Development of a family of β-amino alcohol ligands with two stereocenters for highly efficient enantioselective trimethylsilylcyanation of aldehydes

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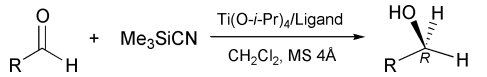
The asymmetric addition of Me_3SiCN to aldehydes catalyzed by titanium(IV) complexes of *N*-sulfonylated derivatives of β-amino alcohols gave excellent ee's up to 96% ee.

Optically pure cyanohydrins are important chiral building blocks for a wide variety of chiral products such as α-hydroxy acids, α-hydroxy aldehydes, α-hydroxy ketones, β-hydroxy amines, β-amino alcohols and α-amino acid derivatives.[1] Therefore, in recent years, a number of synthetic methods have been reported employing enzymes, synthetic peptides, and chiral metal complexes.[1,2] Of chiral metal complexes reported so far, titanium-based Lewis acids have attracted the most interest, and the chiral ligands used include TADDOLs,[3] BINOLs,[4] sulfoximines,[5] peptides,[6] Schiff bases[7] and others.[8–10] For examples, the TADDOL–Ti(O-*i*-Pr)$_2$Cl$_2$ catalytic system reported by Narasaka *et al*. gave a 96% ee for benzaldehyde as a substrate at −65 °C.[3] However, for aliphatic aldehydes, the catalytic system gave low ee values of 68–77% ee. With the use of 20 mol% of the sulfoximine–Ti(O-*i*-Pr)$_4$ catalyst reported by Bolm and Müller, the ee values could be up to 91% ee.[5] Recently, Belokon *et al.* reported a very efficient [(salen)Ti(μ-O)]$_2$ catalyst to give the best ee value of 92% ee with the use of only 0.1 mol% of the catalyst.[7] In these studies, the best enantioselectivities were reported by Uang *et al*. with the use of the diamide–Ti(O-*i*-Pr)$_4$ catalytic system giving ee values higher than 96% ee.[9] Despite extensive studies, limitations such as poor enantioselectivities, the lack of wide-range substrate generality, high catalyst loading, or even a stoichiometric use of chiral ligand, were usually encountered. This makes the development of practical and highly effective catalytic systems for the preparation of chiral cyanohydrins much more challenging. Herein we report the synthesis of a new family of *N*-sulfonylated β-amino alcohols with one or two stereocenters as chiral ligands, and the asymmetric addition of Me_3SiCN to aldehydes was conducted‡ (eqn. 1).



(1)

In this study, we first synthesized the *N*-sulfonylated β-amino alcohols (*S*)-**3** and (*S*)-**4** with only one stereocenter. Unfortunately, the catalytic reaction using (*S*)-**3** or (*S*)-**4** with an equimolar amount of Ti(O-*i*-Pr)$_4$ as a catalyst gave no conversion or low enantioselectivity of 7% ee at 0 °C (entries 1 and 2, Table 1). These results prompted us to develop a novel family of β-amino alcohols with two stereocenters, and based on the route described by Reetz *et al.*,[11] the β-amino alcohols **5** and their *N*-sulfonylated derivatives **6** and **7** with two stereocenters were prepared. The synthetic strategy provides a tremendous pool of various β-amino alcohols *via* variation of both R and R′ groups. While creating the second stereogenic carbon center, it was found that the second stereocenter is controlled by the original amino chiral carbon center, and the major (*R*,*S*)-stereomer and the minor (*S*,*S*)-stereomer can be easily separated by chromatography.

In using the (*R*,*S*)-**6**–Ti(O-*i*-Pr)$_4$ system, the asymmetric addition of Me_3SiCN to benzaldehyde afforded the cyanohydrin in only 14% yield at 0 °C (entry 3). In contrast, employing (*R*,*S*)-**7a** resulted in significant improvement of ee values to 68% ee

Table 1 Enantioselective addition of trimethylsilyl cyanide (Me_3SiCN) to aldehydes catalyzed by *in situ*-formed **3**–**7**–Ti(O-*i*-Pr)$_4$ systems for 48 h

Entry	Ligand/mol%	Aldehyde	Temp./°C	Yield[b] (%)	% ee[c] (Config.)
1	(*S*)-**3** (10)	Benzaldehyde (**1a**)	0	0	—
2	(*S*)-**4** (10)	Benzaldehyde (**1a**)	0	67 (58)	7 (*R*)
3	(*R*,*S*)-**6** (10)	Benzaldehyde (**1a**)	0	14	8 (*R*)
4	(*R*,*S*)-**7a** (10)	Benzaldehyde (**1a**)	0	100	68 (*R*)
5	(*R*,*S*)-**7a** (10)	Benzaldehyde (**1a**)	−40	100	79 (*R*)
6	(*R*,*S*)-**7a** (10)	Benzaldehyde (**1a**)	−65	100 (93)	96 (*R*)
7[a]	(*R*,*S*)-**7a** (10)	Benzaldehyde (**1a**)	−65	52	77 (*R*)
8	(*R*,*S*)-**7a** (5)	Benzaldehyde (**1a**)	−65	90 (81)	94 (*R*)
9	(*R*,*S*)-**7b** (10)	Benzaldehyde (**1a**)	−65	82	62 (*R*)
10	(*R*,*S*)-**7c** (10)	Benzaldehyde (**1a**)	−65	85 (73)	38 (*R*)
11	(*S*,*S*)-**7a** (10)	Benzaldehyde (**1a**)	−65	51 (41)	8 (*S*)
12	(*R*,*S*)-**7a** (10)	4-Chlorobenzaldehyde (**1b**)	−65	93 (85)	90 (*R*)
13	(*R*,*S*)-**7a** (10)	4-Methoxybenzaldehyde (**1c**)	−65	100 (92)	94 (*R*)
14	(*R*,*S*)-**7a** (10)	2-Methoxybenzaldehyde (**1d**)	−65	100 (92)	86 (*R*)
15	(*R*,*S*)-**7a** (10)	2-Naphthaldehyde (**1e**)	−65	95 (88)	96 (*R*)
16	(*R*,*S*)-**7a** (10)	1-Naphthaldehyde (**1f**)	−65	100 (91)	77 (*R*)
17	(*R*,*S*)-**7a** (10)	(*E*)-Cinnamaldehyde (**1g**)	−65	100 (89)	93 (*R*)
18	(*R*,*S*)-**7a** (10)	Isobutyraldehyde (**1h**)	−65	100 (91)	95 (*R*)

[a] Without addition of powdered molecular sieves. [b] Yields were based on ^{1}H NMR analyses of the mixture of cyanohydrin and unreacted aldehyde. In parentheses, isolated yield. [c] Determined by HPLC with Chiralcel OD column for **1a**–**1f**, Chiralcel AS for **1g** and Chiralpak OJ for **1h** after protected as acetyl esters except **1h** as a benzoyl ester. Absolute configurations were determined by comparison of optical rotations with literature values.

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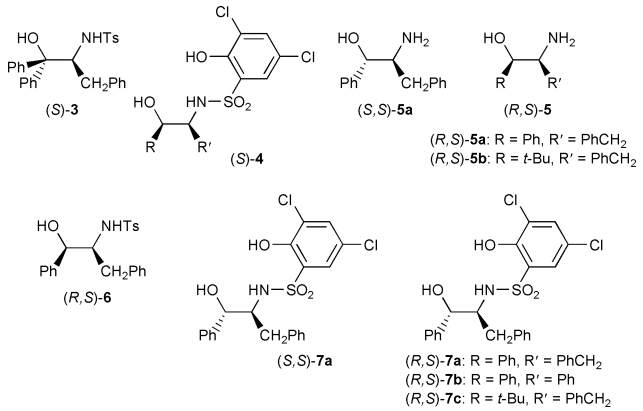

(entry 4). From entries 5 and 6, a significant temperature effect was observed with enantioselectivities of 79% ee at −40 °C (entry 5) and 96% ee at −65 °C (entry 6). Another key factor for the successful practice of highly efficient enantioselective trimethylsilylcyanation of aldehydes is the use of powdered 4 Å molecular sieves. In the absence of molecular sieves, the ee value significantly decreased from 96 to 77% ee with the yield decreased to 52% (entry 7). When as little as 5 mol% of (*R*,*S*)-**7a** was used, an excellent enantioselectivity was still obtained with 94% ee (entry 8). Replacing (*R*,*S*)-**7a** with (*R*,*S*)-**7b** gave a lower enantioselectivity of 62% ee (entry 9). When (*R*,*S*)-**7c** with a benzyl substituent at the amino carbon and a *tert*-butyl substituent at the hydroxy carbon was used, a much lower ee value of 38% ee was obtained (entry 10). For (*S*,*S*)-**7a**, which is a diastereomer of (*R*,*S*)-**7a**, the reaction gave only 8% ee of *S* configuration (entry 11). In addition, other metallic reagents such as $AlMe_3$, $AlEt_3$, Et_2AlCl, $Ti(O\text{-}i\text{-}Pr)_2Cl_2$, $Ti(O\text{-}i\text{-}Pr)Cl_3$ and $TiCl_4$ were also examined. However, the reactions gave low enantioselectivities with the best ee value of only 37% ee. Solvent effect was also studied, and CH_2Cl_2 was the best choice.

The enhanced unique reactivity of the *N*-sulfonylated amino alcohol (*R*,*S*)-**7a** has been suggested to arise from the following factors: (a) phenoxides are known to form strong bonds to group 4 transition metals, and with electron withdrawing halogen groups, the phenoxide moiety may lead to enhanced Lewis acidity at the metal center to improve the reactivity; (b) the phenolic ring further enhances conformational rigidity of these tridendate ligands, which may be an important factor in the transfer of asymmetry.

From entries 12–18, the generality of the asymmetric catalytic reactions employing the (*R*,*S*)-**7a**–$Ti(O\text{-}i\text{-}Pr)_4$ catalytic system was conducted. For aromatic aldehydes (entries 12–16), the asymmetric cyanosilylations gave (*R*)-cyanohydrins with excellent ee values except in the cases of 2-methoxybenzaldehyde (86% ee) and 1-naphthaldehyde (77% ee). The best ee value of 96% ee was obtained for benzaldehyde (entry 6) or 2-naphthaldehyde (entry 15). It is worth noting that, in this study, ee values of 95 and 93% ee were obtained for aliphatic isobutyraldehyde and α,β-unsaturated (*E*)-cinnamaldehyde (entries 17 and 18), respectively.

In conclusion, the first example of highly effective asymmetric addition of a cyano group to aldehydes using *N*-sulfonylated β-amino alcohols as ligands has been reported with excellent enenatioselectivities and with broad substrate generality. Besides, the similar sulfoxamide ligands were also applied to asymmetric diethylzinc addition to aldehydes.[12] This study clearly demonstrates that differences in ligand structures strongly influence the enantioselectivity, and several trends were noted. First, the generation of the second stereocenter greatly improved enantioselectivities. Second, substitution of a flexible benzyl group at the amino carbon ((*R*,*S*)-**7a**) for a rigid phenyl group ((*R*,*S*)-**7b**) resulted in a significant drop in the ee value. Third, aryl substituents on the stereogenic center at the alcoholic carbon proved to be superior to alkyl substituents. The mechanistic study of the catalytic systems and their further applications are currently underway.

Notes and references

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‡ *General procedures for asymmetric cyanosilylation of aldehydes*: Under dry dinitrogen atmosphere, 0.05 mmol of the chiral ligand, 0.05 mmol of $Ti(O\text{-}i\text{-}Pr)_4$, and 100 mg of powdered 4 Å molecular sieves were mixed in 2.0 mL of dry DCM at rt. The mixture was stirred for 1 h and cooled to −65 °C. To the resulting yellow solution were added 1.5 mmol of Me_3SiCN and 0.5 mmol of aldehyde. After the solution was stirred at this temperature for 48 h, the reaction was quenched with 1 M HCl, and the mixture was then vigorously stirred for 4 h. The aqueous phase was extracted with ethyl acetate (3 × 10 mL), and the combined organic layers were dried over $MgSO_4$, and concentrated *in vacuo*. Flash chromatography of the residue on silica gel (elution with 5:1 hexane–ethyl acetate) gave a cyanohydrin. ee was determined by HPLC after protection as acetyl esters (except **1h**, which was protected as a benzoyl ester).

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