

Asymmetric Strecker Reaction of Ketoimines Catalyzed by a Novel Chiral Bifunctional *N,N'*-Dioxide

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Abstract: A novel bifunctional *N,N'*-dioxide derived from L-prolinamide was employed to catalyze the enantioselective Strecker reaction of a range of *N*-tosyl ketoimines, and an effective additive was used to improve the reactivity (up to 99% yield) as well as the enantioselectivity (up to 91% *ee*). In addition, a rational transition state was proposed to elucidate the origin of chiral induction in which an *S*-adduct was produced.

Keywords: asymmetric catalysis; ketoimines; organocatalyst; Strecker reaction

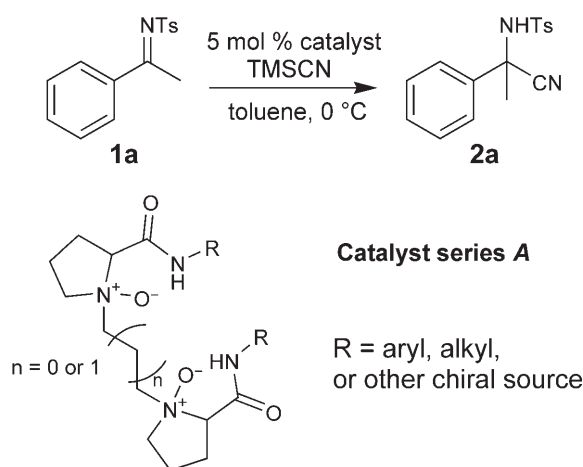
The catalytic asymmetric Strecker reaction is of great importance to modern organic chemistry as it offers one of the most direct and viable methods for the asymmetric synthesis of α -amino acids and their derivatives. Efforts have recently reached a peak of perfection in the efficient catalyzed cyanation of aldimines to afford α -amino nitriles in high optical purity.^[1,2] In principle, the same strategy could be applied to ketoimines to afford α,α -dialkylated amino nitriles. In practice, however, the catalytic enantioselective Strecker reactions of ketoimines are not as easily performed as those of aldimines. There are only four catalysts reported to date: Jacobsen's urea catalyst,^[3a,d] Shibasaki's Gd-complex catalyst,^[3e-g] and Vallée's Ti-complex^[3b] as well as their heterobimetallic^[3c] analogues. There is still room for developing new catalysts for the cyanation of ketoimines. Herein we report a new bifunctional organocatalyst for the enantioselective cyanation of ketoimines.

In our previous studies, we have disclosed that an *N*-oxide was an excellent promoter for the addition of TMSCN to aldimines,^[2i] aldehydes^[4] and ketones.^[5] So we have applied many different kinds of *N*-protected

ketoimines to the catalytic Strecker reaction using *N*-oxides as promoters. As a result, we have found that, without any catalyst, *N*-tosyl ketoimine remained unchanged after treatment with TMSCN at ambient temperature even in the presence of a large amount of methanol (5 equivs.). Consequently, a catalytic amount of a certain *N*-oxide (such as trimethylamine oxide and triethylamine oxide) uniquely promotes this reaction to produce the *N*-protected amino nitrile in quantitative yield.^[6] This finding encouraged us to seek a simple chiral *N*-oxide for the catalytic asymmetric Strecker reaction of ketoimines.

Ketoimine **1a** has been selected as the model substrate. Initial catalyst screening started from the prolinamide-derived alkyl-linked *N,N'*-dioxides^[4] (Scheme 1). Unfortunately, this alkyl-linked series exhibited low enantioselectivities (<35% *ee*) despite their high activities (>95% yield).

Considering that the conformational flexibility of the alkylated linkage of catalyst series **A** may not be



Scheme 1. Catalytic asymmetric cyanation of ketoimine **1a** using the catalyst series **A**.

beneficial to construct an effective fixed chiral pocket, another series of catalysts with more rigidity has been synthesized (Figure 1). As the results in Table 1 show, all these catalysts displayed high reac-

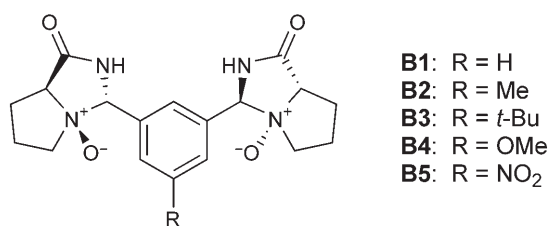


Figure 1. Structures of catalyst series **B**.

tivities, while catalyst **B1** achieved superior enantioselectivity (Table 1, entry 1). Substituents on the phenyl ring of **B1** including an electron-donating group (Table 1, entry 4), an electron-withdrawing group (Table 1, entry 5), a bulky alkyl group (Table 1, entry 3) and a methyl group (Table 1, entry 2), all resulted in inferior asymmetric induction (Table 1, entries 2–5). Higher catalyst loading has no effect on enantioselectivity, but the reaction has been speeded up (Table 1, entry 1 vs. 6). A slight increase of enantioselectivity at lower temperature was accompanied by an intense decrease of reactivity whereby a prolonged reaction time was needed for complete conversion of the substrate (Table 1, entry 10).

Catalyst **B1**, which is a hydrophilic compound with quite strong polarity (Scheme 2), is readily prepared *via* a simple condensation of commercially available L-prolinamide and isophthalaldehyde followed by oxidation with *m*-CPBA. Furthermore, any attempt to produce a single crystal from any one of the **B** series

Table 1. Catalytic asymmetric cyanation of ketoimine **1a**.^[a]

Entry	Catalyst	<i>t</i> [h]	Yield ^[b] [%]	<i>ee</i> ^[c] [%]
1	B1	36	99	70
2	B2	36	92	44
3	B3	36	85	33
4	B4	36	85	15
5	B5	36	82	11
6 ^[d]	B1	24	99	70
7 ^[e]	B1	30	99	70
8 ^[f]	B1	40	90	61
9 ^[g]	B1	30	99	57
10 ^[h]	B1	140	95	75

^[a] All the reactions were carried out in a 0.2 mmol scale of **1a** using 1.5 equivs. of TMSCN in 1 mL toluene with 5 mol % catalyst at 0 °C in a closed system under air unless otherwise specified.

^[b] Isolated yield (for all tables).

^[c] Determined by HPLC on Chiralcel OJ column.

^[d] 10 mol % catalyst was used under an N₂ atmosphere.

^[e] 2.0 equivs. of TMSCN were used.

^[f] 1.2 equivs. of TMSCN were used.

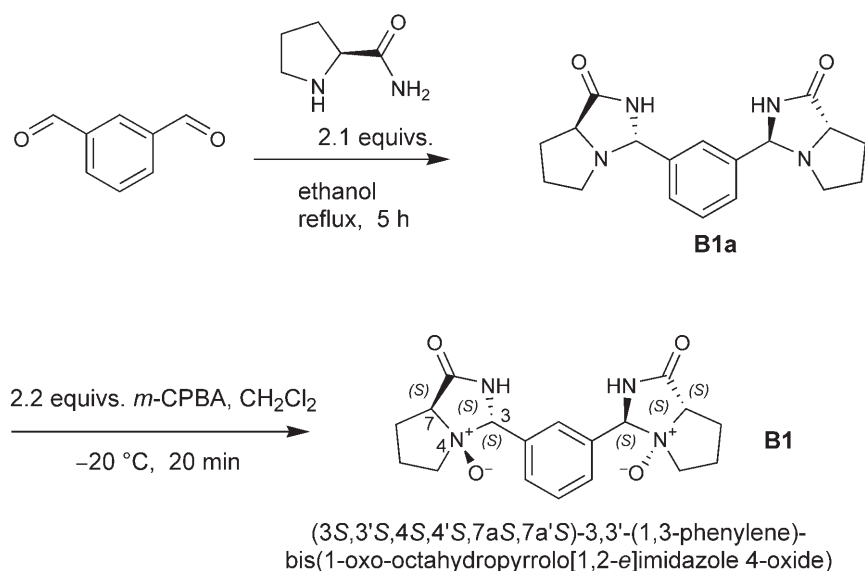
^[g] 2.5 equivs. of TMSCN were used.

^[h] The reaction was performed at –20 °C.

catalyst has failed, but the absolute configuration of **B1** can be estimated according to the literature.^[7,8] Other **B** series catalysts can be obtained in similar procedures using substituted isophthalaldehydes.

In view of the hypersubstituent sensitivity effect on the phenyl ring of **B1** and low reactivity at low temperature, further improvement of enantioselectivity and reactivity was mainly focused on additives.

As displayed in Table 2, a hydroxy group in the additives is essential to accelerate the reaction, while the substituent at the *ortho* position to the hydroxy



Scheme 2. Preparation of catalyst **B1**.

Table 2. Additives screening.^[a]

Entry	Additive	<i>t</i> [h]	Yield [%]	<i>ee</i> ^[b] [%]
1	phenol	20	90	19
2	1-adamantanol	20	95	60
3	<i>o</i> - <i>tert</i> -butylphenol	20	99	53
4	biphenol	20	90	29
5	<i>S</i> -binaphthol	20	90	44
6	<i>R</i> -binaphthol	20	93	42
7	pyrocatechol	40	85	40
8	resorcinol	20	90	61
9	hydroquinone	20	95	74
10	DBHQ ^[c]	20	99	78
11	DAHQ ^[d]	20	99	80
12 ^[e]	DAHQ	20	99	77
13 ^[f]	DAHQ	20	99	45
14 ^[g]	DAHQ	68	99	85
15 ^[h]	DAHQ	120	95	85
16 ^[i]	DAHQ	20	99	53
17 ^[j]	DAHQ	20	99	5
18 ^[k]	DAHQ	60	95	70

^[a] All the reactions were carried out in a 0.2 mmol scale of **1a** using 1.5 equivs. of TMSCN in 1 mL toluene with 5 mol % catalyst and 20 mol % additive at 0 °C in a closed system under air unless otherwise specified.

^[b] Determined by HPLC on Chiralcel OJ column.

^[c] DBHQ: 2,5-di-*tert*-butylhydroquinone.

^[d] DAHQ: 2,5-di-(1-adamantyl)hydroquinone.

^[e] 10 mol % DAHQ was used.

^[f] 40 mol % DAHQ was used.

^[g] The reaction was performed at –20 °C.

^[h] The reaction was performed at –20 °C under N₂ atmosphere.

^[i] CH₂Cl₂ was used as solvent.

^[j] THF was used as solvent.

^[k] Et₂O was used as solvent.

unit plays an important role in enhancement of enantioselectivity. *R*- or *S*-binaphthol obtained similar results (Table 2, entry 5 vs. 6); this may indicate that no visible chiral recognition occurred between **B1** and binaphthol, thus the improved asymmetric inductivity probably could be due to a steric effect of the additives. A more bulky group at the *ortho* position of the hydroxy unit performs basically better than smaller ones as expected (Table 2, entry 1 vs. 3 and entry 10 vs. 11). A superior additive (Table 2, entry 11) proved to be **DAHQ**^[9] which is an extremely sterically hindered species.

Other optimizations have also been investigated: the best amount of additive proved to be 20 mol % (Table 2, entry 11); decreasing the reaction temperature to –20 °C led to a slight increase of enantioselectivity (Table 2, entry 14) whereas further lowering it to –45 °C or more rendered the system nearly unreactive; other solvents have been found to be inferior to toluene (Table 2, entries 16–18). Notably, when the reaction was performed under an N₂ atmosphere

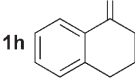
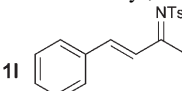
(Table 2, entry 15), the reactivity clearly deteriorated. This may indicate that a trace amount of moisture was important to accelerate the transformation of the substrate; meanwhile, it has also suggested that this catalytic system presents an air-tolerant property.

Substrate generality has been surveyed thereafter. As shown in Table 3 aromatic substrates have generally achieved excellent yield and good enantioselectivity with **1f** (Table 3, entry 6) manifesting the best results under the present protocol (91 % *ee*). Aliphatic substrates as well as heterocyclic substrates have provided results comparable with those for aromatic ones (Table 3, entries 9–11) whereas an α,β -unsaturated substrate (Table 3, entry 12) furnished a moderate *ee* value. It should be noticed that the highly enantioselective cyanation of ketoimine bearing a cyclohexyl moiety has not been realized yet. To our delight, in our catalytic system, *N*-tosyl cyclohexylmethylketoimine **1j** could be smoothly transformed to the corresponding *N*-tosylamino nitrile in high yield with good enantiomeric purity (Table 3, entry 10).

As to the mechanism, there are extensive literature precedents that TMSCN reacts rapidly with alcohols and phenols to produce HCN and this has been demonstrated to be the actual cyanating agent in a number of previous Strecker reactions involving TMSCN. In our present system, however, the substrates have proved to be inert to HCN, and in this manner we speculated that hypervalent silicate and hydrogen bonds should be crucial for the asymmetric induction in spite of the HCN produced upon addition of phenol.^[10] Therefore, a possible transition state was propounded as illustrated in Figure 2. Trimethylsilyl cyanide was activated by the twin *N,N'*-dioxides at the same time to produce a hypervalent silicate species whereby a fixed chiral pocket was created, resulting in the cyanide group being polarized to acquire more reactivity; meanwhile, imine **1a** was recognized by **B1** through hydrogen bonding and inserted into the catalytic system *via* a more suitable pathway. In **TS-2**, the phenyl group of **1a** and the phenyl ring of **B1** were repulsing on each other while the carbonyl unit of each one encountered a similar situation, hence the attempt to generate the *R*-product was disfavoured to some extent. On the other hand, however, the *S*-product was smoothly produced according to **TS-1** which was a minimal sterically blocked pathway. Besides, through hydrogen bonding, **DAHQ** assisted **B1** to magnify the steric effect of the activated intermediate formed in the transition state, leading to an improvement of the stereoselectivity.

In summary, we have developed a new bifunctional organocatalyst for the general asymmetric Strecker reaction of ketoimines in high yields with moderate to excellent enantioselectivities. This method possesses the agreeable features of air-tolerance and easy manipulation as well as a facile and low cost access to

Table 3. Substrates scope.^[a]

$ \begin{array}{c} \text{NTs} \\ \parallel \\ \text{R}-\text{C}-\text{R}' \\ \mathbf{1} \end{array} \xrightarrow[\text{TMSCN, Toluene, } -20^\circ\text{C}]{5 \text{ mol } \% \text{ B1, 20 mol } \% \text{ DAHQ}} \begin{array}{c} \text{NHTs} \\ \\ \text{R}-\text{C}^*-\text{CN} \\ \\ \text{R}' \\ \mathbf{2} \end{array} $				
Entry	Substrate	<i>t</i> [h]	Yield [%]	<i>ee</i> ^[b] [%]
1	1a R = phenyl, R' = Me	68	99	85 (<i>S</i>) ^[c]
2	1b R = 4-methylphenyl, R' = Me	80	94	61 (<i>S</i>) ^[d]
3	1c R = 4-chlorophenyl, R' = Me	80	91	71 (<i>S</i>) ^[d]
4	1d R = 4-bromophenyl, R' = Me	80	90	71 (<i>S</i>) ^[d]
5	1e R = 4-methoxyphenyl, R' = Me	80	92	76 (<i>S</i>) ^[d]
6	1f R = 3,4-dimethoxyphenyl, R' = Me	70	95	91 (<i>S</i>) ^[d]
7	1g R = 2-naphthyl, R' = Me	80	98	71 (<i>S</i>) ^[d]
8	1h 	80	96	65 (<i>S</i>) ^[d]
9	1i R = 2-thiophenyl, R' = Me	80	92	81
10	1j R = cyclohexyl, R' = Me	68	99	85
11	1k R = <i>t</i> -butyl, R' = Me	70	95	77
12	1l 	80	99	61

^[a] All the reactions were carried out on a 0.2 mmol scale of **1** using 1.5 equivs. of TMSCN in 1 mL toluene with 5 mol % **B1** and 20 mol % **DAHQ** at -20°C in a closed system.

^[b] Determined by HPLC analysis on OJ or AS-H column.

^[c] The absolute configuration was assigned after transformation to the corresponding amino acid.

^[d] The absolute configuration was determined by comparing the Cotton effect of the CD spectra with that of **2a**.

catalyst and reactants. Further investigations are underway in our laboratory including exploration of a relative catalyst library, detailed mechanism, extended substrate scope and enhancement of enantioselectivity.

Experimental Section

General Remarks

All the catalytic manipulations were carried out under air in a closed system. NMR spectra were recorded on a Bruker 300 MHz or 600 MHz spectrometer. Chemical shifts are reported downfield from TMS ($\delta=0$) for ^1H NMR. For ^{13}C NMR, chemical shifts are reported on the scale relative to the solvent used as an internal reference. Data for ^1H NMR are reported as follows: chemical shift (δ ppm), multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad), coupling constant (Hz), integration and assignment. Data for ^{13}C NMR are reported in terms of chemical shift (δ ppm). Melting points are uncorrected. Solvents used were purified by usual methods. Other commercially available reagents were used as received. Optical purity was determined by HPLC analysis on Daicel Chiralcel OJ or Chiralpak ASH column at 254 nm. Optical rotations were measured on a Rudolph-Autopl V polarimeter.

General Procedures for the Preparation of *N*-Tosylimines^[11]

To a stirred solution of ketone (20 mmol), Ts-NH₂ (30 mmol) and ZnCl₂ (4 mmol) in toluene (100 mL), Ti(*O*-*i*-Pr)₄ (24 mmol) was added dropwise then the mixture was heated to reflux for 12 h. 2 N NaOH (4 mL) was added to the reaction mixture after cooling down to quench the reaction, then the solid formed was filtered off and washed with 200 mL ether. The combined filtrate was washed successively by 2 N NaOH (2 × 100 mL), brine (1 × 100 mL) and dried over MgSO₄. Solvents were removed under reduced pressure, and the residue was purified by either recrystallization or silica gel chromatograph to afford the corresponding imine in 15–80 % yield.

Preparation of **B1**

A solution of L-prolinamide (10.5 mmol) and isophthalaldehyde (5 mmol) in 10 mL anhydrous ethanol was heated to reflux for 5 h, then after solvent had been removed under reduced pressure, the residue was purified by silica gel chromatography using ethyl acetate/methanol as eluent to afford *trans* **B1a** as white solid (and a trace amount of *cis* product as a later eluting fraction can be collected together with unreacted L-prolinamide).

To a stirred solution of 800 mg **B1a** in 40 mL CH₂Cl₂ at -20°C , 940 mg (2.2 equivs.) of *m*-CPBA were added in one portion and the mixture allowed to stir for 20 min (TLC analysis to ensure the complete consumption of **B1a**; and a

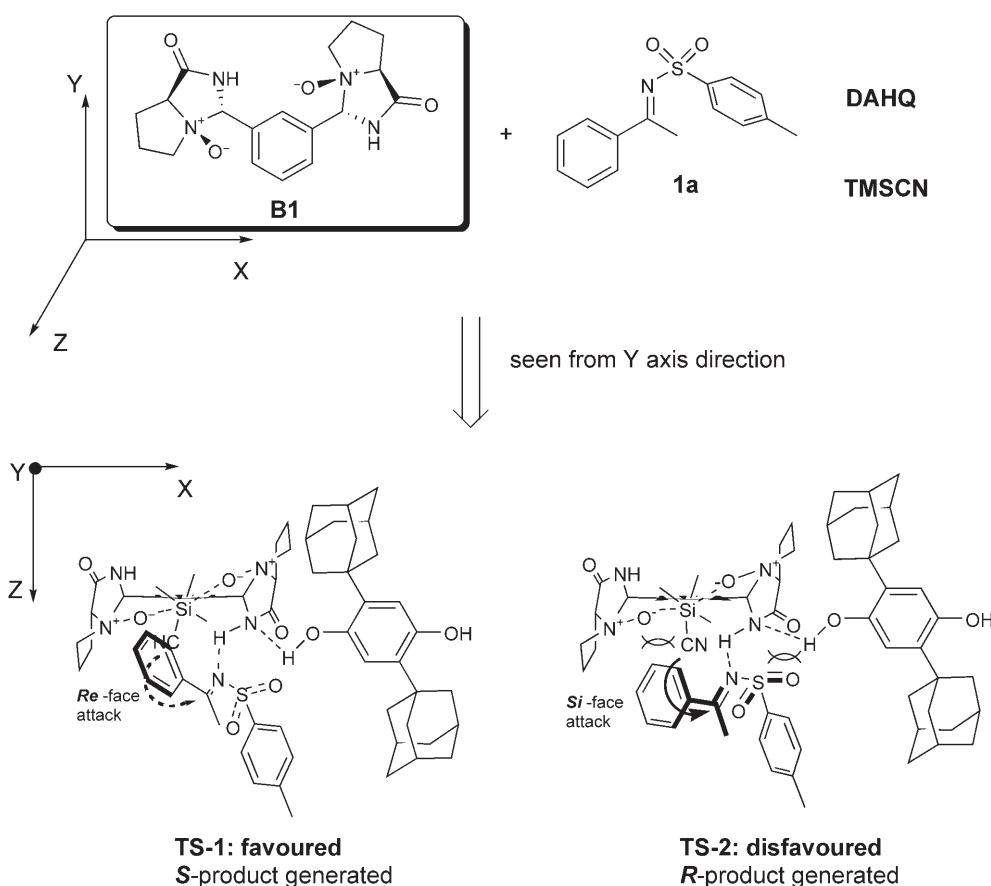


Figure 2. A simplified model of proposed transition state.

single product was detected by TLC), then the solvent was removed under vacuum with the temperature not exceeding 40 °C. The residue was purified on silica gel using methanol then NH₃ in methanol as eluent to obtain **B1** in 95 % yield.

Typical Procedure for Racemic Reaction

To a stirred solution of **1a** (54.7 mg, 0.2 mmol) and trimethylamine oxide (3 mg, 0.04 mmol) in toluene (1 mL), TMSCN (42 µL, 1.5 equivs.) was added in one portion at ambient temperature. After complete conversion (monitored by TLC), the residue was purified by flash chromatography on silica gel using EtOAc/petroleum ether (1:3, v/v) as eluent to afford **2a** in 99 % yield.

Typical Procedure for Catalytic Cyanation of Ketoimine

To a stirred solution of **1a** (54.7 mg, 0.2 mmol), DAHQ (15.2 mg, 0.04 mmol, 20 mol %) and **B1** (3.6 mg, 0.01 mmol, 5 mol %) in toluene (1 mL), TMSCN (42 µL, 1.5 equivs.) was added in one portion at –20 °C. After complete conversion (monitored by TLC, 68 h), the residue was purified by flash chromatography on silica gel using EtOAc/petroleum ether (1:3, v/v) as eluent to afford **2a** in 99 % yield.

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- [10] There should be an equilibrium between TMSCN and HCN in the presence of phenol, and it is TMSCN, not HCN, combined with the *N,N*-dioxide that could generate a highly reactive cyanating agent. To support this hypothesis we have done the following experiment: Method **I**: To a stirred solution of **1a** (27.3 mg, 0.1 mmol) and **B1** (3.6 mg, 0.01 mmol, 10 mol %) in 0.5 mL toluene, ethyl cyanoformate (20 μ L, 2 equivs.) was added in one portion at ambient temperature, followed by addition of acetic acid (12 μ L, 2 equivs.). Method **II**: To a stirred solution of **1a** (27.3 mg, 0.1 mmol) and **B1** (3.6 mg, 0.01 mmol, 10 mol %) in 0.5 mL water-saturated toluene, ethyl cyanoformate (20 μ L, 2 equivs.) was added in one portion at ambient temperature. These two methods are alternative ways instead of using TMSCN and phenol that could produce HCN which could serve as cyanating agent. As predicted, after 30 h stirring at ambient temperature, no product was detected (by TLC) for both methods. This could demonstrate that the silicon reagent plays an important role in the present catalytic system and TMSCN is very likely to be the real cyanating agent. Or we may suggest that a highly reactive intermediate might be generated by combination of TMSCN and *N,N*-dioxide. Comparably, there is no such interaction between HCN and *N,N*-dioxide with the result that no addition occurred.
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