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Asymmetric Cyanation of Aldehydes, Ketones, Aldimines, and Ketimines Catalyzed by a Versatile Catalyst Generated from Cinchona Alkaloid, Achiral Substituted 2,2′-Biphenol and Tetraisopropyl Titanate

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Abstract: Full investigation of cyanation of aldehydes, ketones, aldimines and ketimines with trimethylsilyl cyanide (TMSCN) or ethyl cyanoformate (CNCOOEt) as the cyanide source has been accomplished by employing an in situ generated catalyst from cinchona alkaloid, tetraisopropyl titanate [Ti(O*i*Pr)$_4$] and an achiral modified biphenol. With TMSCN as the cyanide source, good to excellent results have been achieved for the Strecker reaction of *N*-Ts (Ts = *p*-toluenesulfonyl) aldimines and ketimines (up to >99% yield and >99% *ee*) as well as for the cyanation of ketones (up to 99% yield and 98% *ee*). By using CNCOOEt as the alternative cyanide source, cyanation of aldehyde was accomplished and various enantioenriched cyanohydrin carbonates were prepared in up to 99% yield and 96% *ee*. Noteworthy, CNCOOEt was successfully employed for the first time in the asymmetric Strecker reaction of aldimines and ketimines, affording various α-amino nitriles with excellent yields and *ee* values (up to >99% yield and >99% *ee*). The merits of current protocol involved facile availability of ligand components, operational simplicity and mild reaction conditions, which made it convenient to prepare synthetically important chiral cyanohydrins and α-amino nitriles. Furthermore, control experiments and NMR analyses were performed to shed light on the catalyst structure. It is indicated that all the hydroxyl groups in cinchona alkaloid and biphenol complex with Ti^{IV}, forming the catalyst with the structure of (biphenoxide)Ti(OR*)(O*i*Pr). The absolute configuration adopted by biphenol **4m** in the catalyst was identified as *S* configuration according to the evidence from control experiments and NMR analyses. Moreover, the roles of the protonic additive (*i*PrOH) and the tertiary amine in the cinchona alkaloid were studied in detail, and the real cyanide reagent in the catalytic cycle was found to be hydrogen cyanide (HCN). Finally, two plausible catalytic cycles were proposed to elucidate the reaction mechanisms.

Keywords: asymmetric catalysis · cinchona alkaloid · cyanation · cyanohydrins · Strecker reaction

Introduction

Background: Since the first synthesis of cyanohydrin by Winkler in 1832[1] and the first synthesis of α-amino nitrile using a three-component condensation method by Strecker in 1850,[2] α-functionalized nitriles have attracted considerable attention of organic chemists due to the rich chemistry of cyano group (CN).[3] For example, chiral cyanohydrins could be elaborated into a number of key intermediates, including α-hydroxy acids, α-hydroxy ketones, α-hydroxy aldehydes, β-hydroxy amines, and so on.[4–8] Whereas, chiral α-amino nitriles could be conveniently converted to a variety of useful chiral α-amino acids and 1,3- diamines.

Before 1986, the efficient catalysts developed for the preparation of optically active cyanohydrins were merely restricted to enzymes[4a–c,e] (*R*- or *S*-oxynitrilase) and cyclic dipeptides.[4a,c,e] Over the past two decades, great advances have been achieved in the chemically catalytic asymmetric cyanation of carbonyl compounds, which provided convenient ways to access various enantioenriched cyanohydrins.[4d,f–l,5–7] For the cyanation of aldehydes, the procedures developed by Belokon′ and North,[4h] Shibasaki,[4i] Choi,[5i]

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Kagan,[5j] Uang,[5l] Saá,[5m] Feng,[5n] Corey,[5o] Pu,[5p] Ishihara,[5q] and Ohkuma[5v] are the pinnacle of what has been achieved. However, cyanation of ketones was more challenging due to the greater steric congestion and lower electrophilicity of ketones. Recently, breakthroughs have been accomplished in this longstanding problem.[8] The impressive catalysts comprised the titanium catalysts by Shibasaki[8b,c] and Feng,[8i] the lanthanide systems by Shibasaki,[8d,g,h,p] the aluminium catalysts by Snapper and Hoveyda,[8f] as well as Feng,[8l] the nucleophilic catalyst by Deng,[8e,j,k] the boron catalyst by Corey,[8q] the thiourea catalyst by Jacobsen,[8r,x] the amino acid salt catalyst by Feng,[8s] and so on.

As to the asymmetric cyanation of imines (Strecker reaction), the first catalytic version was reported by Lipton's group in 1996,[10a] after which many efficient catalysts were successively developed.[9–11] For the cyanation of aldimines,[10] efficient chiral metal complexes included Al^{III},[10c,h] Ti^{IV},[10f,k,n,11j] and Zr^{IV}.[10d] Chiral metal-free catalysts involved guanidine,[10e] urea and thiourea,[10b,g,t,u,y] *N*,*N*′-dioxide,[10i,j,aa] chiral ammonium salt,[10o] chiral quaternary ammonium salt,[10p,w] Brønsted acid,[10q] and bisformamide.[10v] For the similar difficulties encountered in the cyanation of ketones, Strecker reaction of ketimines was not as fruitful as that of aldimines. Highly efficient catalysts were rare and could be counted on one's fingers: Jacocsen's urea Schiff base,[11a,c] Shibasaki's glucose derived ligand-Gd complex,[11d–g] Feng's *N*,*N*′-dioxide,[11h,i,k] and Feng's cinchonine/Ti/biphenol complex.[11j]

General ligand/catalyst for the catalytic asymmetric cyanation of C=O and C=N bonds: Exploiting ligand/catalyst with wide applications was challenging and appealing. In the field of asymmetric cyanation of C=X (X = O, N), such ligands/catalysts were listed as follows. The glucose-derived ligand developed by Shibasaki was efficient for the cyanation of aldehydes, ketones and ketimines by using its Al^{III}, Ti^{IV}, Sm^{III} or Gd^{III} complex.[4d,i] The Al^{III} or Ti^{IV} complex of the tripeptide Schiff base ligand developed by Snapper and Hoveyda could efficiently promote the asymmetric cyanation of ketones[8f] and aldimines.[10f] The Al^{III} or Ti^{IV} complex of C_2 symmetric Schiff base was successfully used in the cyanation of aldehydes and ketones by Belokon′ and North,[4h] in the cyanation of ketones by our group,[8i,l] and in the Strecker reaction of aldimines by Jacobsen.[10c] The BINOL-based bifunctional Al^{III} catalyst was suitable for the cyanation of aldehydes, aldimines, and Reissert reaction (analogous Strecker reaction).[4d,i] The urea and thiourea catalyst developed by Jacobsen was suitable for the asymmetric cyanation of aldimines,[10g,t,u,y] ketimines,[11a,c] ketones,[8r,x] and aldehydes[8r] (two examples were reported for aldehydes). In this article, a general catalyst system accommodated aldehydes, ketones, aldimines and ketimines for the asymmetric cyanation is described.

Development of cinchona alkaloid/Ti/diol catalyst system for the cyanation reaction and the phenomenon of asymmetric activation: Cinchona alkaloids, 1,1′-bi-2-naphthol (BINOL) and their derivatives are well known for their excellent performance in the catalytic asymmetric synthesis. However, the combined use of these two ligands within one catalyst system was not attempted until recently. At the very beginning, we found that cinchonine/[Ti(O*i*Pr)$_4$] could catalyze the cyanation of aldehydes with CNCOOEt and *N*-Ts aldimines with TMSCN, although very low *ee* values were obtained. To our delight, by combining (*R*)-BINOL as a second ligand, the results were significantly improved, suggesting that an improved chiral environment was created around the catalytic center. Based on these findings, two catalyst systems have been evolved. Firstly, a four-component catalyst system consisted of cinchonine, (*S*)-6,6′-dibromo-1,1′-bi-2-naphthol, (1*R*,2*S*)-(−)-*N*-methylephedrine, and [Ti(O*i*Pr)$_4$] was discovered to be highly efficient for the asymmetric cyanocarbonylation of aldehydes.[6i] Secondly, a relatively simple catalyst generated from cinchonine, achiral 3,3′-disubstituted biphenol, and [Ti(O*i*Pr)$_4$] was developed for the asymmetric Strecker reaction of *N*-Ts imines, affording the desired products in high yields with excellent *ee* values.[11j] Especially, a phenomenon of "asymmetric activation"[12] was observed in the latter case. The inducing ability of the chiral ligand was significantly magnified by the axially flexible achiral ligand through coordinative interaction with the central metal Ti^{IV}.

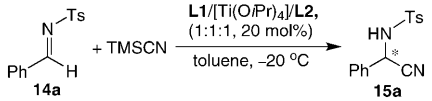
Herein, a full investigation of cinchona alkaloid/[Ti(O*i*Pr)$_4$]/achiral 3,3′-disubstituted 2,2′-biphenol in the asymmetric cyanation of aldehydes, ketones, aldimines and ketimines was presented.[13] Besides trimethylsilyl cyanide (TMSCN), an alternative cyanide source, ethyl cyanoformate (CNCOOEt), was also studied in full detail. Excellent results have been achieved in the cyanation of aldehydes, aldimines and ketimines. Noteworthy, to the best of our knowledge, CNCOOEt has never been successfully employed in the Strecker reaction before. The catalyst structure and reaction mechanism were studied in detail by control experiment, ^{1}H NMR and ^{13}C NMR analyses. Plausible catalytic cycles were proposed to explain the reaction course.

Results and Discussion

Catalytic asymmetric cyanation of aldimines, ketimines, ketones and aldehydes with TMSCN as the cyanide source

Catalytic asymmetric cyanation of aldimines with TMSCN as the cyanide source: In our initial studies on the cyanation of *N*-Ts benzaldimine **14a** with TMSCN, it was found that while **1a**, **1a**/[Ti(O*i*Pr)$_4$] or (*R*)-**3**/[Ti(O*i*Pr)$_4$] gave low catalytic activity or poor enantioselectivity, the combinatorial catalyst, cinchonine **1a**/[Ti(O*i*Pr)$_4$]/(*R*)-BINOL **3**, provided moderate enantioselectivity (66% *ee*) with quantitative yield in toluene at −20°C (Table 1, entries 1–4). Surprisingly, replacing (*R*)-BINOL with (*S*)-BINOL in the catalyst system led to comparable *ee* value with the same stereochemistry control, suggesting that the absolute configuration

Table 1. Searching for an efficient combinatorial catalyst system.[a]



Entry	Catalyst[b]	*ee* [%][c]	Entry	Catalyst[b]	*ee* [%][c]
1[d]	**1a**	−16	19	**1a**/Ti/**4n**	94
2	**1a**/Ti	48	20	**1a**/Ti/**4o**	95
3[d]	(*R*)-**3**/Ti	12	21	**1a**/Ti/**4p**	94
4	**1a**/Ti/(*R*)-**3**	66	22	**1a**/Ti/**5a**	65
5	**1a**/Ti/(*S*)-**3**	62	23	**1a**/Ti/**5b**	−11
6	**1a**/Ti/**4a**	71	24	**1a**/Ti/**5c**	6
7	**1a**/Ti/**4b**	62	25	**1a**/Ti/**6**	58
8	**1a**/Ti/**4c**	64	26	**1a**/Ti/**7**	55
9	**1a**/Ti/**4d**	4	27	**1a**/Ti/**8**	72 (69)[e]
10	**1a**/Ti/**4e**	34	28	**1a**/Ti/**9**	40
11	**1a**/Ti/**4f**	74	29	**1a**/Ti/**10**	36
12	**1a**/Ti/**4g**	70	30	**1a**/Ti/**11**	24
13	**1a**/Ti/**4h**	72	31	**1a**/Ti/**12**	46
14	**1a**/Ti/**4i**	68	32	**1a**/Ti/**13**	12
15	**1a**/Ti/**4j**	71	33	**1b**/Ti/**4m**	93
16	**1a**/Ti/**4k**	70	34	**2a**/Ti/**4m**	−90
17	**1a**/Ti/**4l**	74	35	**2b**/Ti/**4m**	−79
18	**1a**/Ti/**4m**	95			

[a] Unless noted otherwise, reactions were performed with benzaldimine **14a** (0.1 mmol), TMSCN (0.2 mmol, but 0.12 mmol was used for entries 17–21), catalyst (20 mol%) in toluene (0.5 mL) at −20 °C for 18 h, and full conversion of benzaldimine was observed by TLC detection. [b] The Ti catalyst was **L1**(cinchona alkaloid)/[Ti(O*i*Pr)$_4$]/**L2**(phenol) 1:1:1 or **L1 (L2)**/[Ti(O*i*Pr)$_4$] 1:1. When **L2** = monophenols **6–10** (entries 31–35), **L1**/[Ti(O*i*Pr)$_4$]/**L2** 1:1:2. [c] The negative sign means that the major enantiomer was *R* configuration. [d] Large amount of the unreacted imine and trace of the product were obtained. [e] **L1**/[Ti(O*i*Pr)$_4$]/**L2** 1:1:1.

of the product **15a** was mainly governed by cinchonine rather than chiral BINOL (Table 1, entries 4,5). So, we wondered whether the chiral BINOL **3** could be replaced by the achiral 2,2′-biphenol (bipol) **4a**, which was more advantageous for it could be used without asymmetric synthesis or resolution. The feasibility of this assumption was quickly confirmed and even slightly higher *ee* value (71% *ee*) was obtained (Table 1, entry 6).

It was anticipated that with the chiral ligand unchanged, improved enantioselectivity might be achieved by reasonable modification of achiral 2,2′-biphenol. Therefore, an array of modified bipols **4b–k** (Figure 1) with varying electronic properties and steric hindrances were synthesized and evaluated (Table 1, entries 7–16). Negative effect was observed when electron-withdrawing group, such as Br, was introduced onto the bipol (Table 1, entries 7,8). Substituents at *ortho* position of the hydroxyl groups greatly affected the outcomes of the enantioselectivity. When R^4 was kept constant as *t*Bu, the enantiomeric excess increased along with the increment of the steric hindrance of R^3 (Table 1, entries 9–11). However, the much bulkier 1-adamantyl led to a slight decrease of *ee* (Table 1, entry 12). If R^3 was kept constant as *t*Bu or 1-adamantyl, variation of substituents at the 5,5′-position of bipol had little influence on enantioselectivity (Table 1, entries 11–16). Given no significant improvement of *ee* was achieved by modifying 2,2′-biphenol with halogen or alkyl substituents, biphenols **4l–p** with planar and electron-rich aryl group at the 3,3′-position were synthesized. Excitingly, dramatic improvement of enantioselectivity was generally observed by using these bipols except **4l**, furnishing the desired product **15a** with 94–95% *ee* (Table 1, entries 17–21). It was suggested that the aryl modified bipols were suitable to create a more favorable asymmetric cavity around the metal center.

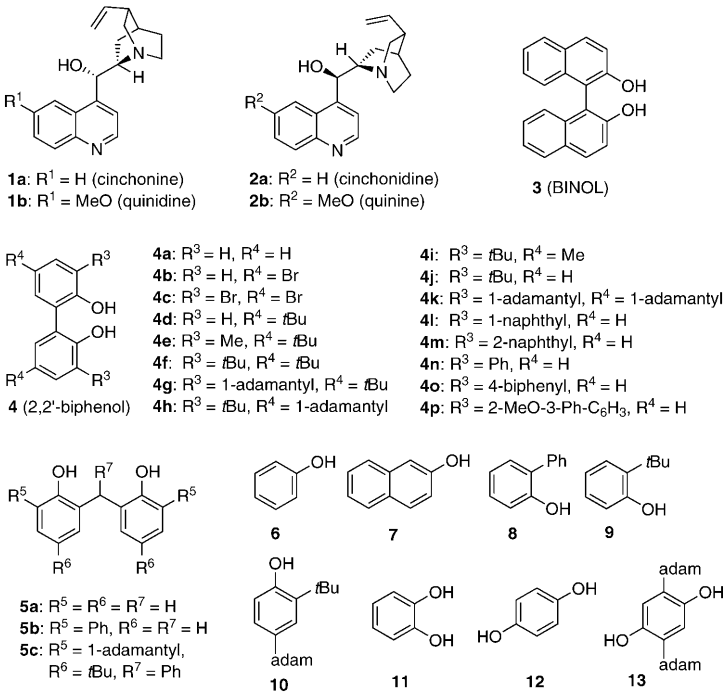


Figure 1. Ligands evaluated in this study.

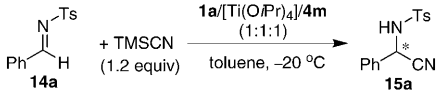
To find out whether the axis presented in bipol was essential to achieve good results, we examined some other diols. As could be seen, inferior results were observed when biphenol **4** was replaced by the structurally similar diols 2,2′-methylene-bis-(phenol) (**5**) with a methylene linking two phenol fragments (Table 1, entries 22–24). Phenols **6–10** which were monomers of the corresponding biphenols **3** and **4** gave poor results either (Table 1, entries 25–29). For instance, when two equiv of 2-phenyl phenol **8** was used instead of 3,3′-diphenyl 2,2′-biphenol (**4n**), low enantioselectivity was obtained. Moreover, pyrocatechol **11** and hydroquinone **12–13** with two hydroxyls attached on one benzene ring also showed bad results compared with 2,2′-biphenol (**4a**; Table 1, entries 30–32). As has been demonstrated, the axis in the biphenol was very crucial and indispensable to achieve excellent enantioselectivity.

Other cinchona alkaloids were tried to replace cinchonine, but none of them exhibited superior result (Table 1, entries 33–35). Noteworthy, when cinchonidine **2a**, the diastereomer of **1a**, was used, the product was obtained in 90% *ee* with inversed configuration, which made it facile to

obtain the *R* enantiomer of α-aminonitrile **15a** (Table 1, entry 34).

Interestingly, when the catalyst loading was gradually decreased from 30 to 5 mol%, not only the reaction became sluggish but the enantioselectivity decreased steadily from 97 to 84% *ee* (Table 2, entries 1–5). Inspired by the previous reports using protic additives to improve results,[14] *i*PrOH (1.2 equiv) was added to the reaction mixture of catalyst (5 mol%), aldimine **14a**, and TMSCN in toluene at −20°C. To our delight, the reaction proceeded smoothly, giving the product **15a** in high yield with high *ee* (Table 2, entry 6). Triggered by this, we reasoned that under high catalyst loadings (20 or 30 mol%), the large amount of *i*PrOH (ca. 60 or 90 mol%) generated from the catalyst preparation must be responsible for the excellent results obtained without addition of *i*PrOH (Table 2, entries 1,2). To verify this assumption, some control experiments were performed. As expected, when the released *i*PrOH was removed after the catalyst preparation (**1a**/[Ti(O*i*Pr)$_4$]/**4m** 1:1:1, 20 mol%), both the yield and *ee* were dramatically diminished (Table 2, entry 7). Remarkably, the excellent result could be regained by adding 60 mol% of *i*PrOH back to the reaction system (Table 2, entry 8). In addition, presence of excessive *i*PrOH (120–180 mol%) had no adverse influence on the result (Table 2, entries 9,10). Therefore, without the addition of *i*PrOH, the inferior results obtained under low catalyst loadings would not be ascribed to the reduced amount of active catalytic species. The real reason might lie in the fact that the quantity of *i*PrOH produced in the catalyst preparation step was far from enough to give excellent result (for the detailed studies on the role of *i*PrOH, see Section on the Investigation of the role of *i*PrOH).

Table 2. Investigation of the catalyst loading with TMSCN as the cyanide source.[a]

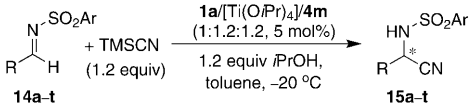


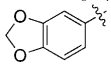
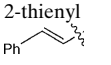
Entry	Catalyst [mol%]	*i*PrOH [mol%]	*t* [h]	Yield[b] [%]	*ee* [%]
1	30	none	4	99	97
2	20	none	4	99	95
3	15	none	24	99	92
4	10	none	24	99	90
5	5	none	54	98	84
6[c]	5	120	2.5	99	97
7[d]	20	none	4	35	46
8[d]	20	60	4	99	94
9[d]	20	120	4	99	96
10[d]	20	180	4	99	95

[a] Unless noted otherwise, reactions were performed with imine (0.1 mmol), TMSCN (0.12 mmol) with catalyst (**1a**/[Ti(O*i*Pr)$_4$]/**4m** 1:1:1, 5–30 mol%) in toluene (0.5 mL) at −20°C. [b] Isolated yield. [c] **1a**/[Ti(O*i*Pr)$_4$]/**4m** 1:1.2:1.2. [d] The produced *i*PrOH was removed under vacuum after catalyst preparation.

To further optimize the reaction conditions, the amount of *i*PrOH and some other protonic reagents were examined with 5 mol% of catalyst (for details, see Supporting Information). It was found that phenol and some other alcohols such as MeOH gave comparable results with *i*PrOH. Reaction parameters such as cyanide source,[15] central metal, solvent, and reaction temperature were also investigated, but no superior result was obtained. The optimal conditions were identified as catalyst (**1a**/[Ti(O*i*Pr)$_4$]/**4m** 1:1.2:1.2, 5 mol%), TMSCN (1.2 equiv), *i*PrOH (1.2 equiv), 0.2 M in toluene at −20°C, under which, a series of *N*-Ts aldimines were examined and generally high yields and *ee* values were obtained (Table 3).

Table 3. Substrate scope for the cyanation of *N*-Ts aldimines with TMSCN.[a]



Entry	R	Product	*t* [h]	Yield [%][b]	*ee* [%][c]
1	Ph	**15a**	2.5	>99	97(*S*)
2	4-FC$_6$H$_4$	**15b**	3	>99	96
3	4-ClC$_6$H$_4$	**15c**	3	97	93
4	4-MeC$_6$H$_4$	**15d**	22	>99	97
5	3-MeC$_6$H$_4$	**15e**	8	>99	94
6	2-MeC$_6$H$_4$	**15f**	18	>99	79
7	4-MeOC$_6$H$_4$	**15g**	8	>99	97
8		**15h**	3	>99	97
9	1-naphthyl	**15i**	4	92	91
10	2-naphthyl	**15j**	22	97	96
11	2-furyl	**15k**	3	93	90
12	2-thienyl	**15l**	5	94	94
13		**15m**	4	96	91
14[d]	cyclohexyl	**15n**	6	>99	92
15[d]	*i*Pr	**15o**	6	96	84
16[d]	*t*Bu	**15p**	6	98	84
17[d]	*n*C$_5$H$_{11}$	**15q**	6	61	79
18[e]	Ph	**15r**	4	>99	94
19[f]	Ph	**15s**	4	94	94
20[g]	Ph	**15t**	4	75	90

[a] Unless otherwise noted, ArSO$_2$=*p*-tosyl (Ts) and reactions were carried out with imine (0.1 mmol), TMSCN (0.12 mmol), catalyst (5 mol%), *i*PrOH (0.12 mmol) in toluene (0.5 mL) at −20°C. [b] Isolated yield. [c] Determined by HPLC. [d] 15 mol% of catalyst was used. [e] Ar=4-ClC$_6$H$_4$. [f] Ar=Ph. [g] Ar=2,4,6-trimethylphenyl.

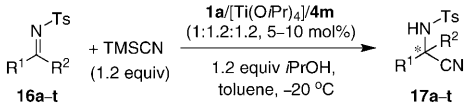
Catalytic asymmetric cyanation of ketimines with TMSCN as the cyanide source: Although **1a**/[Ti(O*i*Pr)$_4$]/**4m** 1:1.2:1.2 was optimized for the reaction of *N*-Ts aldimines, it could be efficiently applied to the cyanation of *N*-Ts ketimines. As the results shown in Table 4, excellent enantioselectivities (up to 99% *ee*) and high yields were attained for a wide spectrum of ketimines using 5 mol% of catalyst. In some cases (e.g., substrates bearing electron-donating group such as methyl or methoxyl, substrates with bulky hindrance, and aliphatic ketimines), 10 mol% of catalyst was required to furnish satisfactory reactivity and enantioselectivity.

Most of the substituted acetophenone derived imines were converted to the products in high yields with excellent enantioselectivities (Table 4, entries 1–9). Cyclic ketimine was also tested, giving the product in high yield with good

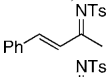
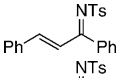
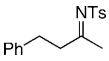
ee with 10 mol% of catalyst (Table 4, entry 10). Heteroaromatic ketimines showed high reactivities and enantioselectivities (Table 4, entries 11,12). Both the aryl ethyl and aryl propyl ketimines gave excellent results, but aryl cyclohexyl ketone derived imine was unreactive (Table 4, entries 13–15). Besides, α,β-unsaturated ketimine **16p** gave the synthetically important product with high *ee* and complete regioselectivity (Table 4, entry 16). As to the chalcone derived imine **16q**, the desired 1,2-adduct was obtained in high yield with moderate *ee* (Table 4, entry 17). Among the aliphatic ketimines evaluated, cyclohexyl methyl ketimine afforded the best result, whereas primary alkyl methyl ketimine **16r** and tertiary alkyl methyl ketimine **16t** provided less satisfactory results (Table 4, entries 18–20).

Chiral diaryl compounds such as diarylmethanols and diarylmethylamines are important intermediates for the synthesis of pharmaceutically relevant products with antihistaminic, antiarrhythmic, diuretic, antidepressive, laxative, local-anesthetic and anticholinergic properties.[16a,b] Although a large number of efficient methods have been established for the asymmetric synthesis of *sec*-diaryl compounds,[16c–j] the reports on the asymmetric synthesis of *tert*-diaryl compounds are quite limited.[16k,l] So, it is interesting to apply the current catalyst to the asymmetric synthesis of tertiary α-amino nitriles with two aryl groups on the chiral center. As shown in Table 5, the reactivity and enantioselectivity drastically depended on the catalyst loading and the substitution pattern of the aryl group. While low reactivity and moderate enantioselectivity (26% yield and 76% *ee*) were observed for the cyanation of 2-fluorobenzophenone derived ketimine **18a** in the presence of 5 mol% of catalyst, excellent result (96% yield and 98% *ee*) could be obtained by increasing the catalyst loading to 10 mol% (Table 5, entries 1,2). Similar to the trend observed in the asymmetric reduction of diarylketones,[16b–d,g] a significant *ortho*-substituent effect was observed, namely, *ortho*-substituted diarylketimines were the most suitable substrates and could be highly enantioselectively converted to the desired products (Table 5, entries 2–5). It should be mentioned that in the Strecker reaction of aldimines and aryl alkyl ketimines, the presence of *ortho*-substituent in substrate was detrimental to the enantioselectivities. Surprisingly, no product was detected when strongly electron-withdrawing group CF_3 was present (Table 5, entry 6). *meta*- and *para*-Substituted benzophenone imines gave the desired products in high yields but poor enantioselectivities (Table 5, entries 7–12). Presumably, the presence of an *ortho*-substituent in the substrate greatly benefited the enantiofacial discrimination for the cyanide attack in the transition state.

Table 4. Substrate scope for the cyanation of *N*-Ts ketimines with TMSCN.[a]



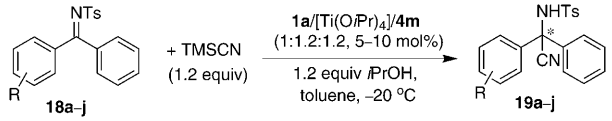
16a–t 17a–t

Entry	Ketimine	Product	Catalyst [mol%]	*t* [h]	Yield [%][b]	*ee* [%][c]
1	R^1=Ph, R^2=Me	**17a**	5	4	>99	>99(*S*)
2	R^1=4-FPh, R^2=Me	**17b**	5	4	90	98
3	R^1=4-ClPh, R^2=Me	**17c**	5	4	>99	>99(*S*)
4	R^1=4-BrPh, R^2=Me	**17d**	5	8	>99	>99(*S*)
5	R^1=4-MePh, R^2=Me	**17e**	10 (5)	4 (50)	>99 (91)	>99 (94)(*S*)
6	R^1=4-MeOPh, R^2=Me	**17f**	10 (5)	4 (50)	99 (95)	>99 (94)(*S*)
7	R^1=3-ClPh, R^2=Me	**17g**	5	4	>99	>99
8	R^1=2-FPh, R^2=Me	**17h**	10 (5)	4 (24)	>99 (>99)	90 (84)
9	R^1=2-naphthyl, R^2=Me	**17i**	5	22	90	>99(*S*)
10		**17j**	10 (5)	51 (50)	99 (76)	82 (70)(*S*)
11	R^1=2-furyl, R^2=Me	**17k**	5	22	97	99
12	R^1=2-thienyl, R^2=Me	**17l**	5	22	97	>99
13	R^1=Ph, R^2=Et	**17m**	10 (5)	4 (4)	>99 (66)	>99 (74)
14	R^1=Ph, R^2=*n*Pr	**17n**	10 (5)	4 (45)	69 (93)	>99 (64)
15	R^1=Ph, R^2=cyclohexyl	**17o**	10	48	–	–
16		**17p**	5	17	97	98
17		**17q**	10	20	>99	71
18		**17r**	5	8	99	45
			10	4	99	67 (77)[d]
19	R^1=cyclohexyl, R^2=Me	**17s**	10 (5)	4 (4)	>99 (77)	94 (80)
20	R^1=*t*Bu, R^2=Me	**17t**	10 (5)	4 (4)	98 (77)	69 (65)

[a] Unless otherwise noted, reactions were carried out with imine (0.1 mmol), TMSCN (0.12 mmol), *i*PrOH (0.12 mmol) in toluene (0.5 mL) at −20 °C. [b] Isolated yield. [c] Determined by HPLC and the absolute configuration was determined by comparison of the optical rotation with literature data.[11h] [d] The reaction was performed at −45 °C.

Catalytic asymmetric cyanosilylation of ketones and aldehydes: Followed the studies of asymmetric cyanation of aldimines and ketimines, **1a**/Ti/**4m** was attempted in the cyanosilylation of ketones. Unfortunately, the reaction proceeded sluggishly and the desired cyanohydrin silyl ether **21a** was obtained in 86% yield and 38% *ee* after four days (Table 6, entry 1). To improve the result, some modified biphenols were screened (see Supporting Information). Surprisingly, 3,3′-di-α-naphthyl biphenol (**4l**) provided the best enantioselectivity (74% *ee*), while it gave the poorest result among the 3,3′-diaryl substituted biphenols in the cyanation of benzaldimine **14a**. Solvent screening (see Supporting Information) revealed that *n*-hexane was the most suitable, although the catalyst was undissolved in it. The reactivity

Table 5. Substrate scope for the catalytic asymmetric Strecker reaction of *N*-Ts diarylketimines.[a]

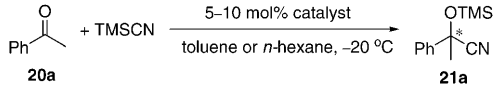


Entry	R	Product	Catalyst [mol%]	*t* [h]	Yield [%][b]	*ee* [%][c]
1	2-F	**19a**	5	45	26	76
2	2-F	**19a**	10	5	96	98
3	2-Cl	**19b**	10	45	95	97
4	2-Me	**19c**	10	45	90	94
5[d]	2-Me	**19c**	10	45	90	97
6	2-CF_3	**19d**	10	45	–	–
7	3-Cl	**19e**	10	11	>99	0
8	3-Me	**19f**	10	8	>99	2
9	4-F	**19g**	10	6	>99	20
10	4-Cl	**19h**	10	20	>99	24
11	4-Me	**19i**	10	8	>99	28
12	4-MeO	**19j**	10	8	>99	28

[a] Unless otherwise noted, reactions were carried out with imine (0.1 mmol), TMSCN (0.12 mmol), *i*PrOH (0.12 mmol) in toluene (0.5 mL) at −20°C. [b] Isolated yield. [c] Determined by HPLC. [d] The reaction was performed at −45°C.

and enantioselectivity were greatly enhanced, giving the product in 97% yield and 87% *ee* within 40 h (Table 6, entry 2 vs. 3). Increasing the concentration of ketone to 2.0 M not only greatly enhanced the reactivity and enantioselectivity of the reaction, but also allowed the catalyst loading and amount of TMSCN to be reduced to 5 mol% and 1.5 equiv, respectively (Table 6, entry 4). Additionally, employing *i*PrOH (0.5–1.0 equiv) as additive had no positive effect on the result.

Table 6. Optimizing conditions for the catalytic asymmetric cyanosilylation of acetophenone.[a]

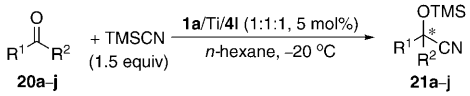


Entry	Catalyst	*t* [h]	Yield [%][b]	*ee* [%]
1	**1a**/Ti/**4m** 1:1:1	96	86	38
2	**1a**/Ti/**4l** 1:1:1	96	55	74
3[c]	**1a**/Ti/**4l** 1:1:1	40	97	87
4[d]	**1a**/Ti/**4l** 1:1:1	20	98	94

[a] Reaction conditions: acetophenone (0.1 mmol), TMSCN (0.2 mmol), catalyst (10 mol%), in toluene (0.5 M) at −20°C. [b] Isolated yield. [c] *n*-Hexane was used as solvent. [d] The reaction was run with catalyst (5 mol%), TMSCN (0.15 mmol), and 2.0 M in *n*-hexane.

As other optimizations gave no superior result, the optimal condition was identified as TMSCN (1.5 equiv), **1a**/Ti/**4l** 1:1:1 (5 mol%), 2.0 M in *n*-hexane at −20°C. Under this condition, the substrate scope was examined. *para*-Substituted acetophenones with either electron donating or withdrawing group were suitable substrates (Table 7, entries 1–7). However, for the *meta*- and *ortho*-substituted substrates, less satisfactory results were obtained (Table 7, entries 8, 9). Propiophenone was transformed to the desired product in good

Table 7. Substrate scope for the catalytic asymmetric cyanosilylation of ketones.[a]



Entry	Ketone	Product	*t* [d]	Yield [%][b]	*ee* [%]
1	$PhCOCH_3$	**21a**	1	98	94(*S*)
2	4-F-$PhCOCH_3$	**21b**	1	99	92
3	4-Cl-$PhCOCH_3$	**21c**	1	98	87(*S*)
4	4-Br-$PhCOCH_3$	**21d**	1	99	98
5	4-Me-$PhCOCH_3$	**21e**	2	95	90(*S*)
6	4-MeO-$PhCOCH_3$	**21f**	2	83	94(*S*)
7	4-NO_2-$PhCOCH_3$	**21g**	1	92	88
8	3-Cl-$PhCOCH_3$	**21h**	1	99	70(*S*)
9	2-F-$PhCOCH_3$	**21i**	1	96	32
10	$PhCOC_2H_5$	**21j**	2	97	74

[a] Reaction conditions: ketone (0.2 mmol), TMSCN (0.3 mmol), **1a**/Ti/**4l** 1:1:1, 5 mol%), 2.0 M in *n*-hexane at −20°C. [b] Isolated yield.

yield and moderate *ee* (Table 7, entry 10). Other ketones such as aliphatic, heterocyclic, and cyclic ketones were also tested, but only 13–30% *ee* values were obtained.

Besides, the cyanosilylation of benzaldehyde **22a** was also investigated. After optimizing the conditions (see Supporting Information), up to 92% *ee* was obtained when **1b**/Ti/**4m** 5:5:2.5 was used as catalyst under the concentration of 0.1 M in toluene at −20°C. However, separation of pure cyanohydrin silyl ether **23a** from the reaction mixture was difficult via flash chromatography as the product was contaminated by some impurity with the same R_f value.[17] Due to this reason, further studies were not proceeded. Despite this, current catalyst system has shown great potential in the asymmetric cyanation of aldehyde. As a matter of fact, it was successfully used in the cyanation of aldehydes with CNCOOEt as the cyanide source (see Section on Catalytic asymmetric cyanation of aldehydes).

Catalytic asymmetric cyanation of aldimines, ketimines, ketones and aldehydes with CNCOOEt as the cyanide source

Undoubtedly, HCN and TMSCN are two of the most commonly used cyanide sources for the cyanation. Although remarkable results have been accomplished, some problems including high cost, high toxicity, or high volatility are associated with them. To overcome these problems, more and more attention has been focused on the development of alternative cyanide sources which are relatively cheap, less toxic and easily handling. Till now, much progress has been achieved for the cyanation of carbonyl compounds (especially for the aldehydes) using carbonyl cyanide RCOCN (R = EtO, MeO, Me, Ph),[6] alkyl cyanophosphorylates,[6] acetone cyanohydrin,[7a–c] and alkali metal cyanides (NaCN/KCN)[7d–f] as cyanide sources, in which, the stable, less toxic, relatively cheap, and readily available ethyl cyanoformate (CNCOOEt) attracted the most attention.[6a–o]

For the asymmetric Strecker reaction, unfortunately, although some cyanide reagents other than HCN and TMSCN have once been tried in some reports, disappointing

results were generally observed.[10f,q,r,u] To the best of our knowledge, the only successful example was reported by List's group who developed a thiourea catalyzed asymmetric cyanation of aldimines with acetyl cyanide (CH_3COCN) as the cyanide reagent, affording highly enantiopure *N*-acetyl amino nitriles.[10t,u,y] However, their attempt to involve ketimines as substrates failed.[10y] Therefore, it is still challenging while desirable to realize a highly efficient Strecker reaction with a relatively cheap and convenient cyanide source.

In this part, the asymmetric cyanation of C=O and C=N with CNCOOEt employing the above developed self-assembled catalyst was described. Considering the problem encountered in the cyanosilylation of benzaldehyde, we would like to begin this part with the study of cyanation of aldehyde with CNCOOEt.

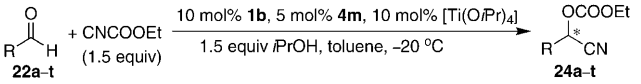
Catalytic asymmetric cyanation of aldehydes with CNCOOEt as the cyanide source: After systematical optimization (see Supporting Information), we found that the optimal catalyst was the same as that optimized for the cyanosilylation of benzaldehyde. When *i*PrOH was used as additive, the reactivity was greatly enhanced with the *ee* slightly improved. Interestingly, varying the amount of *i*PrOH (0.25–3.0 equiv) had no obvious effect on the outcomes.

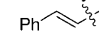
The substrate scope was investigated under the condition of 10 mol% of **1b**, 5 mol% of **4m**, 10 mol% of [Ti(O*i*Pr)$_4$], aldehyde (0.1 mmol), CNCOOEt (1.5 equiv) and *i*PrOH (1.5 equiv) in toluene at −20°C. Various aromatic aldehydes were converted to the corresponding products in high yields and *ee* values (Table 8, entries 1–11). Especially, 3-phenoxybenzaldehyde gave the product in high yield with the best *ee* (up to 96%), which was useful for the synthesis of the insecticide fenvalerate A_α.[4c] 2-Naphthaldehyde and heterocyclic aldehydes also afforded the corresponding products in high *ee* values and high yields (Table 8, entries 12–14). When (*E*)-cinnamaldehyde was subjected to the reaction, only 1,2-addition product was afforded in 99% yield with 84% *ee* (Table 8, entry 15). Some representative aliphatic aldehydes were evaluated too. Excitingly, steric bulkier pivalaldehyde gave the corresponding product with 95% *ee* and 92% yield after 15 h (Table 8, entry 16). Cyclohexanecarbaldehyde and isobutyraldehyde gave 88 and 83% *ee*, respectively (Table 8, entries 17,18). Whereas, linear aldehydes such as *n*-hexanal and (*E*)-but-2-enal gave moderate *ee* values (Table 8, entries 19,20). It is suggested that for the cyanation of aliphatic aldehydes, bulkier steric hindrance significantly benefited the enantioselectivity. In addition, acetophenone was unreactive under the current conditions. It is still a challenge to achieve the asymmetric cyanation of acetophenone with CNCOOEt to date.[18]

Catalytic asymmetric cyanation of ketimines with CNCOOEt as the cyanide source: As there is still no report dealing with the asymmetric Strecker reaction with CNCOOEt as the cyanide source, the contribution to this area was highly desirable. It was found that the catalyst system optimized for the cyanation of aldehydes could be directly employed in the cyanation of ketimines without any modification.[19] Ketimine **16a** could be quantitatively transformed to α-amino nitrile **17a** in 99% *ee* within 42 h (Table 9, entry 1). Interestingly, unlike the cyanation of aldehyde affording the cyanohydrin *O*-carbonate, no *N*-ethoxycarbonyl protected amino nitrile was observed. This might be due to the different reaction mechanisms underwent (see below). Slightly increasing the amount of CNCOOEt and *i*PrOH drastically enhanced the reactivity (Table 9, entry 2 vs. 1).

Under the optimized conditions, a series of *N*-Ts ketimines were tested. The results in Table 9 showed, excellent enantioselectivities (up to 99% *ee* for most of ketimines) and high yields were achieved for the aryl methyl ketimines except *ortho*-substituted imine **16h** (Table 9, entries 2–10). Heteroaromatic ketimines, aryl ethyl and aryl propyl ketimines exhibited high reactivities and enantioselectivities as well (Table 9, entries 11–14). When α,β-unsaturated ketimine was tested, the synthetically important product was given in high yield and *ee* with complete regioselectivity (Table 9, entry 15). Also worthy of note is that cyanation of cyclohexyl methyl ketimine exhibited excellent enantioselectivity (>99% *ee*) (Table 9, entry 16). *tert*-Butyl methyl ketimine gave moderate *ee* (Table 9, entry 17). Furthermore, the catalyst system was extended to the challenging Strecker reaction of unsymmetric diarylketimines. Similar to the case with TMSCN as the cyanide source, *ortho*-substituted diaryl-

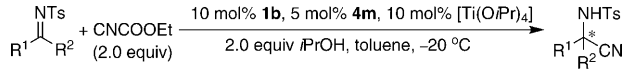
Table 8. Substrate scope for catalytic asymmetric cyanation of aldehydes with CNCOOEt.[a]



Entry	R	Product	*t* [h]	Yield [%][b]	*ee* [%][c]
1	C_6H_5	**24a**	5	98	94(*S*)
2	4-FC_6H_4	**24b**	5	95	90
3	4-ClC_6H_4	**24c**	7	90	92(*S*)
4	4-BrC_6H_4	**24d**	7	91	91
5	4-PhC_6H_4	**24e**	5	94	93
6	4-MeC_6H_4	**24f**	5	97	93(*S*)
7	4-$MeOC_6H_4$	**24g**	7	99	90(*S*)
8	3-$PhOC_6H_4$	**24h**	15	95	96
9	3-$MeOC_6H_4$	**24i**	7	99	93(*S*)
10	3-MeC_6H_4	**24j**	7	99	92
11	2-MeC_6H_4	**24k**	7	98	90
12	2-naphthyl	**24l**	15	99	90
13	2-furyl	**24m**	15	96	93
14	2-thienyl	**24n**	15	98	90
15		**24o**	15	99	84(*S*)
16	*t*Bu	**24p**	15	92	95(*S*)
17[d]	cyclohexyl	**24q**	15	99	88(*S*)
18	*i*Pr	**24r**	15	91	83(*S*)
19	nC_5H_{11}	**24s**	15	98	72(*S*)
20		**24t**	15	85	76(*S*)

[a] Reaction conditions: **1b** (10 mol%), **4m** (5 mol%), [Ti(O*i*Pr)$_4$] (10 mol%), aldehyde (0.1 mmol), CNCOOEt (0.15 mmol), *i*PrOH (0.15 mmol) in toluene (0.2 mL) at −20°C. [b] Isolated yield. [c] Determined by HPLC or GC. The absolute configurations were determined by comparison with literature data (for detail, see Supporting Information). [d] **1b** (15 mol%), **4m** (7.5 mol%) and [Ti(O*i*Pr)$_4$] (15 mol%) were used.

Table 9. Substrate scope for the Strecker reaction of *N*-Ts ketimines with CNCOOEt.[a]



16 17

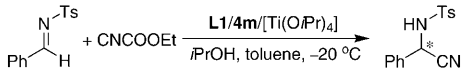
Entry	R^1	R^2	Product	*t* [h]	Yield [%][b]	*ee* [%][c]
1[d]	Ph	Me	**17a**	42	99	99(*S*)
2	Ph	Me	**17a**	22	99	99(*S*)
3	4-FC_6H_4	Me	**17b**	20	99	99
4	4-ClC_6H_4	Me	**17c**	20	>99	99(*S*)
5	4-BrC_6H_4	Me	**17d**	20	>99	99(*S*)
6	4-MeC_6H_4	Me	**17e**	22	>99	>99(*S*)
7	4-$MeOC_6H_4$	Me	**17f**	30	97	>99(*S*)
8	3-ClC_6H_4	Me	**17g**	30	98	>99
9	2-FC_6H_4	Me	**17h**	22	99	66
10	2-naphthyl	Me	**17i**	72	97	99(*S*)
11	2-furyl	Me	**17k**	22	99	>99
12	2-thienyl	Me	**17l**	30	95	>99
13	Ph	Et	**17m**	22	99	97
14	Ph	*n*Pr	**17n**	22	95	98
15	Ph	Me	**17p**	20	99	96
16	cyclohexyl	Me	**17s**	20	99	>99
17	*t*Bu	Me	**17t**	20	96	65
18	2-FC_6H_4	Ph	**19a**	72	99	96
19	2-ClC_6H_4	Ph	**19b**	60	99	96
20	2-MeC_6H_4	Ph	**19c**	72	98	93
21	3-MeC_6H_4	Ph	**19f**	20	99	8
22	4-MeC_6H_4	Ph	**19i**	20	99	12

[a] Unless noted, reactions were carried out with imine (0.1 mmol), CNCOOEt (0.2 mmol), *i*PrOH (0.2 mmol) in toluene (0.2 mL) at −20 °C. [b] Isolated yield. [c] Determined by HPLC and the absolute configurations were determined by comparing with literature data (for detail, see Supporting Information). [d] CNCOOEt (1.5 equiv) and *i*PrOH (1.5 equiv) were used.

ketimines were the most suitable substrates, while *meta*- or *para*-substituted ones only gave poor enantioselectivities (Table 9, entries 18–22). In general, CNCOOEt showed lower reactivity than TMSCN, and higher catalyst loading, higher concentration and longer reaction time were required to achieve excellent results.

Catalytic asymmetric cyanation of aldimines with CNCOOEt as the cyanide source: Thereafter, the Strecker reaction of *N*-Ts aldimines with CNCOOEt was examined. Under the similar conditions, aldimime **14a** was converted to **15a** in 93% yield and 90% *ee* within 42 h and no *N*-ethoxycarbonyl protected amino nitrile was detected (Table 10, entry 1). Higher *ee* value (93%) was obtained by adjusting the ratio of **1b**/[Ti(O*i*Pr)$_4$]/**4m** to 1:1:1, although the reaction became slightly sluggish (Table 10, entry 2). Among the cinchona alkaloids, cinchonine **1a** gave the best enantioselectivity (up to 97% *ee*) (Table 10, entries 3–5). Moreover, both the high concentration and large amount of *i*PrOH were necessary to achieve high reactivity (Table 10, entries 6, 7). In the absence of *i*PrOH, the reaction proceeded extremely slowly (Table 10, entry 8). Decreasing the catalyst loading to 5 mol% led to low reactivity, either (Table 10, entry 9).

Table 10. Optimization of the reaction conditions for the cyanation of benzaldimine.[a]



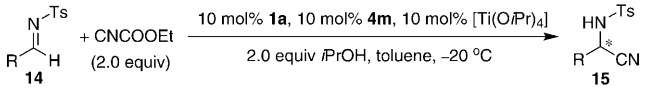
14a 15a

Entry	L1	L1/**4m**/[Ti(O*i*Pr)$_4$] [mol%]	*i*PrOH [mmol]	*c*[b] [M]	*t* [h]	Yield[c] [%]	*ee*[d] [%]
1	**1b**	10:5:10	0.1	0.2	42	93	90
2	**1b**	10:10:10	0.1	0.2	63	90	93
3	**1a**	10:10:10	0.1	0.2	63	93	97
4	**2a**	10:10:10	0.1	0.2	63	89	90(*R*)
5	**2b**	10:10:10	0.1	0.2	63	85	86(*R*)
6	**1a**	10:10:10	0.1	0.5	30	99	96
7	**1a**	10:10:10	0.2	0.5	22	99	96
8	**1a**	10:10:10	0	0.5	144	40	95
9	**1a**	5:5:5	0.2	0.5	46	99	96

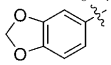
[a] Unless noted, reactions were carried out with imine (0.1 mmol), CNCOOEt (0.2 mmol) in toluene at −20 °C. [b] Concentration. [c] Isolated yield. [d] Determined by HPLC. Unless noted, (*S*)-**15a** was obtained.

Under the conditions applied in Table 10, entry 7, an array of *N*-Ts aldimines were evaluated. As shown in Table 11, most of the aryl aldimines were smoothly converted to the products in the range of 95–97% *ee* with high yields (Table 11, entries 1–7). Condensed aromatic and heterocyclic substrates also gave satisfying results (Table 11, entries 8–10). When α,β-unsaturated aldimine **14m** was tested, the desired 1,2-adduct **15m** was isolated in 80% yield with 84% *ee* (Table 11, entry 11). Besides, this catalyst system was suitable for various *N*-Ts alkyl imines such as cyclic, α-disubstituted, and α-trisubstituted substrates, giving good to excellent *ee* values (Table 11, entries 12–14).

Table 11. Substrate scope for the Strecker reaction of *N*-Ts aldimines with CNCOOEt.[a]



14 15

Entry	R	Product	*t* [h]	Yield [%][b]	*ee* [%][c]
1	Ph	**15a**	22	99	96(*S*)
2	4-FC_6H_4	**15b**	24	95	95
3	4-ClC_6H_4	**15c**	24	97	83
4	4-MeC_6H_4	**15d**	24	99	97
5	3-MeC_6H_4	**15e**	24	99	95
6	4-$MeOC_6H_4$	**15g**	30	99	97
7		**15h**	30	99	97
8	1-naphthyl	**15i**	30	99	93
9	2-naphthyl	**15j**	24	99	95
10	2-thienyl	**15l**	30	99	86
11	Ph	**15m**	48	80	84
12	cyclohexyl	**15n**	30	90	94
13	*i*Pr	**15o**	24	61	86
14	*t*Bu	**15p**	24	58	86

[a] Reaction conditions: imine (0.1 mmol), CNCOOEt (0.2 mmol), *i*PrOH (0.2 mmol) and toluene (0.2 mL) at −20 °C. [b] Isolated yield. [c] Determined by HPLC.

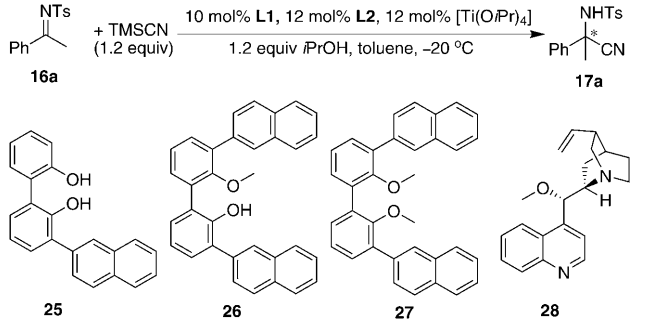
Reaction mechanism

Insight into the catalyst structure

Control experiments for the catalyst structure studies: The catalyst structure studies were focused on the complex of **1a**/Ti/**4m** 1:1:1 because it showed the best performance and widest application among the three catalyst systems described above. In this section, some control experiments were designed to shed some light on the catalyst structure. Taking cyanation of ketimine **16a** with TMSCN as the model reaction, some modified cinchona alkaloids and biphenols were evaluated to probe the relationship between the ligand structure and catalytic efficiency. As demonstrated in Table 12, all the components in the catalyst were very crucial to ensure the excellent activity and enantioselectivity (Table 12, entries 1–4). When one or two of the 2-naphthyl groups at the 3,3′-position of biphenol **4m** were removed, both the yield and *ee* suffered, which indicated that the large steric hindrance at the 3,3′-position of **4m** was critical for the construction of the suitable chiral environment for the asymmetric catalysis (Table 12, entries 5,6). Also, the role of hydroxyl groups in **4m** and **1a** was evident. When one or two hydroxyl groups of **4m** were blocked by methyl, poor results were obtained (Table 12, entries 7,8). Likewise, if the hydroxyl on C-9 of cinchonine **1a** was methylated, extremely low reactivity and enantioselectivity were observed, too (Table 12, entry 9).

Besides the catalytic efficiency, the appearance of the different catalyst solutions was also outlined in Table 12. While cinchonine **1a** in toluene was a suspension, **1a**/[Ti(O*i*Pr)$_4$] gave a relatively clearer solution, and **4m**/[Ti(O*i*Pr)$_4$] was a red clear solution (Table 12, entries 1–3). In contrast, when **1a**, [Ti(O*i*Pr)$_4$], and **4m** were combined to prepare the catalyst, a clear orange solution was formed (Table 12, entry 4). Interestingly, when **4m** was partially or fully methylated, the catalyst solutions were turbid, which had a similar appearance to **1a**/[Ti(O*i*Pr)$_4$], indicating the complexation of **26** or **27** with [Ti(O*i*Pr)$_4$] might hardly occur (Table 12, entries 2, and 7,8). When the hydroxyl in cinchonine was methylated, a solution with similar appearance to that of **4m**/[Ti(O*i*Pr)$_4$] was observed, suggesting **28** might fail to coordinate with Ti^{IV}, and probably the complex formed was the same as that in **4m**/[Ti(O*i*Pr)$_4$] (Table 12, entry 3 vs. 9). Thus, both the difference in catalytic efficacy and the appearance of the catalyst solutions implied that all hydroxyl groups in cinchonine **1a** and biphenol **4m** were very important, and they must have participated into the complexation with Ti^{IV} in the catalyst preparation.

Table 12. Control experiment for the catalyst structure studies.[a]



Entry	Catalyst[b]	Solution appearance		*t* [h]	Yield [%][c]	*ee* [%][d]
1	**1a**	turbid	white	22	76	16(*S*)
2	**1a**/Ti	turbid	white	22	65	27(*S*)
3	**4m**/Ti	clear	red	22	10	–
4	**1a**/Ti/**4m**	clear	orange	3.5	>99	>99(*S*)
5	**1a**/Ti/**4a**	clear	orange	22	29	14(*S*)
6	**1a**/Ti/**25**	clear	orange	22	45	62(*S*)
7	**1a**/Ti/**26**	turbid	white	24	68	26(*S*)
8	**1a**/Ti/**27**	turbid	white	22	40	8(*S*)
9	**28**/Ti/**4m**	clear	red	24	30	8(*S*)

[a] Unless noted, reactions were carried out with catalyst (10 mol%), imine (0.1 mmol), TMSCN (1.2 equiv), *i*PrOH (1.2 equiv) and toluene (0.5 mL) at −20 °C. [b] The Ti catalyst was **L1**(cinchona alkaloid)/[Ti(O*i*Pr)$_4$]/**L2**(phenol) 1:1.2:1.2 or **L1**(**L2**)/[Ti(O*i*Pr)$_4$] 1:1. [c] Isolated yield. [d] Determined by HPLC.

^{1}H NMR and ^{13}C NMR analysis for the catalyst structure studies: To obtain some direct evidences of the catalyst structure, ^{1}H NMR and ^{13}C NMR analysis were performed. It should be mentioned that for the NMR analysis, quinidine **1b** was used instead of cinchonine **1a**, because: 1) **1a** and **1b** showed comparable results in the catalysis; 2) the methoxyl group (MeO) in **1b** was characteristic in NMR analysis, which might supply more useful information.

When the mixture prepared from quinidine **1b**, biphenol **4m**, and [Ti(O*i*Pr)$_4$] in 1:1:1 ratio was subjected to NMR analysis, to our surprise, very clean and resolvable ^{1}H NMR and ^{13}C NMR spectra were obtained, indicating only one kind of Ti^{IV} complex formed in this combination. It was speculated that complex **30**, (biphenoxide)Ti(OR*)(O*i*Pr), was the most possible species generated (Scheme 1). To verify our assumption, assignment of the ^{1}H and ^{13}C NMR spectra was desirable. However, it was found that most of the signals in the downfield were overlapped, which made it difficult to analyze the aromatic region in both ^{1}H NMR (7.0–8.0 ppm) and ^{13}C NMR (120–150 ppm) spectra. As a result, the chemical shifts related to biphenol **4m** and some aromatic protons on quinidine **1b** could not be correctly assigned. Thus, we mainly focused on assigning the resonances in the upfield of the spectra (0–6.5 ppm for ^{1}H NMR and 0–120 ppm for ^{13}C NMR). By using dept-135 and two-dimensional NMR techniques (HMQC and H,H-COSY), partial assignment of the ^{1}H and ^{13}C NMR spectra of complex **30** was accomplished with the data summarized in Table 13. For comparative purposes, the ^{1}H and ^{13}C chemical shifts of quinidine **1b** were also given. Significantly, for the ^{13}C NMR spectrum, the spectral line corresponding to C-8 and C-9 in **1b** shifted from 59.8 and 72.1 ppm to 65.8 and 82.2 ppm, respectively, which provided the direct evidence demonstrating the bond formation between Ti^{IV} and the oxygen atom on C-9 (Figure 3 and Table 13, entries 7,8). Additionally, complex **30** was almost quantitatively formed since no unbound ligand **1b** was detected in ^{1}H NMR and ^{13}C NMR

Table 13. ^{1}H and ^{13}C chemical shifts for **1b** and **1b** moiety in the complex **30**.[a]

Entry	Carbon atom	^{1}H chemical shifts in $CDCl_3$ [ppm][b]		^{13}C chemical shifts in $CDCl_3$ [ppm]	
		quinidine **1b**	**1b** moiety in complex **30**	quinidine **1b**	**1b** moiety in complex **30**
1	C-2	2.87, 3.27	2.33, 2.89	49.6	50.0
2	C-3	2.22	1.33	40.1	38.7
3	C-4	1.75	≈1.18	28.2	27.4
4	C-5	1.50	0.5, ≈1.18	26.5	≈25.3
5	C-6	2.74, 2.87	1.08, 2.55	50.2	51.0
6	C-7	1.16, 2.02	0.84, ≈1.18	21.4	24.9
7	C-8	3.06	3.61	59.8	65.8
8	C-9	5.54	5.55	72.1	82.2
9	C-10	6.01	4.52	140.8	137.3
10	C-11	5.0	4.21, 4.39	114.4	115.0
11	C-2′	8.6	8.42	147.4	147.4
12	C-3′	7.49	6.95	118.4	120.0
13	C-4′	–	–	147.7	ND[c]
14	C-5′	7.18	6.51	101.3	101.6
15	C-6′	–	–	157.6	157.0
16	C-7′	7.30	7.30	121.5	121.1
17	C-8′	7.95	8.02	131.5	131.5
18	C-9′	–	–	126.7	ND
19	C-10′	–	–	144.2	ND
20	CH_3O	3.94	3.74	55.6	55.3

[a] The sample was prepared with quinidine **1b** (0.1 mmol), $[Ti(OiPr)_4]$ (0.1 mmol), and biphenol **4m** (0.1 mmol) in $CDCl_3$ (0.5 mL) at 35 °C for 0.5 h. Then, it was directly transferred to NMR tube for analysis. For the full spectra, see Supporting Information. [b] The chemical shifts of the hydrogen on the corresponding carbon atom. [c] The chemical shift was not determined.

spectra (Figures 2 and 3). Moreover, from the spectra, 1.0 equiv of isopropoxyl group (*i*PrO) bound to Ti^{IV} and 3.0 equiv of released *i*PrOH were observed in the catalyst solution (the corresponding chemical shifts were shown in Scheme 1), which was agree with the generation of the proposed structure **30**.

Overall, although the high complexity of the catalyst structure made the complete assignment of the NMR spectra impossible, all data at hand strongly supported the generation of structure **30** in the catalyst preparation step. ESI-HRMS characterization of the present catalytic system was also performed.[20] However, the peak corresponding to the complex **1b**/Ti/**4m** 1:1:1 was not detected. Instead, the signal corresponding to quinidine exhibited overwhelming intensity. Obviously, this contradicted the result from the NMR analysis that nearly no unbound quinidine existed in the catalyst solution. Thus, it was supposed that the complex **30** must be unstable under ESI-HRMS conditions.

Interestingly, as shown in Table 13, the upfield shifts for nearly all the aliphatic protons on the quinuclidine moiety in quinidine **1b** (except the hydrogen atom on the C-8) were observed upon complexation, indicating that quinuclidine moiety might be in the shielding zone of the naphthalene of **4m** (Table 13, entries 1–6, 9, 10).

The absolute configuration of biphenol 4m in complex 30

Control experiments for the studies of the absolute configuration of biphenol 4m: It is well-known that achiral biphenols such as **4m** have two low energy chiral conformations which interconvert rapidly at room temperature. But once it complexed with a metal such as Ti^{IV}, the conformation would be locked.[12] It thus led to two questions: 1) which configuration would be preferentially adopted by biphenol **4m** upon complexation to form complex **30**? 2) whether the chirality of biphenol **4m** could be fully controlled by chiral quinidine **1b**? To probe these problems, 3,3′-di-2-naphthyl-1,1′-bi-2-naphthol (**29**) which had an analogous structure with biphenol **4m** was synthesized from BINOL. Unlike the axially flexible achiral biphenol **4m**, both the *R* and *S* enantiomers of **29** were available.

Considering that the 2-naphthyl groups at the 3,3′-position of biphenol **4m** played an important role in constructing an ideal chiral environment for the highly efficient asymmetric catalysis, the distinct spacial orientations of 3,3′-di-2-naphthyl influenced by the axial chirality of (*R*)- and (*S*)-**29** must lead to different catalytic outcomes. As expected, while **1a**/Ti/(*R*)-BINOL and **1a**/Ti/(*S*)-BINOL gave comparable results in the cyanation of *N*-Ts aldimine **14a** (Table 1, entries 4, 5), **1a**/Ti/(*R*)-**29** and **1a**/

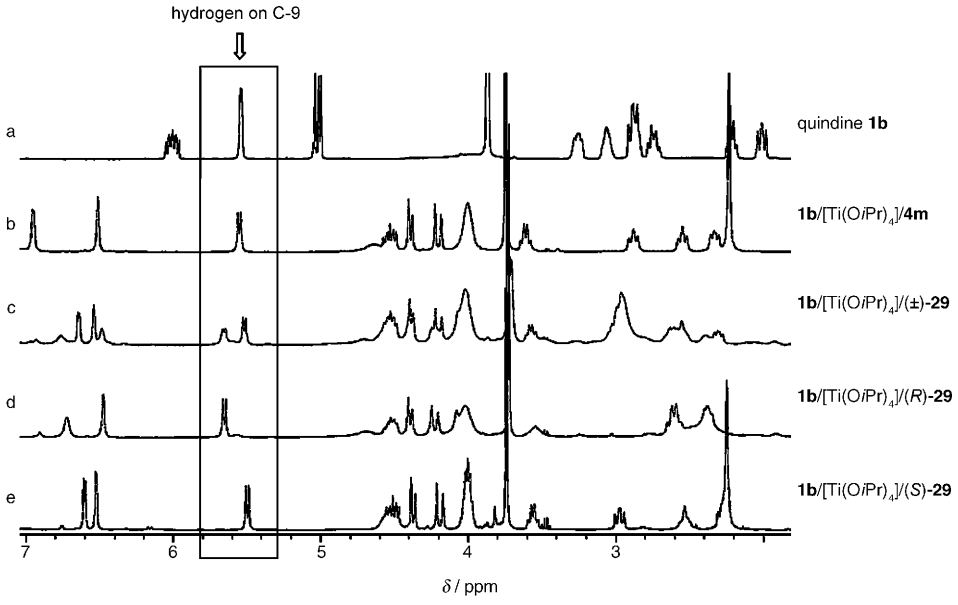


Figure 2. ^{1}H NMR spectra were taken in $CDCl_3$. a) **1b**, b) **1b**/$[Ti(OiPr)_4]$/**4m** 1:1:1, c) **1b**/$[Ti(OiPr)_4]$/(±)-**29** 1:1:1, d) **1b**/$[Ti(OiPr)_4]$/(*R*)-**29** 1:1:1, and e) **1b**/$[Ti(OiPr)_4]$/(*S*)-**29** 1:1:1. For the full spectra, see Supporting Information.

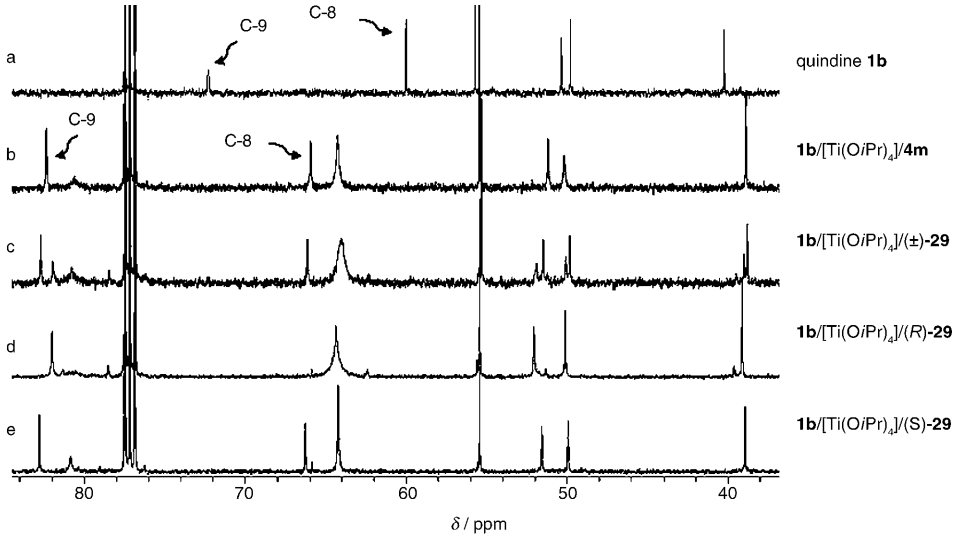
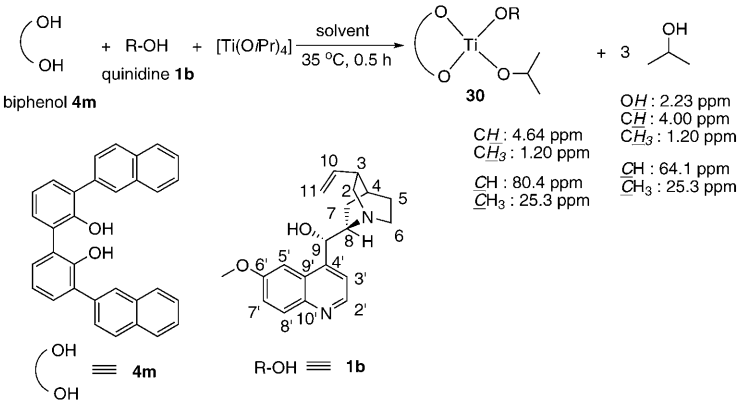


Figure 3. ^{13}C NMR spectra were taken in $CDCl_3$. a) **1b**, b) **1b**/[Ti(O*i*Pr)$_4$]/**4m** 1:1:1, c) **1b**/[Ti(O*i*Pr)$_4$]/(±)-**29** 1:1:1, d) **1b**/[Ti(O*i*Pr)$_4$]/(*R*)-**29** 1:1:1, and e) **1b**/[Ti(O*i*Pr)$_4$]/(*S*)-**29** 1:1:1. For the full spectra, see Supporting Information.



Scheme 1. Generation of the complex **30**.

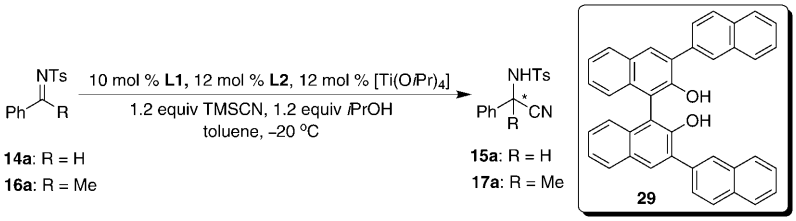
Ti/(*S*)-**29** showed remarkable difference in enantioselectivity (Table 14, entries 1,2). Similarly, in the Strecker reaction of *N*-Ts ketimine **16a**, the axial chirality of **29** dramatically affected the result as well. It should be mentioned that (*S*)-**29**/Ti could not catalyze the reaction (Table 14, entry 3). When **1a**/Ti/(*R*)-**29** was used, the reaction proceeded slowly and gave relatively low *ee* value. In sharp contrast, **1a**/Ti/(*S*)-**29** was as efficient as **1a**/Ti/**4m** (Table 14, entries 4–6). Interestingly, **1a**/Ti/(±)-**29** gave excellent result, indicating the reaction process was dominated by **1a**/Ti/(*S*)-**29** which was much more active than **1a**/Ti/(*R*)-**29** (Table 14, entry 7). When cinchonidine **2a**, diastereomer of **1a**, was employed as the chiral inducer, (*R*)-**29** rather than (*S*)-**29** was found to be the chirally matched ligand. Of note, **2a**/Ti/(*R*)-**29** exhibited inversed asymmetric induction relative to **1a**/Ti/(*S*)-**29** (Table 14, entries 8–10). Based on these observations, it was reasonable to speculate that for catalyst system **1a**/Ti/**4m**, biphenol **4m** must adopt *S* configuration in the most active species.

NMR analyses for the studies of the absolute configuration of biphenol 4m: According to Mikami,[12c] the excellent catalytic behavior of the present catalyst system could arise by either formation of a single, highly enantioselective catalyst or formation of two diastereomeric catalysts with huge differences in activity and selectivity (Scheme 2). Obviously, the above control experiments were unable to tell us which case exactly existed in the current catalyst system. On the other hand, although both ^1H and ^{13}C NMR spectra of **1b**/Ti/**4m** 1:1:1 indicated that probably there was no isomer existing in the solution, the possibility of peak overlapping of the two diastereomeric isomers could not be excluded unambiguously.

To get more information, NMR analyses of **1b**/Ti/(*R*)-**29** 1:1:1, **1b**/Ti/(*S*)-**29** 1:1.1, and **1b**/Ti/(±)-**29** 1:1:1 were conducted. As shown in Figures 2 and 3, both **1b**/Ti/(*R*)-**29** 1:1:1 and **1b**/Ti/(*S*)-**29** 1:1:1 gave similar spectra to **1b**/Ti/**4m** 1:1:1, indicating the complexing behavior of **1b**/Ti/(*R*)-**29** and **1b**/Ti/(*S*)-**29** were similar to that of **1b**/Ti/**4m**, and the analogous complexes **31** and **32** were supposed to form (Figures 2,3 and Scheme 3). Interestingly, the spectrum of **1b**/Ti/(*S*)-**29** was somewhat cleaner than that of **1b**/Ti/(*R*)-**29**, implying chirally matched pair of ligands complexed with Ti^{IV} much better (Figures 2,3). Furthermore, although similar, the NMR spectra of diastereomeric complexes **31** and **32** were apparently different. Characteristically, the proton on C-9 showed different chemical shifts (5.516 and 5.653 ppm for **31** and **32**, respectively) (Figure 2). Also, as shown in ^{13}C NMR spectra, almost all the aliphatic carbons of the alkoxide (-OR*) gave different chemical shifts (Figure 3). Especially, the spectrum of **1b**/Ti/(±)-**29** 1:1:1 was almost identical to the sum of the spectrum of **1b**/Ti/(*R*)-**29** 1:1:1 and **1b**/Ti/(*S*)-**29** 1:1:1; it was an about 1:1 mixture of **31** and **32** (according to the peak integration at 5.516 and 5.653 ppm) (Figure 2, spectrum c). No **1b**/Ti/(*R*)-**29**/(*S*)-**29** or its analogue was observed.

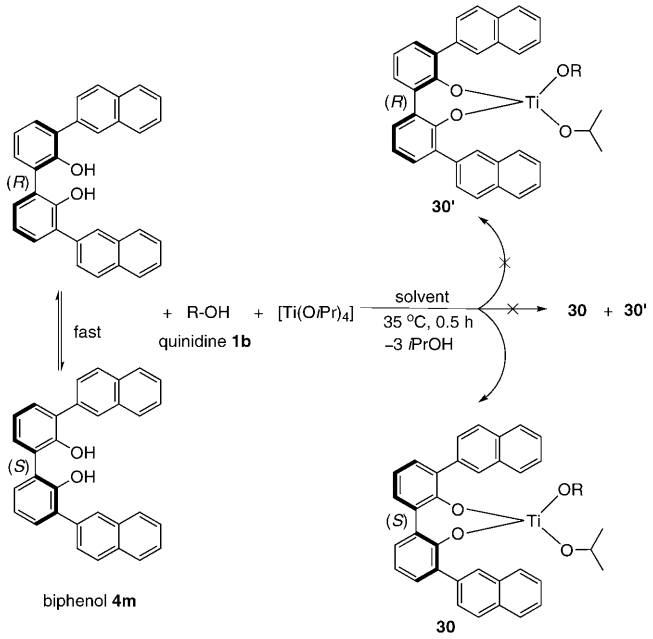
With these observations in hand, supposing biphenol **4m** would not preferentially adopt *R* or *S* configuration during complexation, **1b**/Ti/**4m** would give a similar spectrum to

Table 14. Studies of the absolute configuration adopted by biphenol **4m**.[a]



Entry	Imine	Catalyst[b]	t [h]	Yield [%][c]	ee [%][d]
1	**14a**	**1a**/Ti/(*R*)-**29**	4	98	62(*S*)
2	**14a**	**1a**/Ti/(*S*)-**29**	1	>99	95(*S*)
3	**16a**	(*S*)-**29**/Ti	8	trace	–
4	**16a**	**1a**/Ti/(*R*)-**29**	3.5	25	71(*S*)
5	**16a**	**1a**/Ti/(*S*)-**29**	3.5	>99	>99(*S*)
6	**16a**	**1a**/Ti/**4m**	3.5	>99	>99(*S*)
7	**16a**	**1a**/Ti/(±)-**29**	3.5	>99	>99(*S*)
8	**16a**	**2a**/Ti/(*R*)-**29**	8	95	98(*R*)
9	**16a**	**2a**/Ti/(*S*)-**29**	8	49	68(*R*)
10	**16a**	**2a**/Ti/**4m**	8	87	94(*R*)

[a] Unless noted, reactions were carried out with catalyst (10 mol%), imine (0.1 mmol), TMSCN (1.2 equiv), *i*PrOH (1.2 equiv) and toluene (0.5 mL) at −20 °C. [b] The Ti catalyst was **L1**(cinchona alkaloid)/[Ti(O*i*Pr)$_4$]/**L2**(phenol) 1:1.2:1.2 or **L2**/[Ti(O*i*Pr)$_4$] 1:1. [c] Isolated yield. [d] Determined by HPLC.



Scheme 2. Reaction of **4m**, quinidine **1b** and [Ti(O*i*Pr)$_4$].

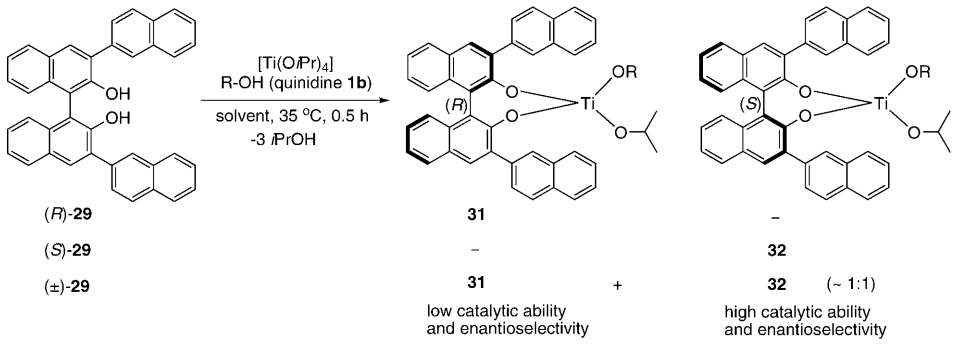
1b/Ti/(±)-**29**. However, as shown in Figures 2 and 3, both the ^{1}H and ^{13}C NMR spectra of **1b**/Ti/**4m** and **1b**/Ti/(±)-**29** were completely different, suggesting biphenol **4m** must have preferred adopting *R* or *S* configuration upon complexing. In addition, the ^{1}H and ^{13}C NMR spectra of **1b**/Ti/**4m** exhibited considerable similarity to that of **1b**/Ti/(*S*)-**29** rather than **1b**/Ti/(*R*)-**29**. All of these observations combined with the conclusions from control experiments strongly supported that biphenol **4m** must selectively adopt *S* configuration to form complex **30** (Scheme 2).

We also investigated the NMR spectra of **1b**/Ti/(±)-**29** 1:1:2 and **1b**/Ti/(±)-**29** 1:2:2 (for spectra, see Supporting Information). As expected, selective generation of **1b**/Ti/(*S*)-**29** 1:1:1 was observed. Therefore, the chirality matched **1b**/Ti/(*S*)-**29** 1:1:1 was much easier to form than **1b**/Ti/(*R*)-**29** 1:1:1 under otherwise identical conditions. It also provided a clue to the question why **1b**(**1a**)/Ti/(*S*)-**4m** was selectively formed in the catalyst preparation.

Investigation of the role of *i*PrOH, the actual cyanide reagent in the catalytic cycle, and the role of tertiary amine in the cinchona alkaloid: In the Strecker reaction of aldimines and ketimines with either TMSCN or CNCOOEt as cyanide source, as well as in the cyanoformation of aldehydes, *i*PrOH proved requisite to enhance the catalytic efficiency. So, searching for the exact role of *i*PrOH was necessary. Initially, we thought that the added *i*PrOH might transform complex **30** to some more effective species. But it was quickly ruled out by the NMR analysis, in which no notable change was observed for the ^{1}H and ^{13}C NMR spectra of complex **30** (prepared on 0.2 mmol scale in 0.5 mL $CDCl_3$) after the addition of *i*PrOH (1.5 mmol). Then, it was envisaged that *i*PrOH would react with TMSCN or CNCOOEt to produce HCN, which might act the actual nucleophilic cyanide reagent in the catalytic cycle.

Surprisingly, although it was reported that alcohols involving primary, secondary, and tertiary alcohols reacted with TMSCN very fast under neat reaction conditions (generally, >95% yield in 5 min at 25 °C),[21] the reaction of secondary alcohol such as *i*PrOH with TMSCN hardly occurred in diluted conditions. When equimolar amount of TMSCN and *i*PrOH (0.2 mmol) were sequentially added and mixed in 0.5 mL $CDCl_3$ at room temperature, only about 3% conversion was detected by NMR even after 16 h (Table 15, entry 1). By adding 20 mol% of quinidine **1b**, the reaction proceeded swiftly and TMSCN was consumed within 0.5 h (Table 15, entry 2). Also, the reaction of TMSCN and *i*PrOH could be catalyzed by 5 mol% of **1b**/[Ti(O*i*Pr)$_4$]/**4m** 1:1:1, and TMSCN could be consumed within 1.5 h (Table 15, entry 3).

Considering there were two basic nitrogen atoms in quinidine **1b**, their difference in catalytic ability was then examined. In the presence of 20 mol% of tertiary amine such as Et_3N, TMSCN was completely converted to HCN within 5 min (Table 15, entry 4). In contrast, when 20 mol% of quinoline was used, only 10% TMSCN reacted with *i*PrOH after 5 min, and about 60% TMSCN was converted to HCN after 2 h (Table 15, entry 5). Therefore, the tertiary amine of



Scheme 3. The reaction of **29**, quinidine **1b** and $[Ti(OiPr)_4]$.

Table 15. Investigation of the reaction of TMSCN/CNCOOEt with alcohols.[a]

TMSCN/CNCOOEt + R-OH $\xrightarrow[0.5\text{ mL }CDCl_3,\ RT]{\text{catalyst}}$ HCN + TMS-OR/ROCOOEt

Entry	Cyanide source	R-OH	Catalyst ([mol%])	t	Conv. [%][b]
1	TMSCN	*i*PrOH	none	16 h	≈3
2	TMSCN	*i*PrOH	quinidine (20)	0.5 h	>99
3	TMSCN	*i*PrOH	**1b**/Ti/**4m** (5:5:5)	<1.5 h	>99
4	TMSCN	*i*PrOH	Et_3N (20)	<5 min	>99
5	TMSCN	*i*PrOH	 (20)	10 min (2 h)	14 (60)
6	TMSCN	MeOH	none	10 min	>99
7	CNCOOEt	*i*PrOH	none	15 h	0
8	CNCOOEt	MeOH	none	15 h	0
9	CNCOOEt	*i*PrOH	quinidine (20)	0.5 h	50
10	CNCOOEt	MeOH	quinidine (20)	0.5 h	>99
11[c]	CNCOOEt	*i*PrOH	**1b**/Ti/**4m** (10:10:10)	3 h	38
12[c]	CNCOOEt	*i*PrOH	**1b**/Ti/**4m** (10:10:5)	1.5 h	55

[a] Reactions were carried out with TMSCN or CNCOOEt (0.2 mmol), *i*PrOH or MeOH (0.2 mmol) in $CDCl_3$ (0.5 mL) at room temperature. [b] Conversion of TMSCN or CNCOOEt; Determined by NMR. [c] 1.0 M $[Ti(OiPr)_4]$ in $CDCl_3$ was used to prepare **1b**/Ti/**4m**.

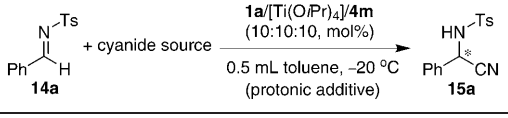
quinuclidine in quinidine **1b** should be more efficient than the quinoline moiety to promote the HCN generation. Accordingly, the observed high catalytic ability of quinidine **1b** as well as complex **1b**/$[Ti(OiPr)_4]$/**4m** must be primarily contributed by the tertiary amine in quinuclidine. Specially, MeOH was so reactive that it could react with TMSCN without any catalyst in $CDCl_3$, and the reaction completed in less than 10 min (Table 15, entry 6).

With respect to CNCOOEt, we found it was inert to MeOH and *i*PrOH in $CDCl_3$ at room temperature. No reaction was observed even after 15 h (Table 15, entries 7,8). In the presence of 20 mol% of quinidine, the reaction of CNCOOEt with MeOH proceeded swiftly, and CNCOOEt was completely consumed within 0.5 h (Table 15, entry 9). In contrast, only about half of the CNCOOEt was consumed when *i*PrOH was used under otherwise identical conditions (Table 15, entry 10). As expected, the reaction of CNCOOEt and *i*PrOH could also be catalyzed by 5 mol% of **1b**/$[Ti(OiPr)_4]$/**4m** 1:1:1. But the reaction proceeded very slowly, and only 38% CNCOOEt was converted after 3 h (Table 15, entry 11).

As shown in the cyanation of aldehyde and Strecker reaction with CNCOOEt as cyanide source, generally **1b**/Ti/**4m** 2:2:1 was more reactive than **1b**/Ti/**4m** 1:1:1 while giving comparable enantioselectivity. Why? According to the NMR analysis, the spectra of **1b**/Ti/**4m** 2:2:1 were almost identical to the sum of the spectra of **1b**/Ti 1:1 and **1b**/Ti/**4m** 1:1:1. So, the most catalytically active species in **1b**/Ti/**4m** 2:2:1 was probably the same as that in **1b**/Ti/**4m** 1:1:1. Then, the reactivity difference between **1b**/Ti/**4m** 2:2:1 and **1b**/Ti/**4m** 1:1:1 might be attributed to the higher catalytic ability of the former to accelerate the HCN release step, which might be the rate-determining step in the asymmetric catalysis, especially for the asymmetric Strecker reaction. Indeed, when **1b**/Ti/**4m** 2:2:1 was used to catalyze the reaction of CNCOOEt and *i*PrOH, it was much faster than the case employing **1b**/Ti/**4m** 1:1:1, and 50% CNCOOEt was converted after 1.5 h (Table 15, entry 12 vs. 11).

The significant importance of *i*PrOH, combined with the above observations that *i*PrOH would smoothly react with TMSCN/CNCOOEt in the presence of catalyst involving **1b**/Ti/**4m**, implied that HCN might be the real cyanide reagent in the cycle. This assumption was further verified by some control experiments. As shown in Table 16, either HCN (prepared from TMSCN and MeOH) or TMSCN/MeOH (added separately) gave identical result to TMSCN/*i*PrOH in the Strecker reaction of aldimines **14a** (Table 16, entries 1–3).

Table 16. Investigation of the real cyanide reagent for the Strecker reaction.[a]



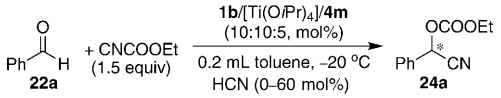
Entry	Cyanide source and additive ([mmol])	t [h]	Yield [%]	*ee* [%]
1	TMSCN (0.12) + *i*PrOH (0.12)	1.0	99	96
2	TMSCN (0.12) + MeOH (0.12)	0.5	99	96
3	HCN (0.12)[b]	0.5	99	96
4	CNCOOEt (0.2) + *i*PrOH (0.2)	60	93	96
5	CNCOOEt (0.2) + MeOH (0.2)	2.0	99	84
6[c]	HCN (0.12) + MeOH (0.12)	1.0	99	84
7	CNCOOEt (0.2) + MeOH (0.1)	2.0	99	95
8	CNCOOEt (0.12) + MeOH (0.12)	5.0	99	92

[a] Reactions were performed with aldimines **14a** (0.1 mmol), catalyst (**1a**/$[Ti(OiPr)_4]$/**4m** 1:1:1, 10 mol%) in toluene (0.5 mL) at −20 °C. [b] HCN was freshly prepared in situ from equimolar MeOH and TMSCN in toluene at room temperature. [c] Before the addition of HCN, to the mixture of catalyst (**1a**/Ti/**4m** 1:1:1, 10 mol%) and aldimines (0.1 mmol) was added MeOH (1.2 equiv, relative to imine), and the mixture was stirred for 0.5 h at −20 °C.

On the other hand, as the asymmetric addition of HCN to imines was extremely fast, the HCN release step would become the rate-determining step if it proceeded slowly. Actually, it was the case in the Strecker reaction with CNCOOEt as the cyanide source. Due to the low reactivity of CNCOOEt toward *i*PrOH even at room temperature (Table 15, entry 11), it was not surprising that the Strecker reaction would require extremely long time to reach completion at −20 °C (Table 16, entry 4). We speculated that if the rate of HCN release step could be significantly increased, the reaction time would be greatly shortened. Inspired by the above finding that MeOH reacted with CNCOOEt more quickly than *i*PrOH, MeOH was attempted as an additive in the Strecker reaction of aldimines **14a**. To our delight, the reactivity was greatly enhanced under otherwise identical conditions, although slight decrease of *ee* was observed (Table 16, entry 5). It was supposed that the reduced *ee* might be attributed to the adverse effect of MeOH to the catalyst system. As anticipated, in the presence of 1.2 equiv of MeOH (relative to imine), the reaction of HCN with aldimines **14a** exhibited decreased enantioselectivity (84 % *ee*) (Table 16, entry 6). So, with the dosage of CNCOOEt maintained (2.0 equiv), decreasing the amount of MeOH to 1.0 equiv was attempted. Excitingly, both the high reactivity (2 h) and enantioselectivity (95 % *ee*) were obtained (Table 16, entry 7). However, when CNCOOEt and MeOH were synchronously reduced from 2.0 to 1.2 equiv, slightly low reactivity (5 h) and enantioselectivity (92 % *ee*) were shown (Table 16, entry 8).

As the cyanocarbonylation of aldehydes was concerned, addition of *i*PrOH could also enhance the reactivity without affecting the yield and enantioselectivity. Thus, the real cyanide source might also be HCN. As for the fact that the cyanation reaction finished in very short time (5 h) while CNCOOEt reacted with *i*PrOH slowly under the same reaction conditions, we assumed that HCN release step must not be the rate-determining step in this case. It was hypothesized that the small amount of HCN produced at the early stage of the reaction should be recyclable. This assumption was strongly supported by the following control experiments, in which instead of *i*PrOH (the in situ produced *i*PrOH during the catalyst preparation was also removed under reduced pressure), 0–60 mol % of HCN was used as additive. As shown in Table 17, it was found that in the absence of *i*PrOH or HCN, the reaction proceeded very slowly (Table 17, entry 1). When 5–10 mol % of HCN was added, the reaction was gradually accelerated and high *ee* was obtained, implying that the small amount of HCN could smoothly drive the reaction to completion (Table 17, entries 2,3). Although further increasing the amount of the HCN steadily enhanced the reactivity, the enantioselectivity suffered (Table 17, entries 4–6). One possible explanation would be that the reaction would partially proceed through the uncatalytic pathway in the presence of large amount of highly reactive HCN (as the control experiment showed, benzaldehyde could react with HCN without catalyst in toluene at −20 °C). Above all, catalytic amount of HCN was sufficient to promote the cyanation of aldehyde with CNCOOEt, which was remarkably different from the Strecker reaction in which stoichiometric amount of HCN was required.

Table 17. Investigation of the real cyanide reagent for cyanation of benzaldehyde with CNCOOEt.[a]



Entry	HCN [mol %][b]	*t* [h]	Conversion [%][c]	*ee* [%]
1	0	22	40	86
2	5	22	99	92
3	10	6	99	90
4	20	4	99	84
5	40	4	99	68
6	60	2	99	62

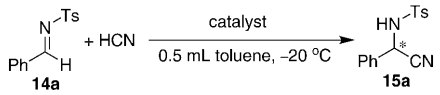
[a] Reactions were performed with benzaldehyde **22a** (0.1 mmol), **1a**/[Ti(O*i*Pr)$_4$]/**4m** 10:10:5 (mol %) (the produced *i*PrOH was removed after catalyst preparation), and HCN (0–60 mol %) in toluene (0.2 mL) at −20 °C. [b] HCN was freshly prepared in situ from equimolar MeOH and TMSCN in toluene at room temperature. [c] The conversion of benzaldehyde.

Moreover, no obvious influence on the yield and *ee* value was observed when 0–3.0 equiv of *i*PrOH was used as additive (see Supporting Information). It could be explained by the fact that the intermediate product cyanohydrin was much more reactive than *i*PrOH to react with CNCOOEt. Thus, once the reaction was initiated, CNCOOEt would prefer to react with continually generated cyanohydrin. As a result, the reaction of *i*PrOH and CNCOOEt was greatly suppressed, and the HCN would be maintained at a certain suitable concentration until the reaction finished.

Finally, as demonstrated, the tertiary amine of cinchona alkaloid in the catalyst complex played a critical role in the generation of nucleophilic HCN. Moreover, it was expected to work as Lewis base to activate HCN in the catalytic cycle. To demonstrate this assumption, some control experiments were performed. As shown in Table 18, when (*S*)-**29**/Ti 10:10 was used as catalyst, the reaction of aldimine **14a** and HCN proceeded very slowly and no *ee* was observed (Table 18, entry 1). In contrast, when Et_3N was added, the reaction proceeded very fast (Table 18, entry 2). Furthermore, when quinidine hydrochloride (QD·HCl) or *N*-Me quinidinium iodide (QD·MeI) was used instead of quinidine **1b**, poor reactivity and *ee* were observed, which verified the dual role of the tertiary amine in the cinchona alkaloid moiety of the catalyst (Table 18, entries 3,4).

Catalytic cycles and transition states: According to the above control experiments, spectra data and discussions, the catalyst structure and the real cyanide reagent were identified. It is reasonable to assume that the reaction proceeds through a dual activation mechanism.[4i,6f,t] As illustrated in Scheme 4 and 5, Ti^{IV} acts as Lewis acid to activate the electrophile (C=O or C=N) while the tertiary amine in cinchona

Table 18. Investigation of the dual role of cinchona alkaloid moiety in the catalyst.[a]

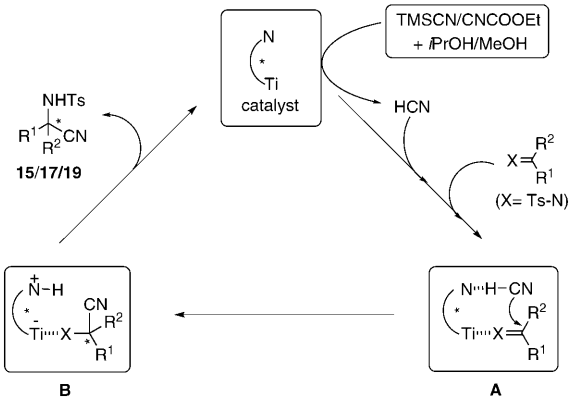


Entry	Catalyst [mol%]	t [h]	Yield [%][b]	ee [%]
1	(*S*)-**29**/Ti 10:10	8	<22	0
2	(*S*)-**29**/Ti/Et_3N 10:10:10	3	99	0
3	**4m**/Ti/QD·HCl 10:10:10	8	30	10
4	**4m**/Ti/QD·MeI 10:10:10	8	10	0

[a] Reactions were performed with aldimines **14a** (0.1 mmol), HCN (0.12 mmol), catalyst (10 mol%) in toluene (0.5 mL) at −20°C. [b] Isolated yield.

alkaloid works as the Lewis base to activate nucleophile HCN generated in situ from alcohol (*i*PrOH/MeOH) and TMSCN/CNCOOEt.

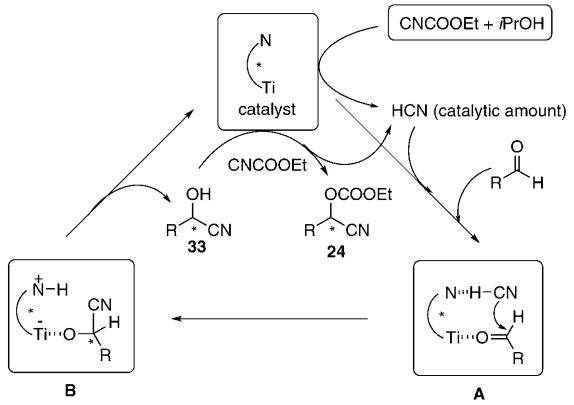
For the Strecker reaction, after the formation of active species **A**, enantioselective addition of cyanide ion (CN^-) to C=N can easily occur to give intermediate **B**. Then, a catalytic cycle finishes by intramolecular combination of a proton to give the product and regenerate the catalyst (Scheme 4).



Scheme 4. Proposed catalytic cycle for the Strecker reaction of imines with TMSCN or CNCOOEt.

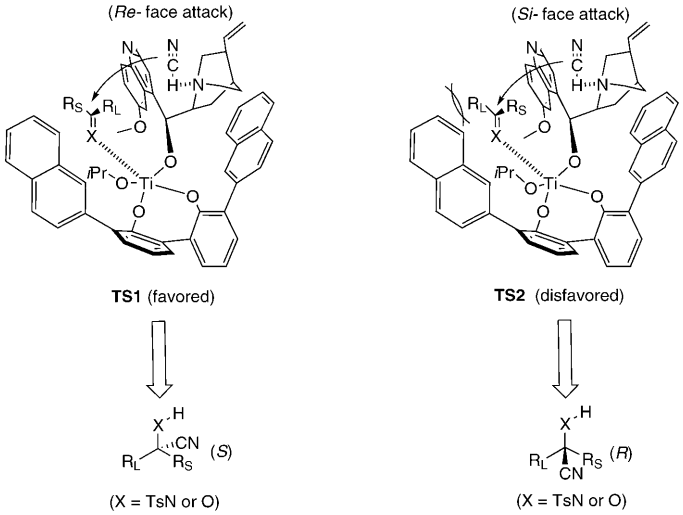
Otherwise, for the cyanation of benzaldehyde with CNCOOEt, the real cyanide reagent is catalytic amount of recyclable HCN. As depicted in Scheme 5, likewise, active species **A** is formed via dual activation of the substrates. Then, enantioselective addition of C≡N to C=O gives intermediate **B** which readily affords the cyanohydrin by intramolecular combination of a proton. Meanwhile, the catalyst was regenerated. Promoted by the catalyst, the cyanohydrin would easily react with CNCOOEt to give the desired product and reproduce the recyclable HCN. Then, the next catalytic cycle starts (Scheme 5).

Based on the experimental observations, two plausible transition states **TS1** and **TS2** are proposed to elucidate the asymmetric induction (Scheme 6). As the repulsion between the larger group R_L in the substrate and the 2-naphthyl in the catalyst might occur for **TS2**, the transition state **TS1** is



Scheme 5. Proposed catalytic cycle for the cyanation of aldehydes with CNCOOEt.

more favorable. Moreover, in **TS1** the *Re* face attack is much more accessible than the *Si* face because the *Si* face was well shielded by the 2-naphthyl in the catalyst. As a result, the product with *S* configuration is selectively produced.



Scheme 6. Proposed transition states.

Conclusion

The asymmetric cyanation of aldehydes, ketones, aldimines and ketimines with TMSCN or CNCOOEt as the cyanide source was studied in detail. Excellent reactivities and enantioselectivities have been achieved for most of these reactions employing a powerful versatile catalyst system generated from readily available cinchona alkaloid, achiral 3,3′-disubstituted 2,2′-biphenol and [Ti(O*i*Pr)$_4$] under mild reaction conditions. For instance, **1a**/[Ti(O*i*Pr)$_4$]/**4m** 1:1:1 was general for the cyanation of *N*-Ts imines (including aldimines, aryl alkyl ketimines and unsymmetrical diarylketimines) with TMSCN as well as for the cyanation of aldimines with

CNCOOEt; **1a**/[Ti(O*i*Pr)$_4$]/**4l** 1:1:1 was efficient for the cyanosilylation of ketones; **1b**/[Ti(O*i*Pr)$_4$]/**4m** 2:2:1 was generally applicable to the cyanation of aldehydes and *N*-Ts ketimines with CNCOOEt. Most significantly, it was for the first time that CNCOOEt was successfully used in the asymmetric Strecker reaction of aldimines and ketimines, affording various α-amino nitriles in high yields and *ee* values. Compared with the case using TMSCN as the cyanide source, CNCOOEt showed relatively low reactivity but gave comparable *ee* values and yields. Moreover, control experiments and NMR analyses were performed to shed light on the catalyst structure. It has proved that the sterically demanding aromatic substituent at 3,3′-position of biphenol was crucial to achieve high enantioselectivity and all the hydroxyl groups in cinchona alkaloid and biphenol should participate in the complexation with Ti^{IV}. The absolute configuration adopted by biphenol **4m** in the catalyst was determined as *S* configuration according to the evidences from control experiments and NMR studies. The roles of the protonic additive (*i*PrOH) and the tertiary amine in the cinchona alkaloid were studied in detail, and the real cyanide reagent in the catalytic cycle was found to be HCN. Finally, two plausible catalytic cycles were proposed to elucidate the reaction mechanisms. Application of the described catalyst system to other reactions such as cyanation addition to C=C bond as well as ring opening reaction with cyanide reagents is in progress.

Experimental Section

Typical procedure for the cyanation of imines with CNCOOEt: Under Ar atmosphere, [Ti(O*i*Pr)$_4$] was added to a dry tube containing a suspension of cinchona alkaloid, biphenol and dry toluene. The mixture was stirred at 35 °C for 0.5 h. it was diluted with dry toluene to prepare the catalyst solution in a certain concentration (such as 0.05 or 0.1 M). The catalyst prepared above (0.1 M in toluene, 100 uL, 0.01 mmol) was introduced to a dry reaction tube charged with *N*-Ts imine (0.1 mmol) and toluene (0.1 mL) under Ar atmosphere at −20 °C. Then, CNCOOEt (0.2 mmol) and *i*PrOH (0.2 mmol) were added successively with stirring. The reaction was monitored by TLC. When the substrate was consumed, the reaction mixture was subjected to silica gel column chromatography to afford the desired *N*-Ts amino nitrile. The *ee* value was determined by chiral HPLC.

Acknowledgements

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[18] Although CNCOOEt was successfully used in the cyanation of aliphatic ketones, the reaction of CNCOOEt with aromatic ketones was not mentioned in Deng's report (see: ref. [8e]). In addition, Belokon′ and North's attempt to employ CNCOOEt as the cyanide source in the cyanation of ketones also failed (see ref. [6d,e]).

[19] When **1a**/Ti/**4m** 1:1:1 or **1b**/Ti/**4m** 1:1:1 was used instead of **1b**/Ti/**4m** 2:2:1, although the enantioselectivity was excellent (99% *ee*), longer reaction time (78 h) was required to complete the reaction. On the other hand, lowering the catalyst loading from 10 to 5 mol% led to a dramatic decrease in reaction rate, and 95% yield and 99% *ee* were obtained after 5 d.

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