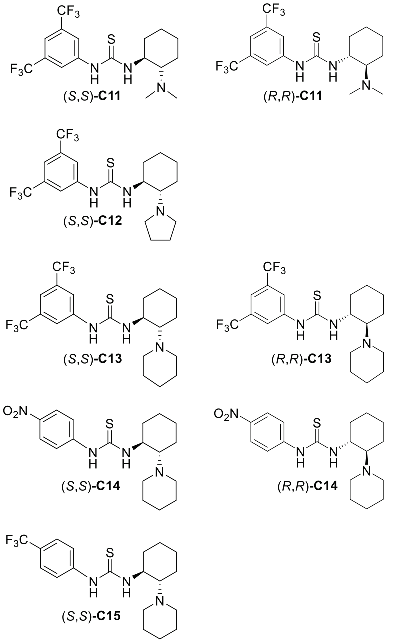


[a]All reactions were performed with **BzCN** (1.1 equiv) and quinidine (0.1 equiv) and 4 Å molecular sieves at −60 °C in dry $CHCl_3$. The products were reported with isolation yield, and the ratio was determined by ^1H NMR. PMP = *p*-methoxyphenyl.

Table 4. Different Thiourea Derivative-Catalyzed Regioselective Benzoylation of 1n with BzCN as Benzoylating Agents[a]



entry	catalyst	temp (°C)	conc. (M)	yield (%)[b] (2n/3n)[c]
1	Et_3N	−78	0.018	83 (1/3.0)
2	(*S*,*S*)-**C11**	−78	0.018	80 (2.3/1)
3	(*S*,*S*)-**C12**	−78	0.018	77 (2.6/1)
4	(*S*,*S*)-**C13**	−78	0.018	75 (3.9/1)
5	(*S*,*S*)-**C14**	−78	0.018	70 (3.5/1)
6	(*S*,*S*)-**C15**	−78	0.018	75 (2.1/1)
7	(*S*,*S*)-**C13**	−78	0.07	77 (4.1/1)
8	(*S*,*S*)-**C13**	−78	0.47	80 (4.7/1)
9	(*S*,*S*)-**C13**	−78	0.57	82 (5.5/1)
10	(*R*,*R*)-**C11**	−78	0.018	85 (1/3.3)
11	(*R*,*R*)-**C13**	−78	0.018	76 (1/1.1)
12	(*R*,*R*)-**C14**	−78	0.018	68 (1/1.2)



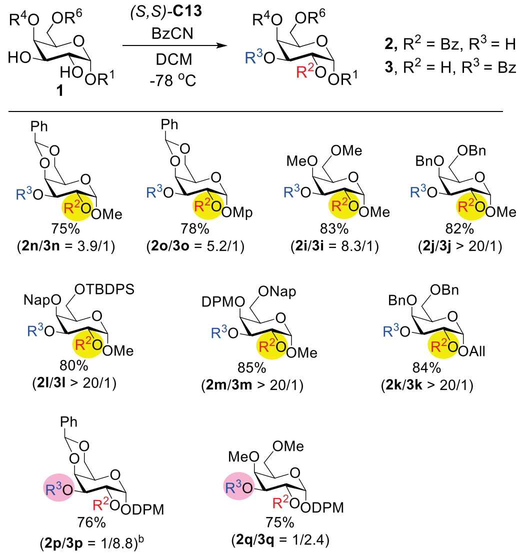
[a]All reactions were performed with **BzCN** (1.1 equiv) and catalyst (0.1 equiv) and 4 Å molecular sieves at −78 °C in dry DCM. [b]Isolation yield. [c]The ratio was determined by ^1H NMR.

benzoylation over the standard reaction (entry 1). Catalysts with less electron-withdrawing N-aryl groups at the thiourea moiety, as in (*S*,*S*)-**C14** and (*S*,*S*)-**C15** (entries 5 and 6), or with (*R*,*R*)-configuration of the 1,2-diaminocyclohexane residue, as in (*R*,*R*)-**C11**, (*R*,*R*)-**C13**, and (*R*,*R*)-**C14** (entries 10−12), showed lower preference for **2n** formation than (*S*,*S*)-**C13**. Comparison of the regioselectivity found for triethylamine as the catalyst (entry 1) with the regioselectivities found for the (*R*,*R*)-catalysts (entries 10−12) implies that the chiral part of these catalysts has, if any, only little influence on the reaction course. The (*R*,*R*)-catalysts seem to act essentially as tertiary amines and, different from the (*S*,*S*)-catalysts, the interaction of the chiral part with the *trans*-diol substrate **1n** seems to be sterically precluded at least in the benzoylation transition state.

The scope of the regioselective 2-*O*-benzoylation of 2,3-*O*-unprotected *α*-D-galactopyranosides with (*S*,*S*)-**C13** as the catalyst was studied with different substrates (Table 5). With a methoxyphenyl (Mp) group at the anomeric oxygen (**1o**), the regioselectivity could be improved (**2o**/**3o** = 5.2:1, 78% yield) compared with the result obtained with **1n**. Increasing the conformational space requirements of the 4-*O* substituents led, as expected, to a dramatic preference for 2-*O*-benzoylation, as exhibited already by replacement of the 4,6-*O*-benzylidene group (**1n**) by 4,6-di-*O*-methyl protection (**1i**): the **2i**/**3i** ratio increased to 8.3:1, 83% yield. Changing the 4,6-*O*-protecting groups to bigger groups, 4,6-di-*O*-benzyl as in **1j** or to even sterically demanding groups, 4-*O*-Nap-6-*O*-TBDPS or 4-*O*-DPM-6-*O*-Nap (DPM = diphenylmethyl) as in **1l** or **1m**, respectively, led practically exclusively to the 2-*O*-benzoylated products **2j**, **2l**, and **2m** (in 82, 80, and 85% yield, respectively). Such a result was also obtained when in **1j**, the anomeric *O*-methyl group was replaced by an allyl group as in **1k**: only the 2-*O*-benzoylated product **2k** was isolated in 84% yield. Hence, (*S*,*S*)-**C13** serves as an efficient chiral catalyst for the transformation of quite an array of different *α*-D-galactopyranosides with **BzCN** as the acylating agent into their 2-*O*-benzoylated products.

The results in Table 5 are mostly in good agreement with the proposed reaction course (see below). However, introducing a sterically very demanding group at the anomeric oxygen should enforce a regioselectivity change. Therefore, DPM 4,6-*O*-benzylidene-*α*-D-galactopyranosides **1p** and **1q** were prepared. Benzoylation of **1p** and **1q** with **BzCN** in the presence of (*S*,*S*)-**C13** as the catalyst led, in agreement with

Table 5. (*S*,*S*)-C13-Catalyzed Regioselective Benzoylation of 2,3-*O*-Unprotected α-D-Galactopyranoside[a,b]



[a] All reactions were performed with **BzCN** (1.1 equiv) and catalyst (*S*,*S*)-**C13** (0.1 equiv) and 4 Å molecular sieves at −78 °C in dry DCM. The products were reported with isolation yield and the ratio was determined by ^{1}H NMR [b] When 0.1 equiv of Et_3N was used as the catalyst, exclusive **3p** (**2p**:**3p** < 1:20) was obtained in 85% yield.

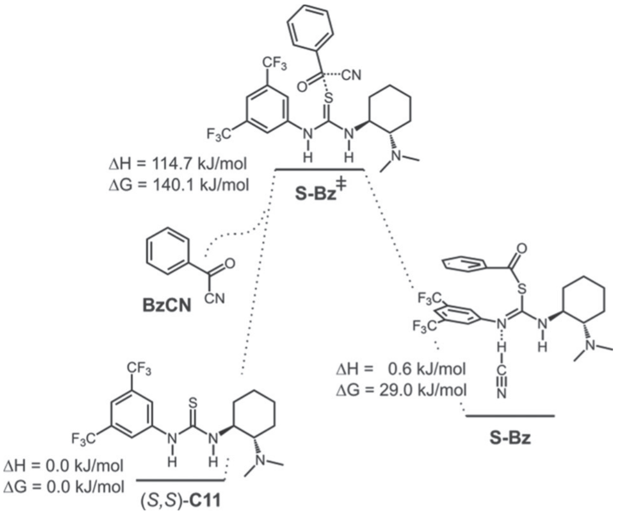
the mechanistic proposal, mainly to 3-*O*-benzoylated products (**2p**/**3p** = 1:8.8, 76% yield; **2q**/**3q** = 1:2.4, 75% yield).

Density Functional Theory Calculations and Mechanistic Proposal. In order to understand the influence of the chiral thiourea catalysts on the regioselectivity, density functional theory (DFT) calculations on the DFT/M06-2X/Def2TZVP/PCM(CH_2Cl_2)-level of theory were conducted for substrate **1n** (PCM = polarizable continuum model).[48−54] Gibbs free energies are reported at −80 °C relative to the sum of the Gibbs free energy of the starting compounds ($\Delta G_{(S,S)\text{-}\mathbf{C11}} + \Delta G_{\mathbf{Bz}} + \Delta G_{\mathbf{1n}} = 0$ kJ/mol; $\Delta H_{(S,S)\text{-}\mathbf{C11}} + \Delta H_{\mathbf{Bz}} + \Delta H_{\mathbf{1n}} = 0$ kJ mol^{-1}). Catalyst (*S*,*S*)-**C11** was selected to minimize the cost of the calculation. The calculations focus on the possible reaction intermediates and their relative energies.

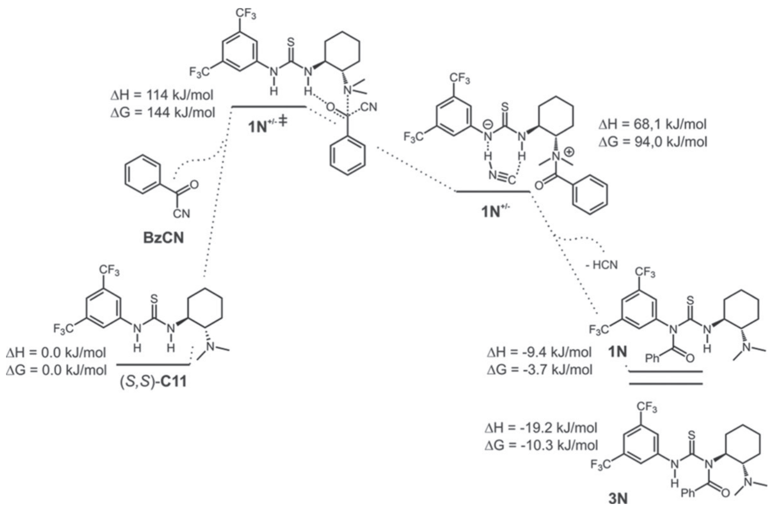
Base-catalyzed benzoylation of alcohols is understood to proceed via activation of **BzCN** by the base forming a reactive intermediate, which is attacked by the hydroxyl group.[55,56] The reaction of (*S*,*S*)-**C11** with **BzCN** depicted in Scheme 2 proceeds over a highly energetic transition state with $\Delta G = 144$ kJ mol^{-1}. The product of this reaction is 94.0 kJ mol^{-1} higher than the educts making this reaction highly unfavorable. We found a rather peculiar intermediate, which is formed by the release of the hydrogen cyanide and a benzoyl shift from the dimethylamino group to the thiourea **3N** or **1N** atom, which is exothermic in relation to the starting compounds by $\Delta G = -10.3$ kJ mol^{-1} (**3N**) and $\Delta G = -3.7$ kJ mol^{-1} (**1N**). We found experimental proof for the existence of this compound class, which is known in the literature,[57,58] although we were not able to isolate the exact compound derived from base (*S*,*S*)-**C11**.

Another possible path is shown in Scheme 3, starting with the benzoylation at the thiourea *S*-atom. This reaction is

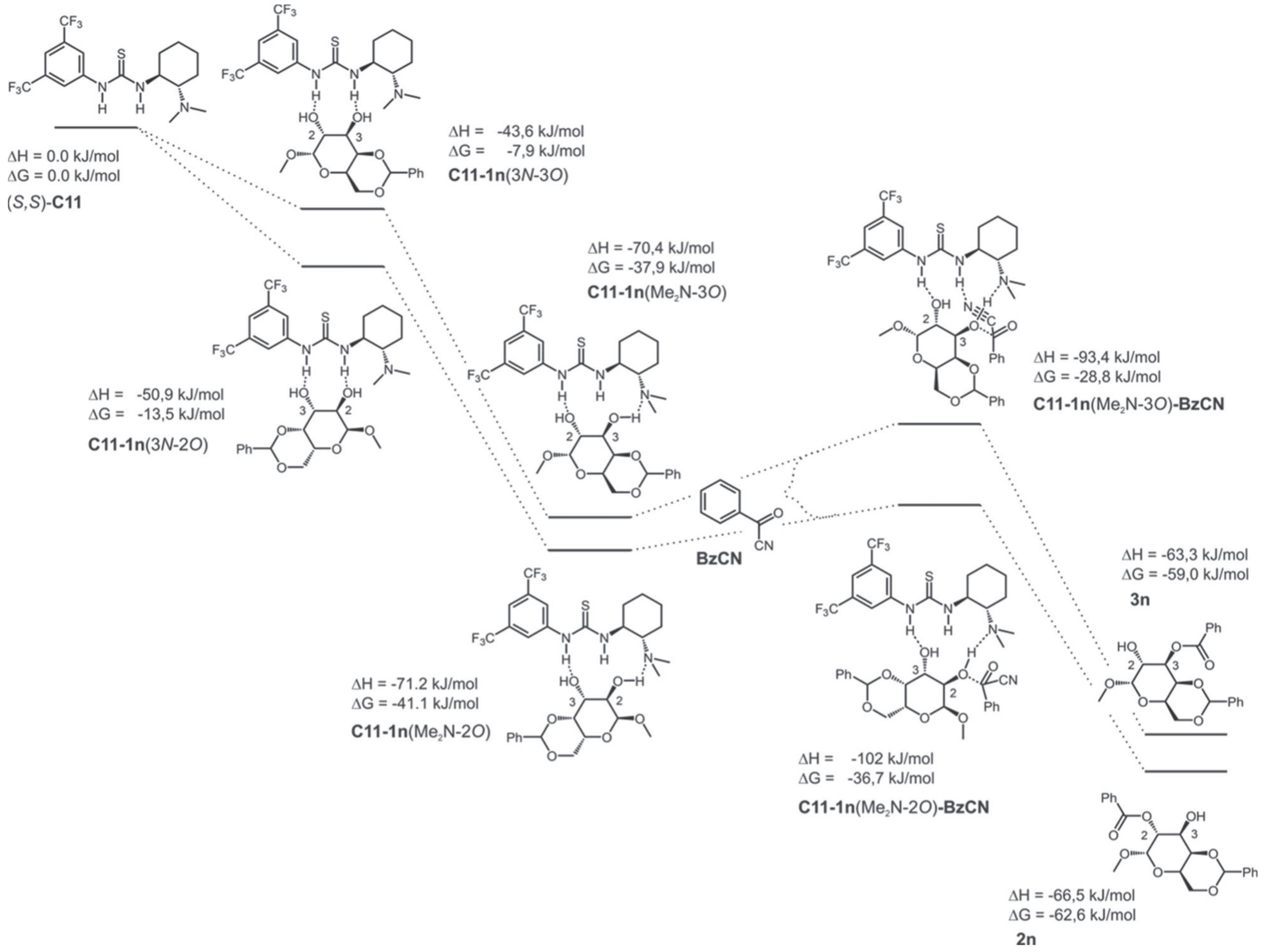
Scheme 3. Thermochemistry Data for the Reaction of BzCN with Catalyst (*S*,*S*)-C11 at the Thiocarbonyl Group



Scheme 2. Thermochemistry Data for the Reaction of BzCN with the Dimethylamino Group of the Catalyst (*S*,*S*)-C11.



Scheme 4. Calculated Thermochemistry Data for the Adduct Formation between the Catalyst (*S*,*S*)-C11 and Substrate 1n and Subsequently with BzCN.



endothermic again, albeit by only ΔG = 29.0 kJ mol^{-1}. The transition state on the other hand is comparable to the transition state found for the benzoylation of the dimethylamino *N*-atom. Both reactions are highly unfavorable. In order to understand the reason for the endothermic nature of this reaction, we investigated the reaction of trimethylamine with **BzCN** and found a transition state for the benzoylation of trimethylamine at ΔG = 112 kJ mol^{-1}. Most probably, the strong covalent CC-bond between the carbonyl *C*-atom and the cyanide *C*-atom is causing this difference as compared to the benzoylation with the more ionic bound benzoyl chloride.

As direct activation of **BzCN** by the catalyst seems energetically not feasible, a different reaction path was considered starting with the association of catalyst (*S*,*S*)-**C11** and diol **1n** (see Scheme 4). All intermediates are exothermic in relation to the starting compounds. Internal redundant coordinate (IRC) scans (on the significantly smaller b3lyp/def2svp-level[52,53,59−62] of theory without solvation) reveal no considerable transition states for the coordination of diol **1n** to the catalyst (*S*,*S*)-**C11** [formation of **C11-1n**(3*N*-2*O*) and **C11-1n**(3*N*-3*O*)] and the formation of the strong hydrogen-bridging interaction of the respective OH-proton to the dimethylamino N-atom [**C11-1n**(Me$_2$N-2*O*) and **C11-1n**(Me$_2$N-3*O*)], respectively (see Figure S2 in the Supporting Information). The last step, the formation of **C11-1n**(Me$_2$N-2*O*)-**BzCN** and **C11-1n**(Me$_2$N-3*O*)-**BzCN**, is not a transition state but an intermediate due to the formation of another hydrogen bond from the cyanide N-atom to one of the acidic protons of the **C11-1n**-adducts. The reactions to the intermediates are best described as conformational rearrangements of the H-bonding motive.

The size of the system is prohibitive for the calculation of transition states; they are however accessible via the IRC scans. Such an IRC scan for 2-*O*-benzoylation (see Figure S3 of the Supporting Information) shows a significantly reduced activation energy of 75 kJ mol^{-1} [self-consistent field (SCF) energy] and of course an exothermic reaction, while the 3-*O*-benzoylation activation energy is still a little bit higher (110 kJ mol^{-1} SCF energy). These energies are of course not reliable enough for interpretation, but the structural differences between the two structures (see Figure 1) can help in the discussion of the reaction outcome, especially as they coincide with the structural differences in the respective minima **C11-1n**(Me$_2$N-2*O*)-**BzCN** and **C11-1n**(Me$_2$N-3*O*)-**BzCN**.

In the case of **C11-1n**(Me$_2$N-3*O*)-**BzCN**, the benzene ring of the benzylidene functionality points toward the dimethylamino function causing significant steric strain (this is difficult to see in the 2D drawn structure, therefore the *xyz*-coordinates are included in the Supporting Information for closer inspection). In consequence, the Me$_2$N···H-3*O* contact is

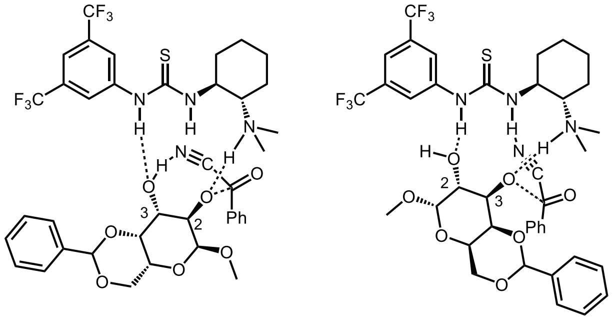


Figure 1. 2-D drawing of the structures obtained at the maxima of the IRC scans in Figure S2 of the Supporting Information. **C11-1n**(Me$_2$N-2*O*)-**BzCN**‡ (left) and **C11-1n**(Me$_2$N-3*O*)−**BzCN**‡ (right).

2.010 Å (1.866 Å for **C11-1n**(Me$_2$N-3*O*)-**BzCN**‡), while the Me$_2$N···H-2*O* contact is by far lower (1.766 and 1,589 Å in **C11-1n**(Me$_2$N-2*O*)-**BzCN**‡) resulting in a stronger activation of the 2-*O*-oxygen atom.

On the other hand, an interaction of the 3-OH proton with the cyanide N-atom can be observed in the case of **C11-1n**(Me$_2$N-2*O*)-**BzCN**‡ (2.845 Å), while it is not present in the minimum **C11-1n**(Me$_2$N-2*O*)-**BzCN** because the closer Me$_2$N···H-2*O* contact leads to a shielding of this proton. For **C11-1n**(Me$_2$N-3*O*)-**BzCN**, a clear interaction between the thiourea **3N**-H proton and the cyanide N-atom [2.309 and 2.214 Å **C11-1n**(Me$_2$N-3*O*)-**BzCN**‡] is found. Both interactions weaken the strong (O=)C···CN-bond, increase the leaving group abilities of the cyanide, and reduce the energy of the transition state, making the reaction energetically feasible.

DISCUSSION

Highly regioselective benzoylation of 1,2-*trans*-diols possessing one axial oxy group is reliably reached with **BzCN** as the acylating agent and an amine base as the catalyst at low temperatures. The operative axial oxy group effect favors mono-*O*-benzoylation of 2,3-*O*-unprotected *β*-galacto- and *α*-glucopyranosides and of 3,4-*O*-unprotected mannopyranosides next to the axial group. The relative reaction rates found for *cis*−*trans*-triols and -tetrols (see, Scheme 1b) display that the axial oxy group effect is stronger than the cyanide effect. With this additional information, the regioselectivity rules can be reliably extended to the frequently occurring *cis*−*trans*-triol and -tetrol moieties in glycopyranosides.

Differentiation of 1,2-*trans*-diols, where each hydroxy group is vicinal to an axial oxy group, that is, each of these pseudohomotopic groups is activated by an axial oxy group effect, is reached with the help of chiral amine bases as the catalyst. This way, 2,3-*O*-unprotected *α*-galactopyranosides can be regioselectively protected at wish at the 2-*O* or the 3-*O*. The preferred steric interaction between the substrate and the chiral thiourea-based catalyst (*S*,*S*)-**C11** is investigated by DFT calculations, which are in agreement with the experimental findings. There is a strong H-bond interaction between substrate **1n** and catalyst (*S*,*S*)-**C11**, where one hydroxyl group is bound to the thiourea NH and the other finally to the dimethylamino group [intermediates **C11-1n**(3*N*-2*O*) and **C11-1n**(3*N*-3*O*)]. Addition of **BzCN** favors for activation of 3-*O*-benzoylation a transition state with a H-bond from the 3-NH to the cyanide-N and for activation of 2-*O*-benzoylation a transition state with a H-bond from the 3-OH to the cyanide-N, which is in addition supported by a H-bond from the quite acidic 1-*NH* to the 3-*O* of **1n**. This way, concomitant **BzCN** and OH group activation, in order to ease *O*-benzoylation, are reached with a preference for 2-*O*-benzoylation.

The use of the "axial oxy group effect" in combination with the previously introduced "cyanide effect" and their relative strength allow for the regioselective access to a wide variety of valuable intermediates. Thus, this protocol provides the desired reliable rules for the regioselective protection of carbohydrates possessing vicinal *cis*- and *trans*-diol, *cis*−*trans*-triol, and -tetrol structures that are the constituents of common glycopyranosides.

COMPUTATIONAL DETAILS

The ground-state electronic structures were calculated by DFT methods using the Gaussian 16 program packages.[48] Geometry optimization followed by vibrational analysis was performed in solvent media. Solvent effects were described by the PCM with standard parameters for DCM.[49] Def2SVP polarized double-zeta-basis sets[52,53] for all atoms together with the B3LYP exchange and correlation functional (b3lyp)[59−62] were employed for preliminary geometry optimizations and IRC scans. Def2TZVP polarized triple-zeta-basis sets[52,53] for all atoms together with the M06-2X basis set were employed for final geometry optimizations and for thermochemistry data.[54] The GaussSum program package was used to analyze the results,[63] while the visualization of the results was performed with the Avogadro program package.[64,65] Graphical representations of molecular orbitals were generated with the help of GNU parallel[66] and plotted using the vmd program package[67] in combination with POV-Ray.[68]

ASSOCIATED CONTENT

Detailed experimental procedures, preparation and characterization of the chiral catalysts, optimization of the reaction conditions, preparation and characterization of products, and the DFT calculated structures (PDF)

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Notes

The authors declare no competing financial interest.

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This paper was originally published ASAP on September 20, 2020. Due to a production error, there was a mistake in the catalysts of entries 10–12 of Table 4. The corrected version was reposted on September 22, 2020.