Asymmetric Cyanosilylation of Aldehydes Catalyzed by Novel Organocatalysts

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Abstract: A novel proline-based *N*,*N*′-dioxide, which is easily prepared from inexpensive chemicals, serves as an effective catalyst for enantioselective cyanosilylation of aldehydes in up to 73% ee.

Key words: proline-based *N*,*N*′-dioxide, aldehydes, organocatalyst, cyanosilylation, enantioselectivity

Chiral *N*-oxides have been used in several asymmetric procedures, such as the allylation of aldehydes,[1] the addition of Et_2Zn to aldehydes,[2] the reduction of ketones,[3] the epoxide openings,[4] the aldol reaction[5] and the Strecker reactions.[6] Herein, we report on a novel class of organic catalysts, proline-based *N*,*N*′-dioxide, that efficiently catalyzes the asymmetric cyanosilylation of aldehydes in up to 73% ee.

Cyanohydrins have a high synthetic potential in organic synthesis, which can easily be converted into a wide variety of important synthetic intermediates including α-hydroxy acids, α-amino acids and β-amino alcohols.[7] A number of methods have been reported for the asymmetric synthesis of cyanohydrins employing enzymes,[8] peptides[9] and chiral metal complexes.[10] In recent years, metal-free organic molecules have played key roles in asymmetric synthesis.[11] However, there are few examples of the asymmetric cyanosilylation of aldehydes using organocatalysts.[12] Hence, it is a very active research effort toward developing new organocatalysts for this addition reaction.

In our previous studies, we found that *N*-oxide played a role of Lewis base to activate TMSCN. Initially, we developed a bifunctional catalyst with *N*-oxide dipolar moieties[13] and a catalytic double activation method (CDAM)[14] for the asymmetric cyanosilylation of ketones. Then, we observed that quaternary ammonium salt together with *N*-oxide[15] or phenolic *N*-oxide alone could efficiently promote the reaction, too.[16] Encouraged by the researches above, we speculated that chiral *N*-oxides with proper structure could catalyze the asymmetric cyanosilylation of aldehydes and ketones. L-Proline, a natural amino acid with a secondary amine functionality, can be converted into chiral *N*-oxides easily. In our preliminary studies, we investigated some proline-based *N*-oxides to catalyze the asymmetric cyanosilylation of aldehydes and ketones. Unfortunately, the results were disappointing.[17] In order to enhance the activity and enantioselectivity, we designed a new class of proline-based *N*,*N*′-dioxides (Figure 1) which could be easily prepared from L-proline and amines.[18,19] The reactivity was greatly improved when *N*,*N*′-dioxides were used compared with *N*-monoxides.

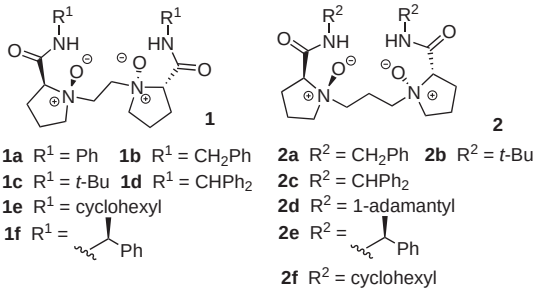
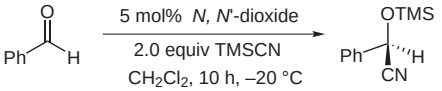


Figure 1

In efforts to identify an effective chiral catalyst, we examined their abilities to promote enantioselective cyanosilylation of benzaldehyde at –20 °C (Scheme 1). The results were summarized in Table 1.



Scheme 1

As illustrated in Table 1, the amide substituent played an important role on the enantioselectivity. The cyclohexyl and (*S*)-methylphenyl groups afforded better ee values (Table 1, entries 5, 6). Elongation of the carbon chain of **1** led to catalysts **2** with increased enantioselectivity (Table 1, entries 7, 8, 11, 12). And **2f** was identified as the most effective catalyst (Table 1, entry 12).

Optimization of other reaction parameters resulted in further improvements in enantioselectivity with catalyst **2f** (Table 2). Solvent effects showed that CH_2Cl_2 was the most favorable solvent (Table 2, entries 1–4). Temperature clearly affected the yield and the enantioselectivity. Lowering the temperature caused a drop in reactivity and an increase in enantioselectivity (Table 2, entries 4–6). The yield was dramatically influenced by catalyst loading

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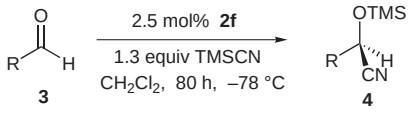
Table 1 Asymmetric Cyanosilylation of Benzaldehyde Catalyzed by **1**, **2**[a]

Entry	Catalyst	Yield (%)[b]	ee (%)[c]
1	**1a**	93	5
2	**1b**	96	17
3	**1c**	98	36
4	**1d**	94	36
5	**1e**	94	40
6	**1f**	98	42
7	**2a**	96	30
8	**2b**	98	48
9	**2c**	95	30
10	**2d**	96	54
11	**2e**	98	48
12	**2f**	98	55

[a] Reactions were carried out on a 0.2-mmol scale of benzaldehyde in 1.0 mL of CH_2Cl_2
[b] Isolated yield of the TMS ether.
[c] The ee values were determined by HPLC on Chiralcel OD column after conversion to the corresponding acetate. The absolute configuration was *R* by comparison of the reported optical rotation.

and concentration of substrate as well. When the amount of catalyst was reduced, the chemical yield decreased stepwise. Fortunately, it was recovered by increasing the concentration of the reaction components without any loss of enantioselectivities (Table 2, entries 6–9).

Under the optimized conditions, a range of aldehydes was investigated (Scheme 2). The results were listed in Table 3.[20] Aromatic aldehydes gave better results, with good yields and up to 73% ee. In general, alkyl, alkoxy and halogen groups at the *meta*-position of aromatic ring were tolerated well (Table 3, entries 3, 5, 6, 9), whereas substituents at the *para*-position gave slightly lower ee (Table 3, entries 2, 4, 10). 2-Naphthaldehyde afforded a higher ee value than 1-naphthaldehyde (Table 3, entries 12, 11). The heterocyclic and aliphatic aldehydes gave moderate enantioselectivities (Table 3, entries 13, 14).



Scheme 2

In summary, we have developed a novel proline-based *N*,*N*′-dioxide that catalyzed the enantioselective addition of TMSCN to aldehydes with reasonable yields and enantioselectivities. Attractive features of the method include the ease of catalyst preparation and the low catalyst loading. To improve enantioselectivity, modification of the *N*,*N*′-dioxide structure can be rationally based and study on the mechanism of the reaction is underway.

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Table 2 Optimization of the Cyanosilylation of Benzaldehyde in the Presence of **2f**[a]

Entry	**2f** (mol%)	Solvent	Temp (°C)	Time (h)	Yield (%)[b]	ee (%)[c]
1	5	THF	–20	11	97	34
2	5	Toluene	–20	12	98	42
3	5	Et_2O	–20	12	96	30
4	5	CH_2Cl_2	–20	10	98	55
5	5	CH_2Cl_2	–45	36	93	61
6	5[d]	CH_2Cl_2	–78	84	51	73
7	10[d]	CH_2Cl_2	–78	84	76	72
8	5[e]	CH_2Cl_2	–78	80	93	73
9	2.5[f]	CH_2Cl_2	–78	80	92	73

[a] Unless otherwise specified, the reaction was carried out on a 0.2-mmol scale of benzaldehyde in 1.0 mL of CH_2Cl_2, TMSCN (2.0 equiv).
[b] Isolated yield of the TMS ether.
[c] Determined by HPLC on Chiralcel OD column, after conversion to the corresponding acetate.
[d] 1.3 Equiv of TMSCN, [benzaldehyde] = 0.2 M.
[e] 1.3 Equiv of TMSCN, [benzaldehyde] = 0.4 M.
[f] 1.3 Equiv of TMSCN, [benzaldehyde] = 1.0 M.

Table 3 Asymmetric Cyanosilylation of Aldehydes Catalyzed by **2f**[a]

Entry	Aldehyde	Yield (%)[b]	ee (%)[c]
1	Benzaldehyde(**3a**)	92	73[d]
2	4-Methylbenzaldehyde (**3b**)	69	69
3	3-Methylbenzaldehyde (**3c**)	80	71
4	4-Methoxybenzaldehyde (**3d**)	57	64
5	3-Methoxybenzaldehyde (**3e**)	78	69
6	3-Phenoxybenzaldehyde (**3f**)	74	71
7	4-Fluorobenzaldehyde (**3g**)	70	69
8	2-Chlorobenzaldehyde (**3h**)	83	67
9	3-Chlorobenzaldehyde (**3i**)	90	66
10	4-Chlorobenzaldehyde (**3j**)	63	65
11	1-Naphthaldehyde (**3k**)	92	59
12	2-Naphthaldehyde (**3l**)	79	71
13	2-Furaldehyde (**3m**)	59	53
14	2-Phenylacetaldehyde (**3n**)	68	62

[a] Concentration of aldehydes = 1.0 M.
[b] Isolated yield of the TMS ether.
[c] The ee values were determined by HPLC or GC after conversion to the corresponding acetates.
[d] The configuration was *R* by comparison of the reported optical rotation.

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(17) Only 10% to 30% ee was obtained using the *N*-monoxide.

(18) **General Procedure for the Preparation of *N,N′*-Dioxides.** To a solution of (*S*)-1-(*tert*-butoxycarbonyl) pyrrolidine-2-carboxylic acid (1.183 g, 5.5 mmol) in CH_2Cl_2 was added Et_3N (2 mL), isobutyl carbonochloridate (0.72 mL, 5.5 mmol) at 0 °C under stirring. After 15 min, cyclohexanamine (0.57 mL, 5 mmol) was added. It was allowed to warm to r.t. and stirred for 3 h. The mixture was washed with 1 M $KHSO_4$, sat. $NaHCO_3$, brine, dried over anhyd Na_2SO_4 and concentrated. The residue in CH_2Cl_2 (20 mL) was added TFA (5 mL) and stirred for 1 h. Then, the solvent was evaporated, and H_2O was added (10 mL). The pH of the mixture was brought into the range of 8–10 by the addition of 2 M NaOH. The aqueous phase was extracted with CH_2Cl_2. The CH_2Cl_2 extracts were pooled, washed with

brine, dried over anhyd Na_2SO_4 and evaporated in vacuo. The residue was used for next step directly.
To a solution of *N*-cyclohexylpyrrolidine-2-carboxamide (980 mg, 5 mmol) in MeCN was added K_2CO_3 (691 mg, 5 mmol) and 1, 3-dibromopropane (0.26 mL, 2.5 mmol) under stirring. It was kept at 80 °C, and monitored by TLC after 10 h. Then, K_2CO_3 was removed by filtration. The residue was purified by silica gel column chromatography (EtOAc) to give 1,1′-(propane-1,3-diyl)bis(*N*-cyclohexylpyrrolidine-2-carboxamide) (974 mg, 90%) as a white solid.
For the oxidation step and stereochemistry of the *N*-oxide, see: O'Neil, I. A.; Miller, N. D.; Peake, J.; Barkley, J. V.; Low, C. M. R.; Kalindjian, S. B. *Synlett* **1993**, 515.

(19) The following are the NMR data of **2f**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.59 (2 H, d, *J* = 6.8 Hz, NH), 3.77 (2 H, m), 3.62 (2 H, m), 3.32–3.60 (8 H, m), 2.39–2.64 (8 H, m), 1.57–2.03 (12 H, m), 1.27–1.35 (10 H, m) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.73, 24.39, 25.32, 27.42, 32.26, 32.73, 47.26, 64.72, 67.55, 76.45, 166.28 ppm. HRMS (ESI): *m/z* calcd for $C_{25}H_{44}N_4O_4$: 465.3435 $[M + H]^+$; found: 465.3428 $[M + H]^+$.

(20) **Typical Procedure for the Trimethylsilylcyanation of Aldehydes.**
To a solution of **2f** (4.7 mg, 0.01 mmol) in CH_2Cl_2 (0.4 mL) was added freshly distilled benzaldehyde (42 μL, 0.4 mmol) under N_2 atmosphere, then TMSCN (68 μL, 0.52 mmol) was added at –78 °C. After stirring for 80 h at this temperature, the reaction was quenched. Further purification was performed by silica gel column chromatography to give the product (76 mg, 92%) as a colorless oil. To the product was added a mixture of 1 M HCl (5 mL) and EtOAc (10 mL) and stirred for 3 h at r.t., the organic layer was washed with distilled H_2O, and dried over anhyd Na_2SO_4. The cyanohydrin was converted into the corresponding acetate by reaction with two equiv of Ac_2O and pyridine in CH_2Cl_2 (5 mL) at r.t. for 1 h. The organic layer was washed with distilled H_2O, dried over anhyd Na_2SO_4 and concentrated. The crude was purified by flash chromatography on silica gel (PE–EtOAc, 10:1) to yield the corresponding acetylated cyanohydrin for further analysis.