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Enantioselective Cyanosilylation of α,α-Dialkoxy Ketones Catalyzed by Proline-Derived in-Situ-Prepared *N*-Oxide as Bifunctional Organocatalyst

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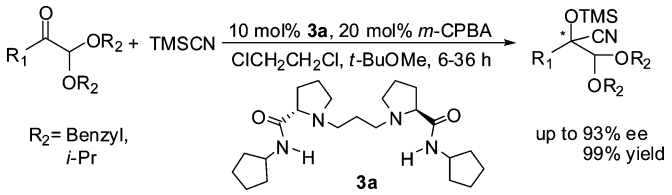

Bifunctional *N*,*N*′-dioxide catalysts have been developed for highly enantioselective cyanosilylation of α,α-dialkoxy ketones. This process, catalyzed by in-situ-prepared proline-derived *N*,*N*′-dioxide **2b**, produced the corresponding cyanohydrin trimethylsilyl ethers in excellent yields (up to 99%) with high enantioselectivities (up to 93% ee). A reasonable mechanism was proposed according to the observation of the linear effect, ^{1}H NMR spectra, isolated cyanohydrin, and the roles of the NH and *N*-oxide moieties of the catalyst.

Introduction

The enantioselective cyanosilylation of carbonyl compounds represents an effective approach for the synthesis of optically active cyanohydrins, which are important intermediates for the preparation of α-hydroxy and α-amino acids.[1] Considerable efforts have been devoted to the development of efficient catalytic asymmetric cyanosilylation.[2] Recently several chiral metal complexes[3−6] have been identified to be highly efficient catalysts for cyanation of ketones. However, there are only a few organocatalytic systems succeeding in the asymmetric cyanosilylation of ketones, such as chiral oxazaborolidinium ion,[7] thiourea catalyst,[8] and amino acid salt.[9] Cyanosilylation of α,α-dialkoxy ketone (acetal ketone) attracted great concern owing to the pivotal importance of the acetal group as precursor to many functionalities.[10] In 2003, Deng and co-workers

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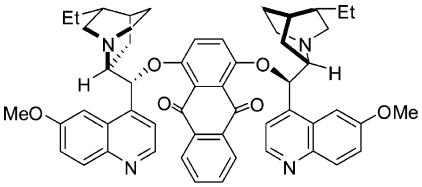
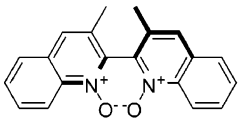
developed the first highly enantioselective cyanosilylation of acetal ketone catalyzed by only 2 mol % $(DHQ)_2AQN$ as commercially available and fully recyclable catalyst.[10b,c]



$(DHQ)_2AQN$

As a versatile catalyst, the *N*-oxide plays a significant role in many asymmetric reactions of organosilicon chemistry.[11] Encouraged by the success of the biquinoline *N*,*N*′-dioxide with the axial chirality (*S*)-**1** in the catalysis of the asymmetric allylation[12] and Strecker reactions,[13] we developed a novel C_2-symmetric chiral *N*,*N*′-dioxide **2a** to catalyze the asymmetric cyanosilylation of aldehydes successfully.[14]



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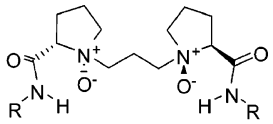


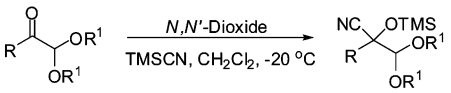
2a R= cyclohexyl
2b R= cyclopentyl

During the course of our study a new method in which the chiral *N*-oxide was generated in situ from *N*-alkyl prolinamide and *m*-CPBA (*m*-chloroperbenzoic acid) was developed to resolve the sensibility of *N*-oxide compounds toward moisture.[15] Herein, we wish to report the asymmetric cyanosilylation of acetal ketones catalyzed by in-situ-prepared *N*,*N*′-dioxide with excellent reactivity and enantioselectivity.

Results and Discussion

For the preliminary study, cyanosilylation of acetophenone with trimethylsilyl cyanide (TMSCN) proceeded sluggishly (entry 1, Table 1). When acetophenone was replaced with α,α-diethoxy-1-phenylethanone **4** in the presence of 20 mol % biquinoline *N*,*N*′-dioxide **1**, no reaction was observed (entry 2, Table 1). *N*,*N*′-Dioxide **2a** bearing the amide moiety was applied to the reaction, resulting in a high yield and moderate ee (entry 3, Table 1). Further study showed that in-situ-generated **2b** from the corresponding amide and *m*-CPBA retained the same asymmetric catalytic activity and enantioselectivity as well as *isolated* **2b** (entry 5 vs 4, Table 1). For the acetal, the bulkier dibenzyl acetal **6a** was superior to the dimethyl and diethyl ones (entry 7 vs entries 5 and 6, Table 1). When the acetal group was *i*Pr in aliphatic ketone, increased reaction rate and comparable enantioselectivity were detected (entry 9 vs 8, Table 1).

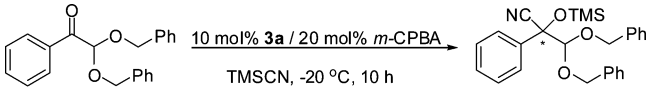
TABLE 1. ***N*,*N*′-Dioxide-Catalyzed Asymmetric Cyanosilylation of Ketone**[a]



entry	ketone	*N*,*N*-dioxide	catalyst loading (mol %)	time (h)	yield (%)[b]	ee (%)[c]
1	acetophenone	**2a**	20	48	28	30
2[d]	**4**	**1**	20	17	n.d.[e]	
3	**4**	**2a**	20	10	99	54
4	**4**	**2b**	20	10	99	60
5[f]	**4**	**3a**/*m*-CPBA	10	10	99	60
6[f]	**5**	**3a**/*m*-CPBA	10	10	95	40
7[f]	**6a**	**3a**/*m*-CPBA	10	10	43	75
8[f]	**7a**	**3a**/*m*-CPBA	10	10	23	72
9[f]	**7b**	**3a**/*m*-CPBA	10	10	82	72

[a] Conditions: the reaction was performed with ketone (0.1 mmol) and TMSCN (2.0 equiv) in CH_2Cl_2. [b] Isolated yield. [c] Determined by HPLC analysis. [d] The reaction was at 0 °C. [e] Not detected. [f] *N*,*N*′-Dioxide was generated in situ from diamide **3a** (10 mol %) and *m*-CPBA (20 mol %).

TABLE 2. Effect of Solvent on Asymmetric Cyanosilylation of Acetal Ketone 6a[a]



6a **8a**

entry	solvent	yield (%)[b]	ee (%)[c]
1	Et_2O	60	64
2	*t*-BuOMe	92	64
3	THF	99	65
4	toluene	90	57
5	CH_3CN	99	37
6	hexane	99	35
7	CH_2Cl_2	43	75
8	$CHCl_3$	trace	79
9	$ClCH_2CH_2Cl$	99	75

[a] Conditions: the reaction was performed with ketone **6a** (0.1 mmol) and TMSCN (2.0 equiv) in solvent (0.5 mL); *N*,*N*′-dioxide was generated in situ from diamide **3a** (10 mol %) and *m*-CPBA (20 mol %). [b] Isolated yield. [c] Determined by HPLC analysis.

To optimize this process, several reaction conditions were investigated using compound **6a** as the model substrate. Initially, we examined the effect of solvents using 10 mol % of *N*,*N*′-dioxide prepared in situ as the catalyst and 2.0 equiv of TMSCN. As shown in Table 2, the cyanosilylation reaction usually proceeded better in halogenated solvents than in the others. Of the conditions screened, 1,2-dichloroethane was the optimal solvent. Under this condition, 99% yield and 75% ee of **8a** was obtained (entry 9, Table 2).

With these leading results in hand we switched our effort to further improving the enantioselectivity by steric modifications of the *N*,*N*′-dioxide. Accordingly, a series of diamides **3** were prepared (Figure 1, see Supporting Information) and evaluated in the asymmetric cyanosilylation of acetal ketone **6a** (Table 3). The results showed that L-proline-derived diamide **3a** was superior to L-piperidinamide derivative **3g** in both yield and ee (entry 1 vs 7, Table 3). As a bulky alkyl group, *tert*-butyl could

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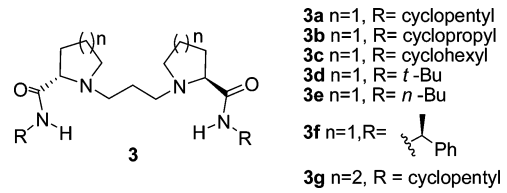
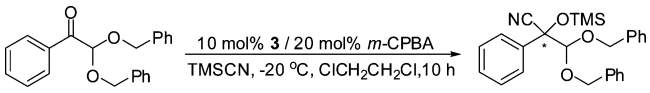


FIGURE 1. Chiral catalyst−precursor employed for asymmetric cyanosilylation of acetal ketone.

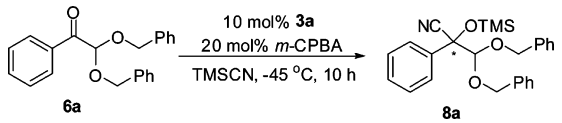
TABLE 3. Effect of Catalyst Structure on the Cyanosilylation of Acetal Ketone 6a[a]



entry	diamide **3**	yield (%)[b]	ee (%)[c]
1	**3a**	99	75
2	**3b**	99	74
3	**3c**	99	69
4	**3d**	99	70
5	**3e**	99	50
6	**3f**	70	66
7	**3g**	50	70

[a] Conditions: the reaction was performed with ketone **6a** (0.1 mmol) and TMSCN (2.0 equiv) in $ClCH_2CH_2Cl$ (0.5 mL); *N*,*N*′-dioxide was generated in situ from diamide **3** (10 mol %) and *m*-CPBA (20 mol %). [b] Isolated yield. [c] Determined by HPLC.

TABLE 4. Effect of Cosolvent on the Cyanosilylation of Acetal Ketone 6a[a]



entry	solvent	cosolvent	ratio (vol.)	yield (%)[b]	ee (%)[c]
1	$ClCH_2CH_2Cl$			58	72
2	$ClCH_2CH_2Cl$	CH_2Cl_2	3:2	63	86
3	$ClCH_2CH_2Cl$	acetone	3:2	96	80
4	$ClCH_2CH_2Cl$	Et_2O	3:2	97	88
5	$ClCH_2CH_2Cl$	THF	3:2	97	85
6	$ClCH_2CH_2Cl$	*t*-BuOMe	3:2	95	90
7	$ClCH_2CH_2Cl$	ethyl acetate	3:2	n.d.[d]	
8	$ClCH_2CH_2Cl$	CH_3CN	3:2	n.d.[d]	
9	$ClCH_2CH_2Cl$	*t*-BuOMe	2:3	99	89
10	$ClCH_2CH_2Cl$	*t*-BuOMe	4:1	99	92

[a] Conditions: the reaction was performed with ketone **6a** (0.1 mmol) and TMSCN (2.0 equiv) in the solvent (0.5 mL). [b] Isolated yield. [c] Determined by HPLC. [d] Not detected.

increase the enantiomeric excess compared to *n*-butyl (entry 4 vs 5, Table 3). Cyclic groups were superior to the (*S*)-phenylethyl group in the enantioselectivity (entries 1−3 vs 6, Table 3). Bearing a moderate cyclic moiety, diamide **3a** was selected for further optimization.

Generally, decreasing the reaction temperature can improve the enantioselectivity. However the system could not tolerate such an operation because of the comparatively high freezing point of $ClCH_2CH_2Cl$ (entry 1, Table 4). To resolve this problem, cosolvent was examined. The product was produced in higher enantioselectivity (86% ee) with 63% yield in the mixed solvent of CH_2Cl_2 and $ClCH_2CH_2Cl$ (ratio 2:3, entry 2, Table 4). When acetone as a cosolvent was added to the reaction,

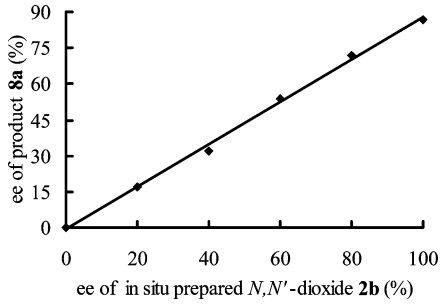


FIGURE 2. Relationship between the ee of product **8a** and that of the chiral in-situ-prepared *N*,*N*′-dioxide **2b**.

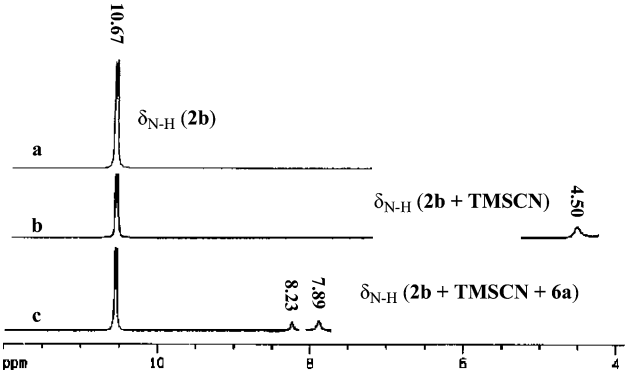


FIGURE 3. ^1H NMR spectra of the NH group of *N*,*N*′-dioxide **2b** in diverse reaction stages: (a) **2b**, (b) **2b** and TMSCN (ratio 1/1), and (c) **2b**, TMSCN, and **6a** (ratio 1/1/1).[18]

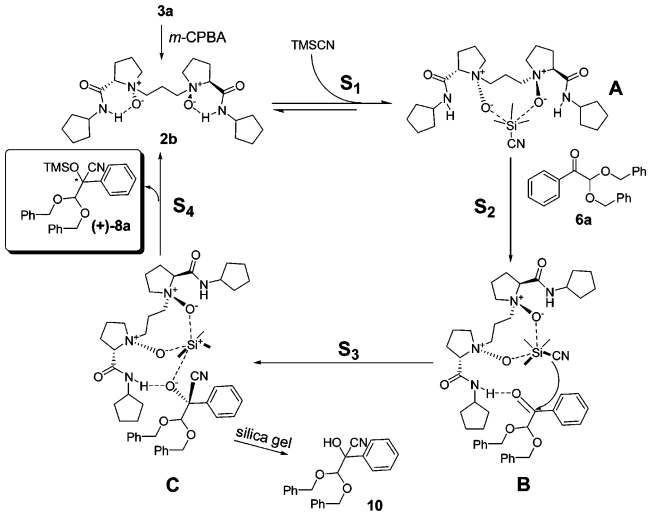
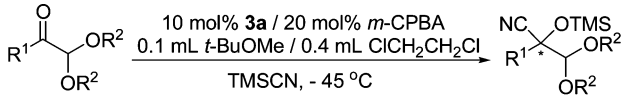


FIGURE 4. Proposed catalytic cycle.

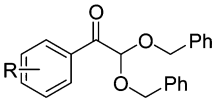
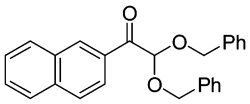
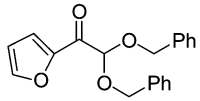
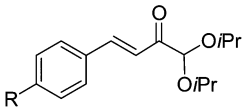
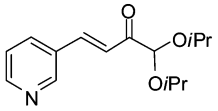
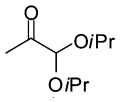
the yield was increased to 96% (entry 3, Table 4). Using *t*-BuOMe as cosolvent, the desired product **8a** was obtained with 90% ee (entry 6, Table 4), whereas in the presence of ethyl acetate and CH_3CN as cosolvent, the reaction could not proceed (entries 7 and 8, Table 4). Furthermore, the best ee value was in the 4:1 mixture of $ClCH_2CH_2Cl$ and *t*-BuOMe (entry10, Table 4).

As demonstrated in Table 5, the aromatic, α,β-unsaturated, heteroaromatic, and aliphatic acetal ketones **6** and **7** were tested. Generally, excellent yield and high enantioselectivities of cyanohydrin trimethylsilyl ethers **8** were obtained with 2.0 equiv of TMSCN and 10 mol % in-situ-prepared *N*,*N*′-dioxide at

TABLE 5. Enantioselective Addition of TMSCN to Acetal Ketones Catalyzed by in-Situ-Prepared *N,N′*-Dioxide[a]



6-7 **8**

entry	ketone		product	time (h)	yield[b] (%)	ee[c] (%)
1		**6a R= H**	**8a**	10	99	92
2		**6b R= *p*-Cl**	**8b**	10	83	88
3		**6c R= *m*-Cl**	**8c**	10	99	93
4		**6d R= *p*-F**	**8d**	6	99	89
5		**6e R= *o*-F**	**8e**	10	92	87
6		**6f R= *m*-O_2N**	**8f**	10	99	85
7		**6g R= *p*-Me**	**8g**	36	73	90
8		**6h R= *p*-MeO**	**8h**	20	99	90
9		**6i R= *3,4*-DiMeO**	**8i**	36	94	88
10		**6j**	**8j**	20	85	93
11		**6k**	**8k**	12	99	90
12		**6l R= H**	**8l**	10	92	92
13		**6m R= Cl**	**8m**	10	88	87
14		**6n R= O_2N**	**8n**	6	99	93
15		**6o R= MeO**	**8o**	20	85	90
16		**6p**	**8p**	10	95	85
17		**7b**	**8q**	10	90	92

[a] Conditions: the reaction was performed with ketone **6** and **7b** (0.2 mmol) and TMSCN (2.0 equiv) in the indicated conditions. [b] Isolated yield. [c] Determined by HPLC analysis as described in the Supporting Information.

−45 °C in the 4:1 mixed solvent of $ClCH_2CH_2Cl$ and *t*-BuOMe. Aromatic ketones as well as heterocyclic ketones reacted smoothly to give the corresponding derivatives **8** in high enantioselectivities (entries 1−11, Table 5). In particular, acetal ketone **6c** and **6j** gave the best enantioselectivities (entries 3 and 10, Table 5). However, the acetal ketones with electron-donating groups such as Me and MeO generally showed lower reactivity (entries 7−9, Table 5). The enones **6l**−**p** gave the 1,2-adducts with complete regioselectivity and high enantioselectivities (entries 12−16, Table 4). Notably, product **8q**, which could be converted to a natural product (+)-bisorbicillinolide, was obtained in 92% ee (entry 17, Table 4).[16]

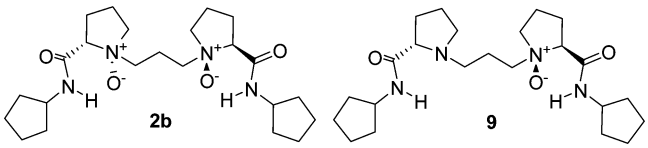
In the study of the activation of TMSCN by *N,N′*-dioxide **2b**, the relationship between the product **8a** and the catalyst **2b** in enantioselectivity was examined and showed a strong linear correlation of this reaction, implying that the Si atom of TMSCN might be activated by one *N,N′*-dioxide molecule (Figure 2).[17]

(16) Hong, R.; Chen, Y.; Deng, L. *Angew. Chem., Int. Ed.* **2005**, *44*, 3478−3481.

(17) For reviews on the nonlinear effect in asymmetric synthesis, see: (a) Girard, C.; Kagan, H. B. *Angew. Chem., Int. Ed.* **1998**, *37*, 2922−2959. (b) Avalos, M.; Babiano, R.; Cintas, P.; Jimenez, J. L.; Palacios, J. C. *Tetrahedron: Asymmetry* **1997**, *8*, 2997−3017.

(18) See Supporting Information for details.

TABLE 6. Effect of *N,N′*-dioxide 2b and *N*-oxide 9 on the Cyanosilylation of Acetal Ketone 6a[a]



entry	catalyst	time (h)	temp (°C)	yield (%)[b]	ee (%)[c]
1[d]	2b	10	−45	99	92
2[e]	9	10	−45	49	7

[a] Conditions: the reaction was performed with ketone **6a** (0.1 mmol) and TMSCN (2.0 equiv) in the solvent (0.4 mL $ClCH_2CH_2Cl$, 0.1 mL *t*-BuOMe). [b] Isolated yield. [c] Determined by HPLC. [d] *N,N′*-Dioxide **2b** was generated in situ from diamide **3a** (10 mol %) and *m*-CPBA (20 mol %). [e] 10 mol % *N*-oxide **9** was used in the reaction.

^{1}H NMR spectroscopy was recorded to obtain preliminary insight into the function of the NH moiety of *N,N′*-dioxide **2b** (Figure 3). The NH proton showed a strong deshielding effect at 10.67 ppm due to the characteristic strong hydrogen bonding between *N*-oxide and the NH proton (Figure 3a). However, upon combination of TMSCN and *N,N′*-dioxide **2b** in a ratio of 1:1, a new chemical shift was observed at δ 4.50 ppm (Figure 3b), suggesting that the NH proton which has been released was no longer bonding to *N*-oxide. It confirmed the interaction between *N*-oxide and TMSCN, which has been observed in a ^{29}Si NMR study.[13b,15] Upon addition of acetal ketone **6a**, the resonance for the NH moiety significantly shifted downfield to δ 7.89 and 8.23 ppm, indicating that the intermolecular hydrogen bonding between C═O of acetal ketone and the NH moiety of *N,N′*-dioxide existed in the catalytic process (Figure 3c). These results clearly showed that *N,N′*-dioxide **2b** was a bifunctional organocatalyst containing *N*-oxide as a Lewis base to activate TMSCN and amide hydrogen as a Brönsted acid to activate the carbonyl group of the substrate.

Compared with *N,N′*-dioxide **2b**, *N*-oxide **9** with one dipolar was prepared and evaluated in the reaction (Table 6). However, only a 7% ee with 49% yield was observed in the cyanosilylation of acetal ketone **6a**. This important piece of evidence proved that TMSCN was synchronously activated by two dipolars of *N,N′*-dioxide **2b** and the hexacoordinated silicon was formed in the reaction. Furthermore, cyanohydrin **10** was detected by TLC and successfully separated during the course of the reaction but disappeared after complete conversion of the substrate, meaning that complex **C** might be the key intermediate of this transformation (Figure 4).

On the basis of our investigations and previous results on the hydrogen bonding of *N*-oxide,[19] the catalytic cycle proposed is shown in Figure 4. In the first stage S_1, the hypervalent silicon intermediate **A** was formed through a combination of TMSCN and *N,N′*-dioxide **2b**, enhancing the nucleophilicity of the CN group; in the second stage S_2, acetal ketone **6a** was activated by the catalyst combined through the hydrogen bonding between C═O and NH to produce B; in the third stage S_3, the activated CN group attacked the "prochiral center" to generate the key intermediate **C**, and then the TMS group shifted smoothly to the cyanohydrin (stage S_4) to complete the catalytic cycle and regenerate the catalyst.

(19) (a) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1520−1543. (b) Derdau, V.; Laschat, S.; Hupe, E.; König, W. A.; Dix, I.; Jones, P. G. *Eur. J. Inorg. Chem.* **1999**, 1001−1007. (c) Aurich, H. G.; Soeberdt, M.; Harms, K. *Eur. J. Org. Chem.* **1999**, 1249−1252. (d) O'Neil, I. A.; Miller, N. D.; Peake, J.; Barkley, J. V.; Low, C. M. R.; Kalindjian, S. B. *Synlett* **1993**, 515−518.

Conclusions

In summary, we developed a new class of C_2-symmetric bifunctional organocatalysts for the asymmetric cyanosilylation of α,α-dialkoxy ketones in excellent yields (up to 99%) with good to high enantioselectivities (up to 93% ee) in mild conditions. The catalytic system could be tolerant of air and moisture with the convenient in-situ generation of *N,N′*-dioxide. Future efforts will be devoted to investigations of the mechanistic features, scope, and synthetic application of this novel approach and search for new amide *N*-oxide catalysts.

Experimental Section

Typical Procedure for the *N,N′*-Dioxide-Catalyzed Asymmetric Cyanosilylation of Acetal Ketones. A mixture of chiral diamide **3a** (8.0 mg, 10 mol %) and *m*-CPBA (7.0 mg, 20 mol %) in $ClCH_2CH_2Cl$ (0.4 mL) was stirred at −20 °C for 10 min; then *t*-BuOMe (0.2 mL) was added to the mixture. Subsequently, TMSCN (56 μL, 0.4 mmol) and acetal ketone **6a** (66 mg, 0.2 mmol) in $ClCH_2CH_2Cl$ (0.4 mL) were added sequentially at −45 °C. After stirring for 10 h, the reaction mixture was directly purified by column chromatography on silica gel eluting with ether/petroleum ether (1/40) to give 3,3-bis(benzyloxy)-2-phenyl-2-(trimethylsilyloxy)propanenitrile **8a**: colorless oil, 99% yield, 92% ee, $[\alpha]^{25}_D$ = +10.2 (c = 0.92, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56−7.60 (m, 2H), 7.35−7.40 (m, 8H), 7.19−7.22 (m, 3H), 6.87−6.90 (m, 2H), 4.76 (d, J = 15.7 Hz, 2H), 4.58 (s, 1H), 4.52 (d, J = 12.3 Hz, 1H), 4.33 (d, J = 12.3 Hz, 1H), 0.16 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.5, 137.3, 136.7, 128.9, 128.4, 128.2, 128.1, 127.9, 127.8, 127.7, 127.7, 126.7, 119.1, 104.0, 78.7, 71.8, 70.7, 0.9; ESI-HRMS calcd for ($C_{26}H_{29}NO_3Si + Na^+$), 454.1809; found, 454.1795.

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Supporting Information Available: Experimental procedures and characterization of products for catalysts and racemates, ^{1}H NMR, ^{13}C NMR spectra, HRMS and HPLC conditions, etc. This material is available free of charge via the Internet at http://pubs.acs.org.

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