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Asymmetric cyanosilylation of ketones catalyzed by novel chiral *N*,*N*′-dioxide titanium complexes

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Abstract—A novel C_2-symmetric chiral *N*,*N*′-dioxide titanium complex was described, which could efficiently catalyze the asymmetric cyanosilylation of ketones in high yields with up to 92% ee under mild conditions. In addition, the catalyst system was simple and the ligands could be easily prepared from commercially available chiral amino acid.

Asymmetric cyanosilylation of ketones is intensively studied due to the importance of cyanohydrins as the versatile synthons.[1] Although several outstanding catalyst systems have been identified for cyanation of carbonyl compounds,[2] the development of asymmetric cyanosilylation of ketones is still a challenge in terms of their low reactivity and the difficulty in controlling facial stereoselectivity in state-of-the-art asymmetric synthetic methodologies. At present, the majority of chiral catalysts used for this goal are chiral metal complexes,[3] cinchona alkaloids,[4] chiral oxazoborolidiniumions,[5] thiourea catalysts,[6] and amino acid salts.[7]

In recent years, chiral *N*-oxide has played an important role in efficiently promoting several synthetically useful transformations.[8] Our group has reported the asymmetric cyanosilylation of aldehydes by proline-based *N*,*N*′-dioxide,[9] as well as enantioselective cyanosilylation of ketones catalyzed by bifunctional *N*-monoxide titanium complex only with moderate enantiomeric excess (up to 69% ee) of the desired product.[10] In order to enhance the activity and enantioselectivity, we designed a new class of proline-based *N*,*N*′-dioxides (Fig. 1), which could be easily prepared from L-proline and amines. The reactivity was greatly improved when *N*,*N*′-dioxides were used compared with *N*-monoxides. Herein, we wish to report the results on the asymmetric cyanosilylation of ketones catalyzed by novel chiral proline-based *N*,*N*′-dioxides titanium complexes.

Ligands **1**, **2a**–**h**, and achiral phenolic *N*-oxide **3** were synthesized according to the literature (Fig. 1).[3j,9]

Our studies were started with acetophenone as a model substrate. In preliminary study, the catalytic activity of different ligands was examined with different metal sources for the catalytic cyanosilylation of acetophenone at −20 °C with 1.5 equiv of trimethylsilyl cyanide (TMSCN). We found that **2e**–Ti(O*i*-Pr)$_4$ complex had the highest capability of asymmetric induction among ligands **1**, **2a**–**g** (Fig. 1), while the alternative enantiomer **2h**–Ti(O*i*-Pr)$_4$ promoted the same selective transformation to afford the alternative product, the antipode (−54% ee).

A study on the solvent effect showed that THF provided the best enantioselectivity (Table 1, entry 2). Effects of the concentration showed that the optimum concentration of acetophenone was 0.5 M (Table 1, entry 5). Further searching for the suitable additive revealed that phenolic *N*-oxide **3** was the most promising one in this catalytic system (Table 1, entry 7). We also found that several parameters were important for both the reactivity and enantioselectivity. Lowering the reaction temperature resulted in a remarkable enhancement in enantioselectivity (Table 1, entry 11, 92% yield with 86% ee at −45 °C). While further lowering the reaction temperature led to a dramatic decrease in reactivity without any

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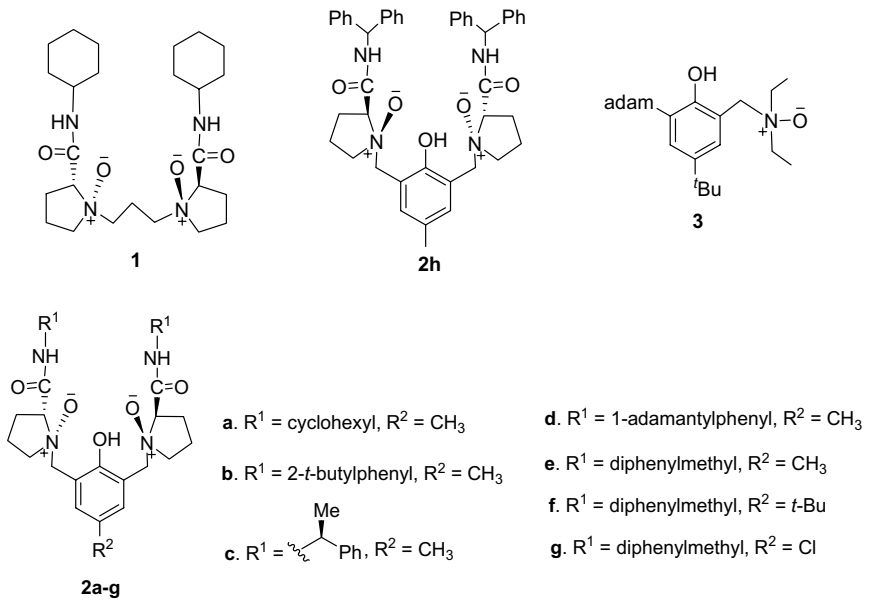
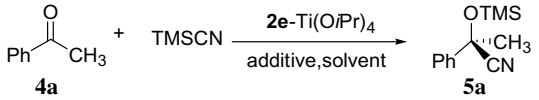


Figure 1. Screening of ligands and achiral phenolic *N*-oxide.

Table 1. Asymmetric cyanosilylation of acetophenone catalyzed by chiral ligand **2e**–Ti(O*i*-Pr)$_4$ complex under various conditions



4a **5a**

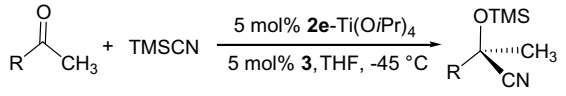
Entry[a]	**2e** (mol %)	Solvent	Additive	Amount of additive (%)	Time (h)	Temp (°C)	Yield[b] (%)	ee (%)[c,d]
1[e]	5	CH_2Cl_2	—	—	48	−20	89	55
2[e]	5	THF	—	—	48	−20	95	58
3[e]	5	Toluene	—	—	48	−20	95	48
4[e]	5	Et_2O	—	—	48	−20	94	48
5[f]	5	THF	—	—	48	−20	92	59
6[g]	5	THF	—	—	48	−20	94	52
7	5	THF	**3**	5	48	−20	93	67
8	5	THF	4 Å MS	5 mg	48	−20	51	52
9	5	THF	*i*-PrOH	5	48	−20	58	53
10	5	THF	$Ph_3P{=}O$	5	48	−20	67	56
11	5	THF	**3**	5	64	−45	92	86
12	5	THF	**3**	5	72	−78	81	86
13	5	THF	**3**	5	25	rt	80	40
14	5	THF	**3**	10	64	−45	90	86
15	5	THF	**3**	2.5	64	−45	88	85
16	5	THF	**3**	1.25	64	−45	85	80
17	10	THF	**3**	5	48	−45	89	86
18	2.5	THF	**3**	5	67	−45	82	86

[a] Conditions: **2e**–metal (1:1), concentration of acetophenone = 0.5 M, TMSCN 1.5 equiv.
[b] Isolated yield.
[c] Determined by GC on Chirasil DEX CB.
[d] The absolute configuration of the major product was *R*, determined by the comparison with the reported values of optical rotation (Ref. 3c).
[e] Concentration of acetophenone = 0.25 M.
[f] Concentration of acetophenone = 0.5 M.
[g] Concentration of acetophenone = 1.0 M.

improvement in enantioselectivity (Table 1, entry 12, 81% yield with 86% ee at −78 °C). When the reaction was carried out at room temperature, enantioselectivity suffered (Table 1, entry 13). Interestingly, the catalyst loading had no effect on the enantioselectivity, but had only a slight impact on the yield (Table 1, entries 11, 17, and 18).

Encouraged by the result obtained from acetophenone, the scope of the reaction was then investigated with different ketones under the current catalytic conditions.[11] As shown in Table 2, most of the aromatic, α,β-unsaturated, heterocyclic and aliphatic ketones could be converted into the corresponding cyanohydrin trimethylsilyl ethers in 62–91% yields with 78–92% ee. The *para*-substituents (methyl, chloro, fluoro) on the aromatic ring led to poorer enantioselectivities than acetophenone (Table 2, entries 1–4), whereas the *meta*-chloro and *ortho*-fluoro substituted ketone gave higher enantioselec-

Table 2. Asymmetric cyanosilylation of ketones catalyzed by **2e**–Ti(O*i*-Pr)$_4$ in the presence of **3**



4a-k **5a-k**

Entry[a]	Ketones	Time (h)	Yield (%)[b]	ee (%)[c]
1	Acetophenone (**4a**)	72	81	86 (*R*)
2	4′-Methylacetophenone (**4b**)	72	86	82
3	4′-Chloroacetophenone (**4c**)	45	90	82
4	4′-Fluoroacetophenone (**4d**)	45	90	81
5	3′-Chloroacetophenone (**4e**)	36	88	90
6	2′-Fluoroacetophenone (**4f**)	30	90	88
7	β-Acetonaphthone (**4g**)	54	76	92[d,f]
8	*trans*-4-Phenyl-3-buten-2-one (**4h**)	45	90	92[e]
9	Benzylacetone (**4i**)	36	91	78
10	2-Acetylthiophene (**4j**)	72	62	83
11	2-Heptanone (**4k**)	36	89	79 (*R*)

[a] Conditions: 5 mol % **2e**–Ti(O*i*-Pr)$_4$ (1:1), 5 mol % additive *N*-oxide **3**, concentration of acetophenone = 0.5 M in THF, TMSCN 1.5 equiv, −45 °C.

[b] Isolated yield.

[c] Determined by GC on Chirasil DEX CB. The absolute configurations were determined by the comparison with the reported values of optical rotation (Ref. 3c).

[d] Determined by HPLC on Chiralcel OJ.

[e] Determined by HPLC on Chiralcel OD.

[f] 5 mol % **2e**–Ti(O*i*-Pr)$_4$ (1:1), 5 mol % additive *N*-oxide **3**, concentration of acetophenone = 0.5 M in THF, TMSCN 1.5 equiv, −78 °C.

tivity and yield than acetophenone (Table 2, entries 5 and 6). *trans*-Cinnamophenone only gave 1,2-addition product in 90% yield with 92% ee (Table 2, entry 8), while benzylacetone gave poor result (Table 2, entry 9). β-Acetonaphthone afforded higher enantioselectivity than acetophenone (Table 2, entry 7). The heterocyclic ketone gave the corresponding product with good enantioselectivity and moderate yield (Table 2, entry 10). Simple aliphatic ketone provided the corresponding product with moderate enantioselectivity and good yield (Table 2, entry 11).

In conclusion, asymmetric cyanosilylation of ketones was achieved using 5 mol % of the chiral *N*,*N*′-dioxide titanium complex and good yields of the corresponding OTMS ethers of cyanohydrins were obtained with high enantioselectivities (up to 92% ee) under mild reaction conditions. Further investigations are planned to provide additional information with regard to the scope and precise mechanism of the reaction.

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11. A representative procedure: $Ti(O\textit{i}\text{-}Pr)_4$ (1 M in toluene, 25 μL, 0.025 mmol) was stirred with **2e** (18.1 mg, 0.025 mmol) and *N*-oxide **3** (9.5 mg, 0.025 mmol) in THF (1 mL) at 35 °C for 1 h under N_2. After the addition of acetophenone (0.5 mmol), the reaction was cooled to −45 °C. Subsequently, TMSCN was added (161 μL, **4M** in THF, 0.75 mmol) in one portion. After 72 h, the solution was concentrated and the residue was purified by silica gel column chromatography (petroleum ether/diethyl ether, 100:1) to afford the corresponding cyanohydrin trimethylsilyl ethers as colorless oil (86.4 mg, 81% yield, 86% ee). The enantioselectivity was determined by GC [Varian, CP-Chirasil DEX determined by Chiral GC analysis on Chirasil DEX CB (0.25 mm × 25 m), column temperature: 105 °C (isothermal), injection temperature: 250 °C, detector temperature: 250 °C, inlet pressure: 8 psi]: t_R (minor, (*S*)) = 21.5 min, t_R (major, (*R*)) = 22.1 min, $[\alpha]_D^{25}$ +7.03 (*c* 1.92, CH_2Cl_2, 86% ee) {Ref. 3k $[\alpha]_D^{22}$ +16.9 (*c* 2.58, CH_2Cl_2, 94% ee)}. ^1H NMR (300 MHz, $CDCl_3$): δ 0.19 (s, 9H), 1.87 (s, 3H), 7.38–7.58 (m, 5H).