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N-Salicyl-β-aminoalcohols as a new class of ligand for catalytic asymmetric Strecker reactions

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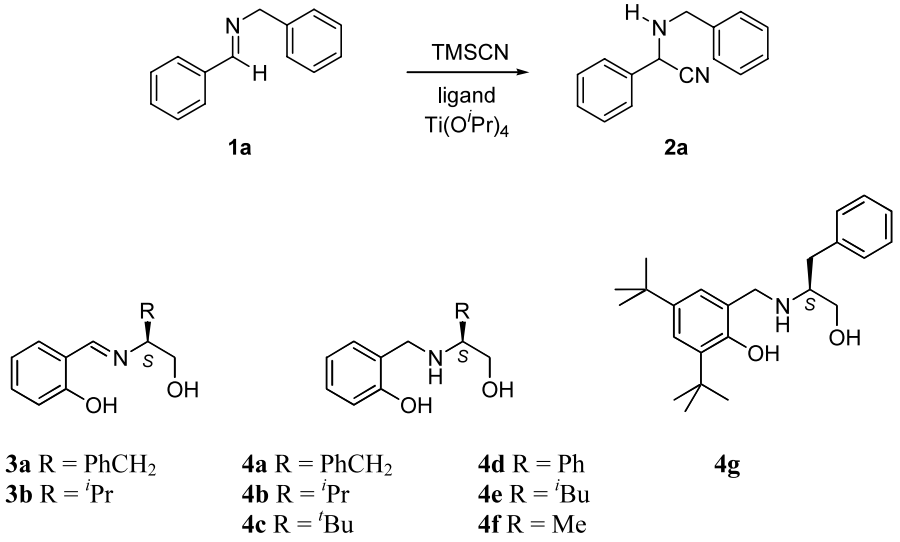
Abstract—An enantioselective Strecker synthesis employing novel chiral titanium complex catalysts derived from structurally simple chiral *N*-salicyl-β-amino alcohols is described. Reactions of *N*-benzylidenebenzylamine with trimethylsilyl cyanide in the presence of the catalyst (10 mol%) gave the corresponding α-aminonitrile in good to excellent yields, along with relatively high enantioselectivity (up to 86% ee). Similar reactions with various imines derived from aromatic aldehydes resulted in moderate to good enantioselectivity (44–81% ee).

The Strecker reaction is one of the most general methods potentially useful for both laboratory and industrial scale syntheses of α-amino acids. Typical Strecker reactions involve addition of a cyanide ion to imines which can be formed in situ from carbonyl compounds and ammonia or primary amines. Due to the presence of a prochiral C=N plane, the α-aminonitriles so formed are racemic, which after hydrolysis yield α-amino acids in racemic form. Although racemic α-aminonitriles and α-amino acids may be converted to their optically active forms by resolution with appropriate optically active resolving agents or by enzymatic methods, direct asymmetric synthesis of α-aminonitriles is still highly desirable. A number of chiral auxiliaries successfully used for this purpose mainly comprise optically active amines.[1] More recently, there has been interest in catalytic asymmetric Strecker reactions.[2] Some recent catalysts successfully employed include metal complexes of



Scheme 1.

Keywords: catalytic asymmetric synthesis; Strecker; imines.

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Table 1. Optimization of the conditions for asymmetric Strecker reaction of **1a**[a]

Entry	**4a** (mol%)	$Ti(O^iPr)_4$ (mol%)	Solvent	Temp. (°C)	Yield[b] (%)	Ee[c] (%)
1	5	5	Toluene	0	90	46
2	10	10	Toluene	0	90	79
3	20	20	Toluene	0	91	75
4	10	10	Hexane–toluene (1:1)	0	95	72
5	10	10	THF	0	83	48
6	10	10	Toluene	−20	69	8
7	10	10	Toluene	25	89	62

[a] The reactions were performed at a 0.2 mmol scale. Reaction time: 6 h.
[b] Yields were estimated from ^1H NMR integration of the crude products.
[c] Ee values were determined by integration of the $C_\alpha\underline{H}$ signals of **2** in the presence of (*S*)-camphorsulfonic acid in $CDCl_3$ (estimated error <±5%).

Schiff's bases,[3] BINOL and related ligands[4] and certain purely organic catalysts.[5]

Oguni and co-workers have pioneered the use and investigated the mechanism of reactions of Ti complexes of chiral Schiff's bases derived from β-amino alcohols which lead to asymmetric cyanosilylation of aldehydes giving silyl protected cyanohydrins in good yields and ee's.[6] In view of the similar mechanistic aspects of trimethylsilylcyanation of aldehydes and imines, it is surprising that no equivalent cyanation reactions of imines using this class of ligands has ever been reported. This prompted us to investigate this possibility.

The Strecker reaction of *N*-benzylidenebenzylamine **1a** (Scheme 1) was chosen as a model reaction since the optical purity of the resulting α-aminonitrile **2a** can be measured conveniently by ^1H NMR in the presence of (*S*)-camphorsulfonic acid in $CDCl_3$.[7] Initially the reaction between **1a** and trimethylsilyl cyanide (TMSCN) was carried out in the presence of 10 mol% of the non-C_2 symmetric Schiff's base ligands **3a** and **3b** and $Ti(O^iPr)_4$. Unfortunately, the enantioselectivity of the product **2a** was disappointingly poor (ca. 10%; conditions: 2 equiv. TMSCN, 10 mol% $Ti(O^iPr)_4$, −5 to 0°C in toluene). However, the reduced Schiff's base ligand **4a**[8] showed much better catalytic activity and gave the desired α-aminonitriles with better ee's.

The conditions for the asymmetric Strecker reaction of **1a** in the presence of ligand **4a** were optimized (Table 1). $Ti(O^iPr)_4$ was found to be the most effective co-catalyst at a co-catalyst:ligand ratio of 1:1.[9] The optimal amount of catalyst used was 10 mol% since poorer ee's were obtained with lower catalyst loadings and improvement in neither yield nor ee was observed with higher catalyst loadings (up to 20 mol%) (entries 1–3). Solvent polarity appears to have some effect on the stereoselectivity of the reaction. The reaction proceeded with higher enantioselectivities in less polar solvents including toluene or a hexane–toluene mixture (entry 4) while a reaction in THF gave a somewhat lower ee (entry 5). The reactions were initially performed at 0°C. Decreasing the temperature to −20°C led to a very slow reaction rate and, surprisingly, very poor selectivity (entry 6). At higher temperature, the reaction was faster, but proceeded with lower selectivity (entry 7). The optimal reaction temperature was found to be between −5 and 0°C. TMSCN was the preferred source of cyanide since poorer selectivities were obtained when HCN (generated in situ from TMSCN by the addition of 1 equiv. of ^{i}PrOH) was employed.[10,11]

In order to investigate the effect of the structure of the ligands on the selectivity of the reaction, the related *N*-salicyl-β-amino alcohol ligands **4b–f** were synthesized by $NaBH_4$ reduction of the corresponding Schiff's bases **3b–f**.[12] These ligands were screened under the best conditions obtained for **4a** and the results are summarized in Table 2. It is evident that the bulkiness of the substituent on the chiral β-amino alcohol plays an important role in determining the degree of selectivity. Ligands **4b**,**c** bearing the highly branched ^{i}Pr and ^{t}Bu groups showed the highest selectivities (82 and 86% ee) followed by those containing benzyl, phenyl, isobutyl and methyl substituents, respectively. Attempts to increase the steric bulk of the salicyl part by using ligand **4g** resulted in a disappointingly poor ee. In all cases the configuration of the major α-aminonitrile was *S* as determined by comparison of the $[\alpha]_D$ and ^1H NMR spectra in the presence of (*S*)-CSA with literature data.[7]

Table 2. Effects of catalyst structure[a]

Entry	Ligand	Yield[b] (%)	Ee[c] (%)	Configuration[d]
1	**4a**	98	76	*S*
2	**4b**	99	82	*S*
3	**4c**	98	86	*S*
4	**4d**	98	66	*S*
5	**4e**	97	48	*S*
6	**4f**	84	20	*S*
7	**4g**	83	8	*S*

[a] The reaction was performed at a 0.2 mmol scale. Conditions: 2 equiv. TMSCN; 10 mol% ligand; 10 mol% $Ti(O^iPr)_4$; toluene; 0°C; 6 h.
[b] Yields were estimated from ^1H NMR integration of the crude products.
[c] Ee values were determined by integration of the $C_\alpha\underline{H}$ signals of **2** in the presence of (*S*)-camphorsulfonic acid in $CDCl_3$ (estimated error <±5%).
[d] The absolute configuration was determined by comparison of the $[\alpha]_D$ and ^1H NMR chemical shifts of the $C_\alpha\underline{H}$ proton in the presence of (*S*)-camphorsulfonic acid with the literature data.[7]

Table 3. Effects of substrate structure[a]

1b-1j **2b-2j**

Entry	Ligand	Substrate	Product	R	Yield[b] (%)	Ee[c,d] (%)
1	**4a**	**1b**	**2b**	4-ClC_6H_4	84	72 (*S*)
2	**4a**	**1c**	**2c**	3-ClC_6H_4	98	80 (*S*)
3	**4a**	**1d**	**2d**	4-BrC_6H_4	86	71 (*S*)
4	**4a**	**1e**	**2e**	3-BrC_6H_4	98	81 (*S*)
5	**4a**	**1f**	**2f**	3-$NO_2C_6H_4$	>99	64 (*S*)
6	**4a**	**1g**	**2g**	4-$CH_3C_6H_4$	>99	67 (*S*)
7	**4a**	**1h**	**2h**	3-$PhOC_6H_4$	90	75 (*S*)
8	**4a**	**1i**	**2i**	4-$MeOC_6H_4$	98	44 (*S*)
9	**4c**	**1i**	**2i**	4-$MeOC_6H_4$	92	48 (*S*)
10	**4a**	**1j**	**2j**	2-$MeOC_6H_4$	92	51 (*S*)
11	**4c**	**1j**	**2j**	2-$MeOC_6H_4$	>99	39 (*S*)

[a] The reaction was performed at 0.2 mmol scale. Conditions: 2 equiv. TMSCN; 10 mol% ligand; 10 mol% Ti(O^{i}Pr)$_4$; toluene; 0°C; 9 h.
[b] Yields were estimated from ^{1}H NMR integration of the crude products.
[c] Ee values were determined by integration of the $C_\alpha\underline{H}$ signals of **2** in the presence of (*S*)-camphorsulfonic acid in $CDCl_3$ (estimated error <±5%).
[d] The absolute configuration was proposed to be (*S*) by analogy with R = Ph.

Finally, the substrate generality of this class of ligand was investigated using the crystalline ligand **4a** as a model. In all cases, optically active α-aminonitriles were obtained in excellent yields and with enantioselectivities ranging from fair to good (44–81% ee) (Table 3). Poor ee values were obtained with methoxy-substituted imines, and employing the more bulky ligand **4c** did not improve significantly the selectivity (entries 8–11). The scope and applications of these *N*-salicylaminoalcohol-catalyzed asymmetric Strecker reactions as well as mechanistic details of the catalysis are currently being explored, details of which will be disclosed elsewhere.

In conclusion, we have demonstrated that *N*-salicyl β-amino alcohol ligands **4** may be used successfully in conjunction with Ti(O^{i}Pr)$_4$ as effective catalysts for catalytic asymmetric Strecker reactions. To the best of our knowledge, this is the first report of asymmetric Strecker reactions being catalyzed by this class of ligand. The availability of the relatively inexpensive starting materials together with the simplicity of the reaction should provide a convenient and efficient access to optically active α-aminonitriles.

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8. Prepared in 68% yield as a white crystalline solid by reduction of **3a** with $NaBH_4$. Ligand **4a** has been previously synthesized from the $Zr(BH_4)_4$ reduction of the salicylimine derived from an α-amino ester. See: Narasimhan, S.; Balakumar, R. *Synth. Commun.* **2000**, *30*, 4387–4396.
9. Although Shibasaki (Refs. 4a,b) and Jacobsen (Ref. 3a) have shown that Al complexes were effective catalysts for asymmetric Strecker reactions, only a racemic product was obtained from the cyanation reaction of the imine **1a** with 1:1 $Al(O^iPr)_3$–**4a** catalyst system at 10 mol%.
10. The poor enantioselectivity when TMSCN was replaced by HCN can probably be accounted for by the high background rate of HCN addition to the imine (Ref. 3d). Addition of a toluene solution of HCN to **1a** in the presence of 10 mol% $Ti(O^iPr)_4$–**4a** gave a completely racemic product **2a**. However, if the concentration of HCN was kept low at all time by slow addition of the HCN solution to **1a** under the same conditions, (*S*)-**2a** was obtained in 94% yield and 63% ee.
11. *General procedure for ligand screening*: The chiral ligand (0.02 mmol) and $Ti(O^iPr)_4$ (0.02 mmol) were placed in an oven-dried 10 mL round bottom flask. The mixture was dissolved in dried toluene (0.3 mL). The reaction flask was capped with a rubber septum, sealed with Teflon tape and the solution was stirred for 10 min at room temperature. Subsequently, *N*-benzylidenebenzylamine **1a** (0.2 mmol) in 0.4 mL of dried toluene was added. The clear yellow solution was then stirred at −5 to 0°C (ice–salt bath). TMSCN (50 μL, 2 equiv.) was added to the solution and the mixture was stirred for 6–8 h. The solution was diluted with toluene and the solvent removed by distillation at reduced pressure to give a crude product. The crude material was passed through a short plug of neutral aluminum oxide (Activity I) in a Pasteur pipette using hexane/ethyl acetate (9/1) as eluent. *N*-Benzylaminophenylacetonitrile **2a** was obtained and analyzed for percent conversion by integration of the ^1H NMR signal of the imine and $C_\alpha H$. Enantioselectivity was determined after addition of 1 equiv. of (*S*)-CSA by integration of the now split $C_\alpha H$ signals.
12. Ligands **4b** and **4d** are known compounds. **4b**: see Ref. 8. **4d**: Suwa, T.; Sugiyama, E.; Shibata, I.; Baba, A. *Synthesis* **2000**, 789–800. All new ligands showed the expected ^1H and ^{13}C NMR and elemental analyses.