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A highly enantioselective Strecker reaction catalyzed by titanium-*N*-salicyl-β-aminoalcohol complexes

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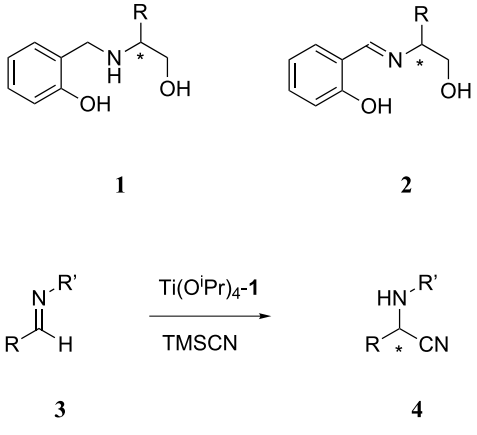
Abstract—*N*-salicyl-β-amino alcohols **1** were synthesized and evaluated as ligands for catalytic asymmetric Strecker reactions. *N*-Benzhydrylaldimines derived from aromatic and aliphatic aldehydes reacted with TMSCN in the presence of 10 mol% of Ti-**1** complex to give the Strecker products in excellent yields and in up to >98% ee. The presence of a protic additive is essential to ensure good conversion and reaction rate. The reaction conditions are simple and the stereochemical outcome is predictable from the configuration of the ligands, both enantiomers of which are readily synthesized.

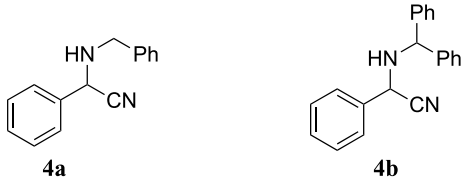
1. Introduction

The Strecker synthesis is one of the most atom-economical methods for the synthesis of α-amino acids. The classical Strecker reaction has been known since 1850, but it was not until 1963 that the first asymmetric Strecker synthesis was reported.[1] The majority of asymmetric Strecker syntheses developed since then involve the use of chiral auxiliaries, generally attached to the imine moiety.[2] Catalytic versions of asymmetric Strecker reactions have a relatively recent history.[3] In 1996, Lipton reported the first enantioselective Strecker reaction catalyzed by a cyclic dipeptide bearing a guanidine side-chain.[4] In less than 10 years, a number of highly effective catalysts have subsequently emerged. These catalysts can be entirely organic molecules such as Corey's cyclic guanidine[5] and Jacobsen's urea-Schiff base.[6] More recently, a number of promising chiral Lewis acid catalysts based on metal complexes of ligands such as BINOL[7] Schiff base,[8] bisoxazoline[9] and a carbohydrate derivative[10] have been developed.

Although many of these catalysts provide excellent enantioselectivities for a wide range of substrates, the most efficient ones are still fairly large and complex molecules with multiple stereogenic centers. From a practical point of view, it would be highly desirable to develop a small molecule catalyst possessing as few stereogenic centers as possible, provided that good reactivity and enantioselectivity can still be retained.



Scheme 1.



The tridentate *N*-salicyl-β-aminoalcohol **1** and its parent Schiff base **2** should form chelating complexes with metals such as titanium or aluminium. These complexes should

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behave as Lewis acids whilst providing a rigid asymmetric environment and, therefore, be potentially useful for catalyzing various types of asymmetric reactions. For instance, a heterobimetallic Li–Al complex of **1** was reported to catalyze the Michael addition of dialkyl malonates to cyclic enones.[11] Titanium complexes of **2** are highly efficient catalysts for enantioselective synthesis of cyanohydrins.[12] In view of the mechanistic similarity between hydrocyanation of aldehydes and imines, we envisaged that such catalysts would also perform well in the enantioselective Strecker reaction. The results of our preliminary investigation indicated that chiral *N*-salicyl-β-aminoalcohols **1** in combination with $Ti(O^iPr)_4$ were effective catalysts for asymmetric Strecker reactions of *N*-benzyl substituted imines **3** with TMSCN (Scheme 1).[13,14] The reported enantioselectivities were, however, rather moderate (maximum 86% ee). We have now discovered that the *N*-substituent of the imine substrate exerts a very significant effect on the degree of enantioselective induction. In this paper we disclose the results of our investigation on enantioselective Strecker reactions employing this versatile class of ligands in detail.

2. Results and discussion

2.1. Development of an NMR method for determination of enantiomeric purity

Although analysis of the enantiomeric purity of Strecker adducts is usually performed by chiral HPLC, this method was not available to us at the time of this investigation. We considered ^{1}H NMR spectroscopy as a potential alternative technique since it should require only a short analysis time, consume less solvent, require no expensive accessories such as chiral columns, and most importantly, the sample can be analyzed without any pre-treatment apart from removal of the reaction solvents. The only remaining problem was to find a suitable chiral media to distinguish the signals of each enantiomer. After trying several different chiral shift or chiral solvating agents, optically active camphorsulfonic acids (CSAs) previously used by Hassan et al. proved to be most effective in resolving the signals of the racemic *N*-benzyl α-aminonitrile (**4a**).[15] The splitting of the $C_\alpha H$ signal by up to 0.14 ppm was observed on a 200 MHz NMR spectrometer upon addition of 1–2 equiv of (*S*)-CSA to a 0.1 M solution of **4a** in $CDCl_3$. The $C_\alpha H$ and Ph_2CH peaks of *N*-benzhydryl substituted α-aminonitrile (**4b**) also split in the presence of CSA although the resolution was to a lesser magnitude than that of the *N*-benzyl analogues (up to 0.03 ppm for $C_\alpha H$ signal and 0.05 ppm for Ph_2CH signal). Nonetheless, a baseline resolution was obtained on a 400 MHz NMR spectrometer. Only a single $C_\alpha H$ peak was detected when enantiomerically pure (*S*)-**4b** was treated with CSA. The 'satellite' peaks can be easily detected in enantiomerically enriched samples containing as little as 1% of the other enantiomer (98% ee) prepared by addition of racemic **4b** to enantiomerically pure **4b** (Fig. 1). No racemization was observed after the CSA-treated sample was left at room temperature for several days. As expected, the position of the enantiomeric $C_\alpha H$ peaks reversed if the

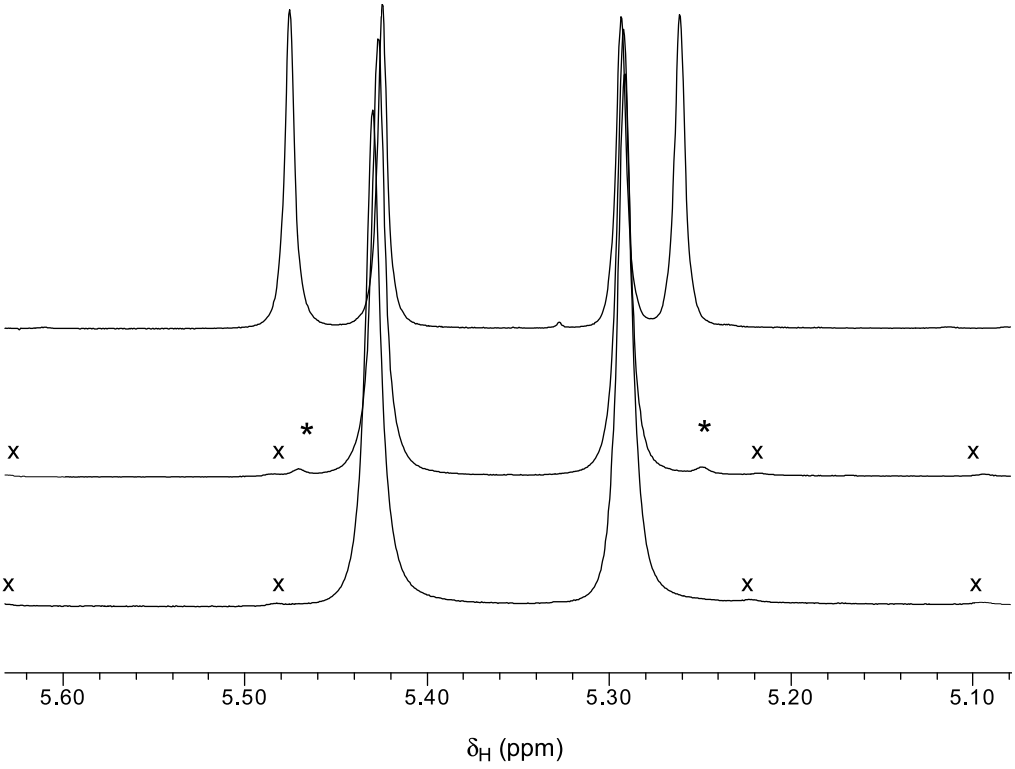
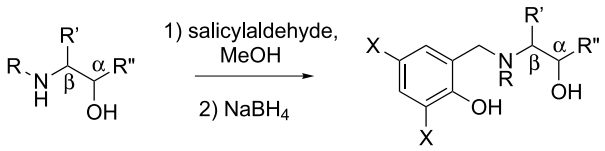


Figure 1. Partial ^{1}H NMR spectra of aminonitrile **4b** (400 MHz, $CDCl_3$) in the presence of (*S*)-CSA showing the Ph_2CH (δ_R: 5.48; δ_S: 5.42 ppm) and $C_\alpha H$ signals (δ_R: 5.26; δ_S: 5.29 ppm): racemic (top); 98% ee (middle); and enantiomerically pure (*S*)-**4b** (bottom). The humps marked by 'x' denote satellites due to ^{1}H–^{13}C couplings ($^1J_{1H-13C} \sim 140$ Hz).

Table 1. Structure and yield of the ligands[a] **1a–1k**



Entry	Ligand	Amino alcohols	R (N)	R′ (β)	R″ (α)	Yield (%)
1	(*S*)-**1a**	(*S*)-phenylalaninol	H	$PhCH_2$	H	74
2	(*R*)-**1a**	(*R*)-phenylalaninol	H	$PhCH_2$	H	72
3	(*S*)-**1b**	(*S*)-alaninol	H	Me	H	51
4	(*S*)-**1c**	(*S*)-valinol	H	^{i}Pr	H	75
5	(*S*)-**1d**	(*S*)-*tert*-leucinol	H	^{t}Bu	H	74
6	(*S*)-**1e**	(*S*)-phenylglycinol	H	Ph	H	73
7	(*S*)-**1f**	(*S*)-leucinol	H	^{i}Bu	H	50
8	(*S*)-**1g**	(*S*)-cyclohexyl-alaninol	H	$^{c}HexCH_2$	H	71
9	(*S*)-**1h**	(*S*,*S*)-isoleucinol	H	^{sec}Bu	H	74
10	(*R*)-**1i**	(*R*)-1-aminopropan-2-ol	H	H	CH_3	49
11	(*S*)-**1j**	(*S*)-prolinol		$-(CH_2)_3-$	H	50
12	(*S*)-**1k**	(*S*)-phenylalaninol	H	$PhCH_2$	H	59

[a] X=H for **1a–1j** (starting from salicylaldehyde); X=^{t}Bu for **1k** (starting from 3,5-di-^{tert}butylsalicylaldehyde).

opposite enantiomer of CSA was added. Importantly, CSA is very general in inducing a chiral environment for many other racemic *N*-benzyl and *N*-benzhydryl substituted α-aminonitriles (**4**) carrying different aromatic and aliphatic α-substituents. Therefore, we conclude that ^{1}H NMR is indeed a very reliable method for the determination of enantiomeric purity of a variety of Strecker adducts.

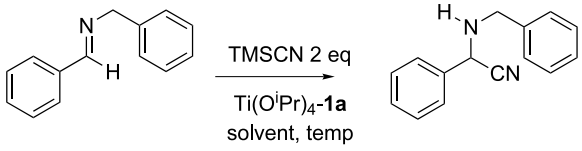
2.2. Synthesis of the ligands

The *N*-salicyl β-aminoalcohol ligand of type **1** is known in the literature. It has been synthesized by several methods including reduction of the salicylimines derived from the corresponding α-amino esters[16] or aminoalcohols.[17] Since a number of chiral β-aminoalcohols are readily available, we chose to synthesize **1** from the corresponding Schiff bases. Ligand (*S*)-**1a** was synthesized in 74% yield from commercially available (*S*)-phenylalaninol and salicylaldehyde via the Schiff base (*S*)-**2a** by $NaBH_4$ reduction. The ligand was obtained as a stable white crystalline solid after routine work-up and column chromatography. It can be kept for years at room temperature without detectable degradation. Many other related ligands can be similarly prepared from the corresponding β-aminoalcohols in 50–75% yield (Table 1).

2.3. Evaluation of the ligands for catalytic asymmetric Strecker reaction and optimization of the reaction conditions

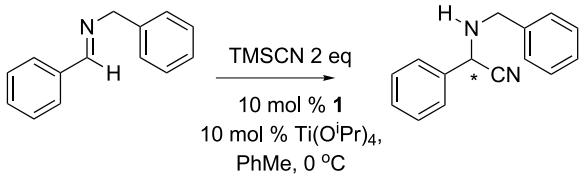
Several 1:1 metal complexes of (*S*)-**1a** and its parent Schiff base (*S*)-**2a** were prepared in situ and tested as catalysts for enantioselective Strecker reactions. The reaction between *N*-benzylidenebenzylamine (**3**: R=Ph; R′=$PhCH_2$) and TMSCN was used as a model. The reaction was performed in toluene at 0 °C in the presence of 10 mol% of the catalyst. Excess TMSCN (2 equiv) was essential to assure a complete reaction. While many complexes of both ligands provided

Table 2. Effect of solvent and temperature



Entry	Solvent	Catalyst (mol %)	*t* (°C)	Time (h)	Conversion (%)	ee (%)
1	Hexanes+PhMe (1:1)	10	0	6	97	72
2	Et_2O	10	0	6	98	52
3	THF	10	0	6	90	48
4	CH_2Cl_2	10	0	6	98	72
5	MeOH	10	0	6	96	0
6	PhMe	10	0	6	98	79
7	PhMe	10	−20	12	36	8
8	PhMe	10	25	6	97	62
9	PhMe	1	0	8	77	24
10	PhMe	5	0	8	96	46
11	PhMe	15	0	8	>99	74
12	PhMe	20	0	8	>99	75

Table 3. Effect of ligand structure



Entry	Ligand	R ligand (position)	Time (h)	Conversion (%)	ee (%)
1	(*S*)-**1a**	$PhCH_2$ (β)	6	98	79 (*S*)
2	(*S*)-**1b**	Me (β)	6	97	20 (*S*)
3	(*S*)-**1c**	^{i}Pr (β)	6	99	82 (*S*)
4	(*S*)-**1d**	^{t}Bu (β)	6	98	86 (*S*)
5	(*S*)-**1e**	Ph (β)	6	98	66 (*S*)
6	(*S*)-**1f**	^{i}Bu (β)	6	97	48 (*S*)
7	(*S*)-**1g**	$^{c}HexCH_2$ (β)	6	98	77 (*S*)
8	(*S*)-**1h**	^{sec}Bu (β)	6	98	87 (*S*)
9	(*R*)-**1i**	Me (α)	8	81	6 (*R*)
10	(*S*)-**1j**	$(CH_2)_3$ (N, β)	8	77	8 (*R*)
11	(*S*)-**1k**	$PhCH_2$ (β)	8	84	16 (*S*)

the desired Strecker product (**4a**) in good to excellent yields, only the titanium complex of the reduced Schiff base (*S*)-**1a** gave a satisfactory outcome in terms of both conversion and enantioselectivity. Interestingly, the presence of TMS groups was not observed in the Strecker adduct, presumably due to the cleavage of the rather labile N–Si bond by trace of moisture during work-up. The reaction parameters including solvent, temperature and catalyst loading were next optimized using this screening system (Table 2). It was evident that toluene is the best solvent for the reaction. Polar solvents resulted in lower degrees of enantioselectivity. The effect of temperature is also quite interesting, the best ee was obtained when the reactions were carried out at 0 °C. Not unexpectedly, higher temperatures resulted in poorer selectivity. At temperatures below 0 °C, the reaction was very slow, and interestingly the enantioselectivity dropped substantially. Decreasing the catalyst loading resulted in lower enantioselectivity while the conversion was not much affected. On the other hand, no improvement in selectivity was found at >10% catalyst loading, therefore, the optimal catalyst loading was 10%.

2.4. Effects of ligand structure

In order to investigate the effect of the ligand structure on the enantioselectivities, the reactions of imine **3** (R=Ph; R′=$PhCH_2$) with TMSCN in the presence of other catalysts were repeated under the best condition obtained for ligand (*S*)-**1a**. A good correlation, at least in a qualitative sense, between the size of the alkyl side-chain and the degree of enantioselectivity was observed. Therefore, only ligands bearing a relatively sterically hindered substituent at the β-position such as **1a** (R=$PhCH_2$), **1c** (R=^{i}Pr), **1d** (R=^{t}Bu), and **1h** (R=^{sec}Bu) provided synthetically useful selectivities (Table 3: entries 1, 3, 4 and 8). Addition of a bulky *tert*-butyl substituent on the salicyl moiety resulted in

Table 4. Enantioselective Strecker reactions of aromatic benzyl and benzhydrylimines (**3**) catalyzed by $Ti(O^{i}Pr)_4$-(*S*)-**1a** complexes[a,b]

Entry	R (substrate)	R′	Conversion (%)	ee (%)
1	Ph	$PhCH_2$	98	79
2	4-ClC_6H_4	$PhCH_2$	96	72
3	4-MeC_6H_4	$PhCH_2$	97	67
4	4-$MeOC_6H_4$	$PhCH_2$	93	45
5	3-$NO_2C_6H_4$	$PhCH_2$	>99	64
6	2-$MeOC_6H_4$	$PhCH_2$	>99	51
7	Ph	Ph_2CH	>99	98
8	4-ClC_6H_4	Ph_2CH	>99	95
9	4-MeC_6H_4	Ph_2CH	>99	96
10	4-$MeOC_6H_4$	Ph_2CH	>99	91
11	3-$MeOC_6H_4$	Ph_2CH	>99	94
12	3-$NO_2C_6H_4$	Ph_2CH	>99	98
13	2-MeC_6H_4	Ph_2CH	>99	97
14	2-ClC_6H_4	Ph_2CH	>99	97[c]
15	2-BrC_6H_4	Ph_2CH	>99	>98[c]
16	2-$MeOC_6H_4$	Ph_2CH	>99	90
17	1-Naphthyl	Ph_2CH	98	98
18	2-Naphthyl	Ph_2CH	97	96
19	2-Furyl	Ph_2CH	>99	98
20	2-Thienyl	Ph_2CH	>99	98

[a] Reaction time: entries 1–6=9 h; entries 7–20=48 h.
[b] For reaction conditions see Table 3.
[c] Baseline separation of the enantiomeric $C_{\alpha}H$ and Ph_2CH signals was not achieved. The reported ee values were estimated by comparison of the optical rotation with known reference compounds (Ref. 8b).

Table 5. Enantioselective Strecker reactions of aliphatic benzhydrylimines catalyzed by Ti(O^iPr)$_4$-**1** complexes[a,b]

Entry	R (substrate)	Ligand	conversion (%)	ee (%)
1	^{t}Bu	(*S*)-**1a**	>99	23
2	^{t}Bu	(*S*)-**1d**	>99	47
3	^{t}Bu	(*S*)-**1h**	>99	51
4	PhCH=CH	(*S*)-**1a**	>99	61
5	PhCH=CH	(*S*)-**1d**	>99	88
6	PhCH=CH	(*S*)-**1h**	>99	91

[a] Reaction time: 24 h.
[b] For reaction conditions see Table 3.

a substantially decreased enantioselectivity (entry 11). In all aforementioned cases, the absolute configuration of the Strecker product **4a** was determined to be *S* based on the chemical shift of the $C_\alpha H$ signal in the presence of (*S*)-CSA and by comparison of the optical rotation with a known standard.[15] Moving the substituent to the α-position also resulted in a poor enantioselectivity (compare entries 2 and 9). Ligand (*S*)-**1j** bearing an *N*-alkyl substituent which is part of a pyrrolidine ring gave, apart from a very low selectivity, the product of opposite absolute configuration (entry 10).

2.5. Effects of substrate structure

The substrate generality of enantioselective Strecker reactions employing this class of ligand was investigated. Various substituted aldimines were subjected to cyanide addition under the best conditions obtained thus far using the Ti complex of (*S*)-**1a**. It was found that optically active α-aminonitriles **4** were obtained in excellent yields and with enantioselectivity ranging from poor to fairly good (45–79% ee) for *N*-benzyl substituted aldimine substrates (**3**: R=Ph; R′=$PhCH_2$) (Table 4, entries 1–6). However, a dramatic breakthrough was achieved when *N*-benzhydryl substituted aldimines (**3**: R′=Ph_2CH) were used as substrates. The Strecker reaction of *N*-benzhydrylimine (**3**: R=Ph; R′=Ph_2CH) in the presence of Ti(O^iPr)$_4$-(*S*)-**1a** required somewhat longer reaction time to reach >99% conversion, but provided the corresponding optically active α-aminonitrile in 98% ee under otherwise identical conditions (Table 4, entry 7). The bulkier ligands **1c**, **1d** and **1h** also gave the same conversion (>99%) and ee range for this substrate (**1c**: 94%; **1d** and **1h**: 97%). Ee values of >90% were routinely observed for various imine substrates derived from aromatic aldehydes and benzhydrylamine (Table 4, entries 8–20). Substituents with various steric and electronic natures appeared to be well-tolerated for virtually all imines derived from substituted benzaldehyde studied. Equally good results were obtained for non-benzaldehyde derived aromatic imines including 1-naphthyl, 2-naphthyl and heteroaromatic substrates. Aliphatic substrates such as those derived from pivalaldehyde and cinnamaldehyde gave much poorer ee's at similar conversion. Nevertheless, the use of ligands bearing bulkier substituents such as **1d** and **1h** gave significantly improved results (Table 5). The *S*-configuration of the Strecker products was assumed in all cases (except for entries 19–20 in Table 4, vide infra) by analogy to **4a** and **4b**.

2.6. The role of protic additives

Upon scaling up the reaction from 0.1 mmol to 0.5 or 1 mmol, the rate of the reaction was found to be significantly slower. In many cases the reaction did not proceed to completion at all although the ee values were practically the same. Previous works in this area have demonstrated the importance of proton sources in similar reactions.[7a,8b] The proton source can generate HCN from TMSCN, which is believed to be the actual cyanating species.[8b] Furthermore, since the catalyst contains free hydroxylic functions which should be susceptible to silylation by TMSCN under the reaction conditions, a proton source should increase the catalyst turnover by preventing silylation of, or by regenerating, the hydroxylic function of the catalyst.[18] We were delighted to find that addition of a proton source such as water or 2-propanol

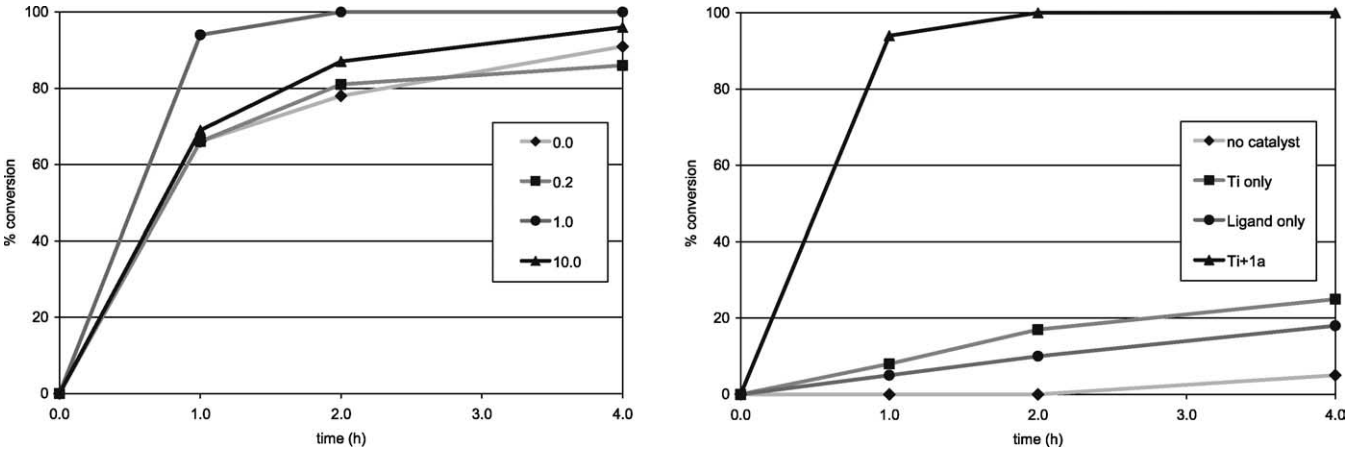
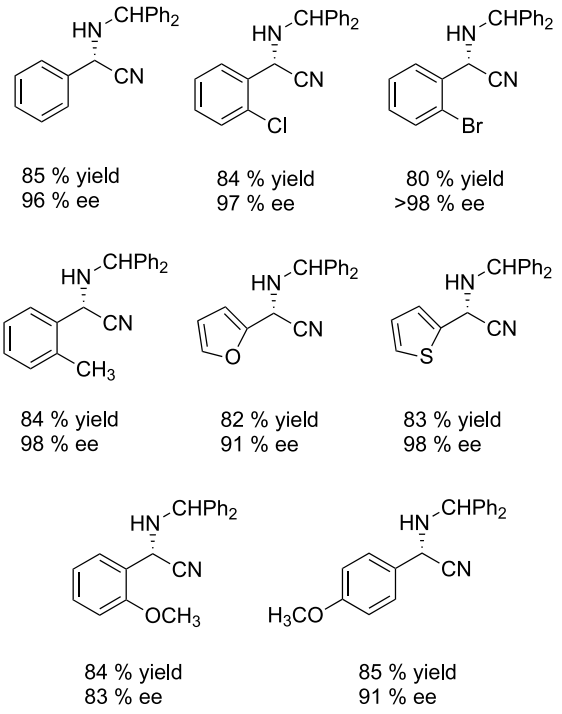


Figure 2. The rate of cyanation of imine **3** (R=Ph; R′=Ph_2CH) at 0 °C the presence of 10 mol% Ti(O^iPr)4-(*S*)-**1a** complex and 0, 0.2, 1.0 and 10 equiv of 2-propanol (left) and in the presence of 10 equiv 2-propanol and with or without Ti(O^iPr)$_4$ and/or (*S*)-**1a** (10 mol%) (right).

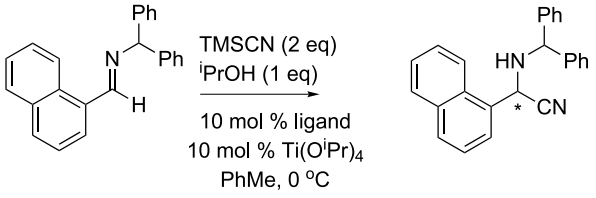
completely restored the catalytic activity. Kinetic analysis by ^{1}H NMR spectroscopy of the Ti-(*S*)-**1a** catalyzed cyanation of imine **3** (R=Ph; R′=Ph_2CH) conducted in the presence of different amounts of 2-propanol additive suggested that the reaction rate was significantly enhanced compared to a reaction without the additive (Fig. 2, left). Most interestingly, the reaction rate reaches a maximum when an equivalent amount of the additive is used and under these conditions. The reaction went to completion within 2 h at 0 °C. A large excess of 2-propanol (10 equiv) resulted not only in a significantly slower reaction rate, but also provided almost racemic product. The reactions in the presence of 1.0 equiv ^{i}PrOH but without the Ti-(*S*)-**1a** catalyst or either of its components were very slow (Fig. 2, right). In all cases the conversion was <20% after 2 h at 0 °C. This suggested that the background hydrocyanation is almost insignificant under the experimental conditions, at least for this particular substrate. Consequently, the slow addition of ^{i}PrOH or performing the reaction at very low temperatures may not be essential to ensure good enantioselectivities. This would greatly simplify the synthetic procedure. Indeed, we have found that the additive can be added at the beginning of the reaction without any adverse effects on the yield and enantioselectivity.[19] The role of the protic additive is probably less important for small scale reactions where the total exclusion of all adventitious moisture was difficult which explains why the reaction proceeded to completion without the need for the protic additive.

To ascertain that the protic additive is generally beneficial for large scale reactions with other substrates, a few more representative reactions were attempted at 1 mmol scale with 1.0 equiv of 2-propanol added at the beginning and 10 mol% catalyst prepared from ligand (*S*)-**1a** (25 mg of the ligand/mmol of substrate). ^{1}H NMR analysis of the crude reaction mixture revealed that all reactions were completed within 4 h at 0 °C, and that the enantioselectivities were comparable to the small scale reactions. Interestingly, after attempted purification by passing through silica gel or an alumina column, significant racemization was observed for products **4** bearing electron donating substituents (e.g., 2-furyl, 2-thienyl, 2-and 4-methoxyphenyls) so that the final products of only 50–75% ee were obtained. We have confirmed that the racemization was catalyzed by weak acids including silica gel and neutral alumina. Fortunately, addition of a small amount of triethylamine to the eluting solvent largely suppressed the racemization. In all cases, the isolated yield of the crystalline products were >80% and the enantioselectivities were good to excellent (Scheme 2). The absolute configuration of all products derived from the ligand (*S*)-**1a** was confirmed to be *S* by comparison of the optical rotations with literature values.[8b] It should be noted that, for R=2-thienyl and 2-furyl, although the sense of asymmetric induction is the same, the absolute configuration must be designated as *R* according to Cahn–Ingold–Prelog sequence rules. The stereoselectivity of the enantioselective Strecker reaction induced by the Ti-**1** catalyst is, therefore, fully controlled by the absolute configuration of the ligand **1** (Scheme 3).

It is obvious that aminonitriles with opposite configuration should be obtained in a highly predictable manner simply by switching to the enantiomeric ligand. The presence of only



Scheme 2.



ligand	yield (%)	% ee (config.)	$[\alpha]_D^{23}$
(*S*)-**1a**	91	> 98 (*S*)	-186 °
(*R*)-**1a**	87	> 98 (*R*)	+185 °

Scheme 3.

one stereogenic center in the ligand moiety means that the other enantiomer is much more easily obtained than those with multiple stereogenic centers. To further demonstrate the application of this novel catalyst system, the two enantiomers of the optically active α-aminonitrile precursor of 1-naphthylglycine were prepared. The reaction of the imine **3** (R=1-naphthyl; R′=Ph_2CH) with TMSCN and 1.0 equiv ^{i}PrOH in the presence of 10 mol% Ti(O^iPr)$_4$-(*S*)-**1a** on a 1 mmol scale afforded the corresponding (*S*)-α-aminonitrile in 91% yield and >98% ee. The opposite enantiomer was similarly obtained in 87% yield and >98% ee by employing (*R*)-**1a** derived from commercially available (*R*)-phenylalaninol as the ligand.

3. Conclusions

In summary, this work has demonstrated that Ti complexes of *N*-salicyl-β-aminoalcohols **1** are highly effective catalysts

for enantioselective Strecker reactions of aldimines. It has been clearly shown that the configuration as well as the bulkiness of the β-substituent exerts a direct influence on both the absolute stereochemical outcome and enantioselectivity of the Strecker product. Furthermore, we have illustrated that excellent yields accompanied by extremely high degrees of enantioselectivity can be obtained when a substrate with a more sterically demanding *N*-substituent was employed. The superiority of this class of optically active ligands can be emphasized due to their low molecular weights and the fact that they possess only one stereogenic center, the starting precursor of which is readily available with any desirable absolute stereochemistry. In addition, it has been shown that the reaction conditions are extremely simple. It is expected that these catalyst systems will offer a very practical access to optically active α-aminonitriles and α-amino acids. Further understanding of the mechanistic details of the catalysis and efforts to improve the catalysts to accommodate aliphatic substrates are currently in progress.

4. Experimental

4.1. General procedure for the preparation of ligands 1

A mixture of ethanol (2 mL), an appropriate amino alcohol (1 mmol), and aldehyde (1 mmol) was stirred at room temperature until the starting materials were totally consumed (monitored by TLC). To the yellow mixture was added $NaBH_4$ (37.8 mg, 1 mmol) with stirring to give a colorless solution. The reaction was then quenched with dil. HCl. After neutralization (sat. $NaHCO_3$), the reaction mixture was concentrated under reduced pressure and the residue was extracted with ethyl acetate and washed with water. The organic layer was dried over anhydrous Na_2SO_4 and the solvent removed. The products were purified by flash column chromatography (hexanes/ethyl acetate).

4.1.1. *N*-(2′-Hydroxyphenyl)methyl-(*S*)-2-amino-3-phenyl-propanol [(*S*)-1a]. White crystalline solid (0.190 g, 74%). Mp 133–134 °C; $[\alpha]_D^{23}=-23.0$ (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.89 (1H, A*B*X, $J_{AB}=13.6$ Hz, $J_{BX}=7.6$ Hz, C$H_a$$H_b$Ph), 2.91 (*A*BX, $J_{AB}=13.6$ Hz, $J_{AX}=6.4$ Hz, CH$_a$$H_b$Ph), 3.02 (1H, m, C*H*NH), 3.58 (1H, A*B*X, $J_{AB}=11.0$ Hz, $J_{BX}=5.0$ Hz, CH$_a$$H_b$OH), 3.78 (1H, *A*BX, $J_{AB}=11.0$ Hz, $J_{AX}=3.8$ Hz, CH_aH$_b$OH), 4.05 (2H, s, CH_2NH), 6.82 (1H, apparent t, $J=7.2$ Hz, Ar), 6.87 (1H, d, $J=8.0$ Hz, Ar), 7.01 (1H, d, $J=7.2$ Hz, Ar), 7.19–7.38 (6H, m, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 37.3, 50.3, 59.7, 62.6, 116.6, 119.2, 122.7, 126.7, 128.3, 128.7, 128.9, 129.2, 138.0, 158.0; Anal. Calcd for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; N, 5.44. Found: C, 74.66; H, 7.41; N, 5.43%.

4.1.2. *N*-(2′-Hydroxyphenyl)methyl-(*S*)-2-amino-propanol [(*S*)-1b]. Viscous yellowish oil (0.092 g, 51%). $[\alpha]_D^{25}=+66.0$ (*c* 1.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz); δ 1.17 (3H, d, $J=6.4$ Hz, CH_3), 2.92 (1H, m, C*H*CH$_3$), 3.54 (1H, A*B*X, $J_{AB}=10.9$ Hz, $J_{BX}=6.6$ Hz, CH$_a$$H_b$OH), 3.75 (1H, *A*BX, $J_{AB}=10.9$ Hz, $J_{AX}=3.6$ Hz, CH_aH$_b$OH), 4.00 and 4.10 (2H, AB, $J=13.8$ Hz, CH_2NH), 4.20 (br s, N*H* and O*H*) 6.81 (1H, apparent t, $J=7.4$ Hz, Ar), 6.86 (1H, d, $J=8.0$ Hz, Ar), 7.03 (1H, d, $J=7.2$ Hz, Ar), 7.19 (1H, apparent t, $J=7.6$ Hz, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz); δ 16.1, 49.8, 53.9, 65.6, 116.5, 119.1, 121.7, 128.4, 128.9, 158.0; Anal. Calcd for $C_{10}H_{15}NO_2$: C, 66.27; H, 8.34; N, 7.73. Found: C, 66.11; H, 8.50; N, 7.75%.

4.1.3. *N*-(2′-Hydroxyphenyl)methyl-(*S*)-2-amino-3-methyl-butanol [(*S*)-1c]. White crystalline solid (0.157 g, 75%). Mp 52–54 °C; $[\alpha]^{26}{}_D=+15.0$ (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.01 and 1.04 (6H, 2×d, $J=6.8$ Hz, 2×CH_3), 1.99 (1H, m, C*H*(CH$_3$)$_2$), 2.54 (1H, m, C*H*NH), 3.69 (1H, A*B*X, $J_{AB}=11.1$ Hz, $J_{BX}=6.0$ Hz, CH$_a$$H_b$OH), 3.87 (1H, *A*BX, $J_{AB}=11.1$ Hz, $J_{AX}=3.8$ Hz, CH_aH$_b$OH), 4.05 (2H, s, CH_2NH), 6.82 (1H, apparent t, $J=7.4$ Hz, Ar), 6.88 (1H, d, $J=8.0$ Hz, Ar), 7.03 (1H, d, $J=7.6$ Hz, Ar), 7.21 (1H, apparent t, $J=7.7$ Hz, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.3, 19.2, 28.7, 51.0, 61.2, 64.0, 116.5, 119.1, 123.1, 128.2, 128.8, 158.1; Anal. Calcd for $C_{12}H_{19}NO_2$: C, 68.87; H, 9.15; N, 6.69; Found: C, 68.65; H, 9.39; N, 6.73%.

4.1.4. *N*-(2′-Hydroxyphenyl)methyl-(*S*)-2-amino-3,3-dimethyl-butanol [(*S*)-1d]. White crystalline solid (0.165 g, 74%). Mp 58−60 °C; $[\alpha]_D^{25}=+5.0$ (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.04 (9H, s, 3×CH_3), 2.41 (1H, AB*X*, $J_{AX}=3.6$ Hz, $J_{BX}=5.8$ Hz, C*H*C(CH$_3$)$_3$), 3.74 (1H, A*B*X, $J_{AB}=10.9$ Hz, $J_{BX}=5.8$ Hz, CH$_a$$H_b$OH), 4.00 (1H, *A*BX, $J_{AB}=10.9$ Hz, $J_{AX}=3.6$, CH_aH$_b$OH), 4.02 and 4.10 (2H, AB, $J=13.3$ Hz, CH_2NH), 6.82 (1H, apparent t, $J=7.4$ Hz, Ar), 6.89 (1H, d, $J=8.0$ Hz, Ar), 7.04 (1H, d, $J=7.2$ Hz, Ar), 7.21 (1H, apparent t, $J=7.8$ Hz, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.5, 34.2, 53.1, 61.2, 67.8, 116.4, 119.3, 123.7, 128.5, 128.8, 157.9; Anal. Calcd for $C_{13}H_{21}NO_2$: C, 69.92; H, 9.48; N, 6.27; Found: C, 69.95; H, 9.52; N, 6.27%.

4.1.5. *N*-(2′-Hydroxyphenyl)methyl-(*S*)-2-amino-2-phenyl-ethanol [(*S*)-1e]. White crystalline solid (0.201 g, 73%). Mp 119–121 °C; $[\alpha]_D^{20}=+64.0$ (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.74 (1H, A*B*, $J=13.6$ Hz, CH$_a$$H_b$NH, 3.76–3.87 (3H, m, C$H_2$OH and C*H*NH), 3.97 (1H, *A*B, $J=13.6$ Hz, CH_aH$_b$NH), 5.05 (br s, N*H* and O*H*), 6.79 (1H, apparent t, $J=7.2$ Hz, Ar), 6.87 (1H, d, $J=8.0$ Hz, Ar), 6.92 (1H, d, $J=6.4$ Hz, Ar), 7.19 (1H, apparent t, $J=8.0$ Hz, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 50.1, 63.9, 66.5, 116.4, 119.4, 122.8, 127.5, 128.2, 128.6, 128.9, 129.0, 138.7, 157.8; Anal. Calcd for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.76. Found: C, 74.07; H, 7.03; N, 5.79%.

4.1.6. *N*-(2′-Hydroxyphenyl)methyl-(*S*)-2-amino-4-methyl-pentanol [(*S*)-1f]. Light yellow crystalline solid (0.114 g, 50%). Mp 87–88 °C; $[\alpha]_D^{22}=+15.0$ (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.95 (6H, t, $J=6.2$ Hz, 2×CH_3), 1.36 and 1.44 (2H, 2×m, CH_2-CH(CH$_3$)$_2$), 1.74 (1H, m, C*H*(CH$_3$)$_2$), 2.81 (1H, m, C*H*NH), 3.56 (1H, A*B*X, $J_{AB}=11.1$ Hz, $J_{BX}=5.6$ Hz, CH$_a$$H_b$OH), 3.84 (1H, *A*BX, $J_{AB}=11.1$ Hz, $J_{AX}=3.4$ Hz, CH_aH$_b$OH), 4.04 (2H, s, CH_2NH), 4.90 (br s, N*H* and O*H*), 6.79 (1H, apparent t, $J=6.4$ Hz, Ar); 6.87 (1H, d, $J=8.0$ Hz, Ar) 7.02 (1H, d, $J=6.8$ Hz, Ar), 7.19 (1H, apparent t, $J=7.8$ Hz, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.7, 22.8, 25.0, 40.2, 49.8, 56.2, 63.2, 116.5, 119.1, 122.8, 128.3, 128.7, 158.1; Anal. Calcd for $C_{13}H_{21}NO_2$: C, 69.92; H, 9.48; N, 6.27. Found: C, 69.74; H, 9.55; N, 6.04%

4.1.7. N-(2′-Hydroxyphenyl)methyl-(*S*)-2-amino-3-cyclohexyl-propanol [(*S*)-1g]. Light yellow crystalline solid (0.200 g, 71%). Mp 82–84 °C; $[\alpha]_D^{25}=+12.0$ (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz); δ 0.85–1.78 (13H, m, ^{c}Hex ring protons and ^{c}HexCH_2), 2.83 (1H, m, C*H*NH), 3.55 (1H, A*B*X, $J_{AB}=11.1$ Hz, $J_{BX}=5.2$ Hz, CCH_aH_bOH), 3.82 (1H, *A*BX, $J_{AB}=11.1$ Hz, $J_{AX}=3.4$ Hz, CH_aH_bOH), 4.03 (2H, s, CH_2NH), 5.02 (br s, N*H* and O*H*), 6.81 (1H, apparent t, $J=7.2$ Hz, Ar), 6.87 (1H, d, $J=8.0$ Hz, Ar), 7.02 (1H, d, $J=7.2$ Hz, Ar), 7.19 (1H, apprent t, $J=7.8$ Hz, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 26.2, 26.5, 33.6, 34.5, 38.6, 49.7, 55.5, 63.2, 116.5, 119.1, 122.8, 128.4, 128.9, 158.1; Anal. Calcd for $C_{16}H_{25}NO_2$: C, 72.96; H, 9.57; N, 5.32. Found: C, 73.16; H, 9.49; N, 5.46%.

4.1.8. *N*-(2′-Hydroxyphenyl)methyl-(*S*)-2-amino-(*S*)-3-methyl-pentanol [(*S*)-1h]. Yellowish oil (0.166 g, 74%). $[\alpha]_D^{22}=+54.0$ (*c* 2.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz); δ 0.95 (6H, m, CH_3CH_2 and CH_3CH), 1.22 and 1.50 (2H, 2×m, CH_3CH_2), 1.75 (1H, m, CH_3CH), 2.66 (1H, m, C*H*NH), 3.63 (1H, A*B*X, $J_{AB}=11.2$ Hz, $J_{BX}=6.8$ Hz, CH_aH_bOH), 3.83 (1H, *A*BX, $J_{AB}=11.2$ Hz, $J_{AX}=3.6$ Hz, CH_aH_bOH), 3.98–4.09 (2H, AB, $J=13.6$ Hz, CH_2NH), 4.85 (br s, N*H* and O*H*), 6.81 (1H, apparent t, $J=7.4$ Hz, Ar), 6.87 (1H, d, $J=8.0$ Hz, Ar), 7.03 (1H, d, $J=7.2$ Hz, Ar), 7.20 (1H, apparent t, $J=7.8$ Hz, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 11.9, 14.8, 26.2, 35.2, 50.7, 61.0, 62.7, 116.5, 119.2, 123.0, 128.4, 128.9, 158.0; Anal. Calcd for $C_{13}H_{21}NO_2$: C, 69.92; H, 9.48; N, 6.27. Found: C, 69.85; H, 9.42; N, 6.20%.

4.1.9. *N*-(2′-Hydroxyphenyl)methyl-(*R*)-1-amino-propanol [(*R*)-1i]. Light yellow crystalline solid (0.089 g, 49%). Mp 87–88 °C; $[\alpha]_D^{25.9}=-24.0$ (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz); δ 1.13 (3H, d, $J=6.4$ Hz, CH_3CH), 2.50 (1H, A*B*X, $J_{AB}=12.0$ Hz, $J_{BX}=8.4$ Hz, CH_aH_bCH), 2.62 (1H, *A*BX, $J_{AB}=12.0$ Hz, $J_{AX}=3.2$ Hz, CH_aH_bCH), 3.91 (1H, m, C*H*OH), 3.90 and 3.99 (2H, AB, $J=14.0$ Hz, CH_2NH), 5.03 (br s, N*H* and O*H*), 6.71 (1H, apparent t, $J=7.4$ Hz, Ar), 6.75 (1H, d, $J=8.2$ Hz, Ar), 6.91 (1H, d, $J=7.2$ Hz, Ar), 7.09 (1H, apparent t, $J=7.6$ Hz, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.5, 52.5, 55.6, 66.5, 116.4, 119.1, 122.4, 128.5, 128.8, 158.1; Anal. Calcd for $C_{10}H_{15}NO_2$: C, 66.27; H, 8.34; N, 7.73. Found: C, 66.14; H, 8.30; N, 7.67%.

4.1.10. *N*-(2′-Hydroxyphenyl)methyl-(*S*)-2-hydroxymethyl-pyrrolidine [(*S*)-1j]. Viscous yellowish oil (0.103 g, 50%). $[\alpha]_D^{24}=-75.0$ (*c* 1.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz); δ 1.76–2.08 (4H, m, pyrrolidine $(CH_2)_2$), 2.37 (1H, m, pyrrolidine N–CH_aH_b), 2.79 (1H, m, pyrrolidine N–CH_aH_b), 3.10 (1H, m, N–C*H*CH_2OH), 3.57 (1H, AB, $J=14.0$ Hz, $ArCH_aH_bN$), 3.69 (1H, A*B*X, $J_{AB}=11.2$ Hz, $J_{BX}=4.8$ Hz, CH_aH_bOH), 3.75 (1H, *A*BX, $J_{AB}=11.2$ Hz, $J_{AX}=3.8$ Hz, CH_aH_bOH), 4.33 (1H, AB, $J=14.0$ Hz, $ArCH_aH_bN$), 6.18 (br s, O*H*), 6.80 (1H, apparent t, $J=7.2$ Hz, Ar), 6.84 (1H, d, $J=8.0$ Hz, Ar), 7.00 (1H, d, $J=7.6$ Hz, Ar), 7.18 (1H, apparent t, $J=7.6$ Hz, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.2, 27.5, 54.5, 58.3, 64.0, 65.5, 116.0, 119.1, 122.9, 128.1, 128.6, 157.6; Anal. Calcd for $C_{12}H_{17}NO_2$: C, 69.54; H, 8.27; N, 6.76. Found: C, 69.14; H, 8.29; N, 6.71%.

4.1.11. *N*-(3′,5′-Di-*tert*-butyl-2′-hydroxyphenyl)methyl-(*S*)-2-amino-3-phenyl-propanol [(*S*)-1k]. Viscous yellowish oil (0.219 g, 59%). $[\alpha]_D^{22}=-33.0$ (*c* 2.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz); δ 1.32 and 1.45 (2×9H, 2×s, $C(CH_3)_3$)), 2.86 (1H, A*B*X, $J_{AB}=13.6$ Hz, $J_{BX}=7.6$ Hz, CH_aH_bPh), 2.97 (1H, *A*BX, $J_{AB}=13.4$ Hz, $J_{AX}=6.4$ Hz, CH_aH_bPh), 3.03 (1H, m, C*H*NH), 3.58 (1H, A*B*X, $J_{AB}=11.2$, $J_{BX}=4.8$ Hz, CH_aH_bOH), 3.76 (1H, *A*BX, $J_{AB}=11.2$, $J_{AX}=3.6$ Hz, CH_aH_bOH), 3.99–4.08 (2H, AB, $J=13.6$ Hz, CH_2NH), 6.90 (1H, s, Ar), 7.22–7.37 (6H, m, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 29.8, 31.8, 34.3, 35.0, 37.4, 51.1, 59.9, 62.7, 122.3, 123.2, 123.3, 126.7, 128.8, 129.4, 136.3, 138.2, 140.9, 154.4; Anal. Calcd for $C_{24}H_{35}NO_2$: C, 78.00; H, 9.55; N, 3.79. Found: C, 78.16; H, 9.71; N, 3.61%.

4.1.12. *N*-(2′-Hydroxyphenyl)methyl-(*R*)-2-amino-3-phenyl-propanol [(*R*)-1a]. White crystalline solid (0.185 g, 72%). Mp 133–134 °C; $[\alpha]_D^{22}=+24.0$ (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.85 (1H, A*B*X, $J_{AB}=13.6$ Hz, $J_{BX}=7.6$ Hz, CH_aH_bPh), 2.94 (1H, *A*BX, $J_{AB}=13.6$ Hz, $J_{AX}=6.4$ Hz, CH_aH_bPh), 3.03 (1H, br, C*H*NH), 3.57 (1H, A*B*X, $J_{AB}=11.2$ Hz, $J_{BX}=4.8$ Hz, CH_aH_bOH), 3.76 (1H, *A*BX, $J_{AB}=11.2$ Hz, $J_{AX}=3.2$ Hz, CH_aH_bOH), 4.04 (2H, s, CH_2NH), 6.80 (1H, apparent t, $J=7.2$ Hz, Ar), 6.85 (1H, d, $J=8.0$ Hz, Ar), 7.00 (1H, d, $J=7.2$ Hz, Ar), 7.19–7.38 (6H, m, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 37.1, 50.1, 59.7, 62.5, 116.6, 119.3, 122.6, 126.7, 128.4, 128.8, 129.0, 129.2, 137.9, 157.9; Anal. Calcd for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; N, 5.44. Found: C, 74.43; H, 7.29; N, 5.41%.

4.2. General procedure for Ti-catalyzed addition of TMSCN to imines (small scale)

Ligand **1** (0.02 mmol) was dissolved in anhydrous toluene (0.3 mL). $Ti(O^iPr)_4$ (6.0 μL, 0.02 mmol) was added to the reaction and stirred for 10 min at ambient temperature to give a clear yellow solution. The selected imine (0.2 mmol) was added and then cooled to 0 °C (ice–salt bath) for 15 min. TMSCN (50 μL, 0.4 mmol) was then added using syringe. The progress of the reaction and enantioselectivity was monitored by ^{1}H NMR analysis.

4.3. General procedure for Ti-catalyzed addition of TMSCN to imines (large scale)

Ligand (**1a**) (25 mg, 0.1 mmol) placed in a screw-cap vial was dissolved in anhydrous toluene (1.5 mL). $Ti(O^iPr)_4$ (29.8 μL, 0.1 mmol) was added to the reaction and stirred for 10 min at ambient temperature to give a clear yellow solution. 2-Propanol (76.5 μL, 1.0 mmol) was added and left for another 10 min. The selected imine (1.0 mmol) was then added and the reaction cooled to 0 °C. Finally, TMSCN (250 μL, 2.0 mmol) was quickly added in one portion. After 8 h, the crude product was purified by passing through a plug of neutral alumina eluting with ethyl acetate–hexanes plus 0.1% Et_3N to yield the corresponding α-aminonitriles.

4.3.1. (*S*)-Diphenylmethylamino-phenylacetonitrile. White solid (0.253 g, 85%), 96% ee: $[\alpha]_D^{22}=-63.0$ (*c* 1.0, $CHCl_3$) {lit.[8b] $[\alpha]_D^{24}$ (97% ee, *c* 5.0, $CHCl_3$)$=-64.2$}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.18 (1H, d, $J=12.0$ Hz, N*H*CH), 4.63 (1H, d, $J=12.0$ Hz, C*H*CN), 5.28 (1H, s, $CHPh_2$), 7.23–7.55 (11H, m, Ar), 7.60 (4H, m, Ar); ^{13}C

NMR ($CDCl_3$, 100 MHz) δ 52.4, 65.6, 118.8, 127.2, 127.3, 127.5, 127.8, 128.0, 128.8, 129.0, 129.1, 129.2, 135.0, 141.2, 142.8.

4.3.2. (*S*)-Diphenylmethylamino-2-bromophenylacetonitrile. White solid (0.280 g, 80%), >98% ee: $[\alpha]_D^{22} = -121.0$ (*c*1.0, $CHCl_3$) {lit.[8b] $[\alpha]_D^{24}$ (>99% ee, *c* 5.0, $CHCl_3$) = −122}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.92 (1H, s, C*H*CN), 5.24 (1H, s, C*H*Ph_2), 7.22–7.45 (8H, m, Ar), 7.50 (2H, d, *J*=7.2 Hz, Ar), 7.58–7.68 (4H, m, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 52.6, 65.7, 118.3, 123.4, 127.2, 127.8, 127.9, 128.0, 128.3, 128.8, 128.9, 129.4, 130.8, 133.8, 134.5, 140.7, 142.6.

4.3.3. (*S*)-Diphenylmethylamino-2-chlorophenylacetonitrile. White solid (0.256 g, 84%), 97% ee: $[\alpha]_D^{22} = -118.0$ (*c*1.0, $CHCl_3$) {lit.[8b] $[\alpha]_D^{24}$ (>99% ee, *c* 3.5, $CHCl_3$) = −122} ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.93 (1H, s, C*H*CN), 5.26 (1H, s, C*H*Ph_2), 7.22–7.42 (8H, m, Ar), 7.28 (2H, d, *J*=7.2 Hz, Ar), 7.60 (4H, m, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 50.3, 65.8, 118.2, 127.2, 127.6, 127.7, 127.8, 128.0, 128.8, 128.9, 129.3, 130.4, 130.6, 132.8, 133.5, 140.7, 142.6.

4.3.4. (*S*)-Diphenylmethylamino-2-methylphenylacetonitrile. White solid (0.245 g, 84%), 98% ee: $[\alpha]_D^{24} = -161.0$ (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.03 (1H, br, N*H*CH), 2.33 (3H, s, CH_3), 4.62 (1H, s, C*H*CN), 5.32 (1H, s, C*H*Ph_2), 7.22–7.36 (7H, m, Ar), 7.40 (2H, m, Ar), 7.48 (2H, d, *J*=7.2 Hz, Ar), 7.60 (3H, m, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.0, 50.4, 65.9, 118.9, 126.8, 127.1, 127.6, 127.7, 128.0, 128.2, 128.9, 129.0, 129.3, 131.2, 133.3, 136.6, 141.1, 142.9.

4.3.5. (*S*)-Diphenylmethylamino-2-methoxyphenylacetonitrile. White solid (0.253 g, 84%), 83% ee: $[\alpha]_D^{24} = -57.0$ (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.92 (3H, s, OCH_3), 4.71 (1H, s, C*H*CN), 5.23 (1H, s, C*H*Ph_2), 7.03 (2H, m, Ar), 7.28–7.43 (8H, m, Ar), 7.48 (2H, d, *J*=7.6 Hz, Ar), 7.56 (2H, d, *J*=7.6 Hz, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 48.6, 55.7, 65.4, 111.5, 119.2, 121.1, 123.5, 127.4, 127.6, 127.7, 127.8, 128.8, 128.9, 129.0, 130.7, 141.6, 143.0, 157.1.

4.3.6. (*S*)-Diphenylmethylamino-4-methoxyphenylacetonitrile. White solid (0.256 g, 85%), 91% ee; $[\alpha]_D^{24} = -38.0$ (*c* 1.0, $CHCl_3$) {lit.[8b] $[\alpha]_D^{22}$ (94% ee, *c* 0.54, $CHCl_3$) = −27.7}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.94 (1H, d, *J*=12.0 Hz, N*H*CH), 3.66 (3H, s, OCH_3), 4.39 (1H, d, *J*=12.0 Hz, C*H*CN), 5.06 (1H, s, C*H*Ph_2), 6.78 (2H, d, *J*=8.8 Hz, Ar) 7.02–7.22 (6H, m, Ar), 7.29 (4H, m, Ar), 7.40 (2H, d, *J*=7.6 Hz, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 51.9, 55.4, 65.6, 114.4, 119.1, 127.1, 127.2, 127.5, 127.7, 128.0, 128.6, 128.8, 129.1, 141.3, 142.9, 160.1.

4.3.7. (*R*)-Diphenylmethylamino-furan-2-ylacetonitrile. White solid (0.214 g, 82%), 91% ee: $[\alpha]_D^{21} = -25.0$ (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.37 (1H, br, N*H*CH), 4.65 (1H, s, C*H*CN), 5.20 (1H, s, C*H*Ph_2), 6.42 (1H, dd, *J*=3.2, 2.0 Hz, C*H*-furan), 6.49 (1H, d, *J*=3.2 Hz, C*H*-furan), 7.24–7.42 (6H, m, Ar), 7.48 (3H, d, *J*=7.6 Hz, C*H*-furan and Ar), 7.55 (2H, d, *J*=7.2 Hz, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 46.2, 65.2, 109.0, 110.7, 117.1, 127.3, 127.4, 127.9, 128.0, 128.9, 129.1, 140.9, 142.4. 143.7, 147.3.

4.3.8. (*R*)-Diphenylmethylamino-thiophen-2-ylacetonitrile. White solid (0.239 g, 83%), 98% ee: $[\alpha]_D^{24} = -76.0$ (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.22 (1H, d, *J*=12.0 Hz, N*H*CH), 4.62 (1H, d, *J*=12.0 Hz, C*H*CN), 5.08 (1H, s, C*H*Ph_2), 6.84 (1H, dd, *J*=5.2, 3.6 Hz, C*H*-thiophene), 7.05–7.28 (8H, m, C*H*-thiophene and Ar), 7.30 (2H, d, *J*=7.2 Hz, Ar), 7.40 (2H, d, *J*=7.2 Hz, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 48.3, 65.5, 118.2, 126.2, 126.8, 127.0, 127.2, 127.4, 127.9, 128.2, 128.9, 129.2, 138.4, 140.9, 142.6.

4.3.9. (*S*)-Diphenylmethylamino-1-naphthylacetonitrile. White solid (0.316 g, 91%), >98% ee: $[\alpha]_D^{23} = -186.0$ (*c*1.0, $CHCl_3$) {lit.[8b] $[\alpha]_D^{22}$ (>99% ee, *c* 2.0, $CHCl_3$) = −182.2}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.24 (1H, br, N*H*CH), 5.20 (1H, s, C*H*CN), 5.41 (1H, s, C*H*Ph_2), 7.21–7.60 (11H, m, Ar), 7.66 (2H, d, *J*=7.2 Hz, Ar), 7.82–7.91 (2H, m, Ar), 7.95 (2H, d, *J*=7.2 Hz, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 50.5, 66.1, 118.9, 123.1, 125.3, 125.9, 126.3, 126.9, 127.0, 127.7, 128.1, 128.3, 128.7, 128.9, 129.0, 130.2, 130.4, 130.6, 134.0, 141.1, 142.6.

4.3.10. (*R*)-Diphenylmethylamino-1-naphthylacetonitrile [from (*R*)-1a ligand]. White solid (0.303 g, 87%), >98% ee: $[\alpha]_D^{23} = +185.0$ (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.20 (1H, br, N*H*CH), 5.20 (1H, s, C*H*CN), 5.40 (1H, s, C*H*Ph_2), 7.20–7.60 (11H, m, Ar), 7.64 (2H, d, *J*=7.2 Hz, Ar), 7.82–7.90 (2H, m, Ar), 7.95 (2H, d, *J*=7.2 Hz, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 50.5, 66.1, 118.9, 123.2, 125.3, 125.9, 126.3, 126.9, 127.0, 127.7, 128.1, 128.3, 128.8, 128.9, 129.0, 130.2, 130.4, 130.7, 134.0, 141.1, 142.7.

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