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The synthesis of novel tetradentate ligands derived from salen and their application in enantioselective silylcyanation of aldehydes

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ABSTRACT

Two new tetradentate ligands derived from salen have been prepared and their titanium complexes are used as chiral catalysts in the enantioselective silylcyanation of aldehydes, which give the silyl ethers of cyanohydrins in moderate to good enantiomeric excesses.

1. Introduction

During the last few decades, chemists witnessed a remarkable advancement of catalytic asymmetric synthesis. Important efforts have been devoted to the development of more efficient catalysts and various types of chiral metal- and organocatalysts have been developed.[1] Among these, chiral metal–salen complexes have been demonstrated as one of the most versatile catalysts owing to their high asymmetry-inducing ability, ready availability, and structural diversity, which endow them with various catalytic performances.[2] To date the easy to prepare chiral metal–salen complexes have been used as excellent catalysts for a wide range of organic transformations including epoxidation, aziridination, sulfoxidation and Michael reaction, epoxide opening, and Henry reaction, amongst others.[1,3] In order to construct some more efficient catalysts that have the ability to efficiently enhance reactivity and to regulate orientation in an asymmetric atmosphere, considerable efforts have been made and a series of tetradentate ligands derived from salen ligands have been synthesized, such as a semi-reduced salen-type ligand (so-called salalen) or a fully reduced salen (salan). The recent work by Katsuki et al. based on salalen and salan complexes has successfully achieved high enantioselectivity in a number of asymmetric reactions.[3d,e,4–6]

The asymmetric addition of cyanide to carbonyl compounds is one of the most useful carbon–carbon bond-forming reactions in organic synthesis for producing optically active cyanohydrin derivatives. This is because the resultant compounds can be easily converted to a variety of chiral building blocks such as optically active α-hydroxy carboxylic acids and α-amino alcohols.[7] After the pioneering work by Oguni and Hayashi on the enantioselective silylcyanation of aldehydes using an optically active Schiff base ligand,[8] many efforts have been devoted to this reaction and many effective chiral catalysts have been introduced. Among them, salen–Ti complexes are highly promising catalysts for this reaction.[7]

However, the asymmetric silylcyanation of a broad range of substrates including aliphatic aldehydes and ketones with low catalyst loadings under mild reaction conditions is still a challenge.[9] We have previously reported the use of salen derivatives as catalysts in the oxidative carbonylation of β-amino alcohols,[10] oxidative kinetic resolution of secondary alcohols,[11] and asymmetric epoxidation of olefins.[12] In this manuscript, in order to expand the catalyst library and enhance the catalytic efficiency, we describe a simple and practical method for the synthesis of two novel ligands prepared from salen and Grignard reagents and focus on their application in enantioselective cyanohydrin synthesis.

2. Results and discussion

Recently, we have successfully synthesized a series of new chiral tetradentate nitrogen ligands together with their manganese complexes, which exhibit rapid, highly enantioselective epoxidation of various α,β-enones.[13] Encouraged by this conceptual strategy to improve the stereoselectivity and reactivity of catalysts, we design and prepare some new ligands by the same method of reacting the Grignard reagents with the C=N of salen ligands to construct the C–N bond. The experimental procedure is shown in Scheme 1. Different Grignard reagents such as Ph-MgBr, *p*-$MeOC_6H_4$-MgBr, *p*-(*t*-Bu)-C_6H_4-MgBr, *t*-Bu-MgCl, and CH_3-MgI were used toward the synthesis of the desired ligands containing the C–N bond, but only Ph-MgBr could react with the salen ligand successfully. The *t*-Bu-MgCl reagent could not react with the salen ligand. Other Grignard reagents led to very complicated products that were difficult to isolate by chromatography. The corresponding Ti complexes were obtained by the reaction of equimolar amounts of ligand and $Ti(Oi\text{-}Pr)_4$ in CH_2Cl_2 under an argon atmosphere at reflux for 12 h. Based on our previous study, the configurations of the ligands **3** and **4** are shown in Scheme 1.[13,14]

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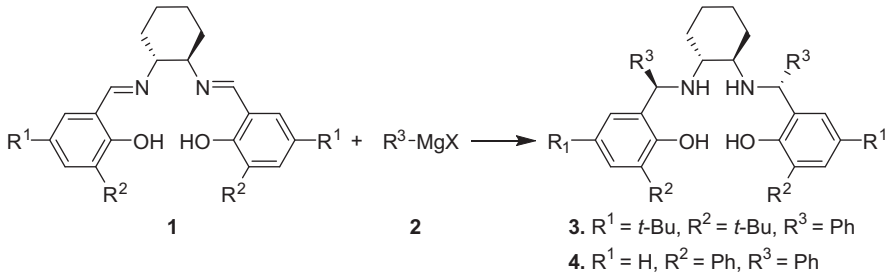
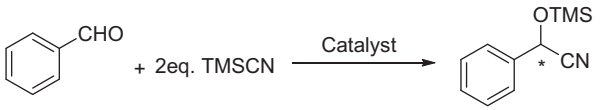


Scheme 1. Synthesis of the ligands derived from salen.

With ligands **3** and **4** in hand, their catalytic properties in silylcyanation were evaluated. Initially, benzaldehyde was chosen as a model substrate with an excess (2 equiv) of TMSCN in the presence of ligand **3** or **4** in combination with an equimolar amount of Ti(O*i*-Pr)$_4$, and the reaction was performed at 0 °C for 24 h. The catalytic system was first prepared in situ by stirring ligand **3** or **4** with Ti(O*i*-Pr)$_4$ at room temperature for 1 h in the appropriate solvent. As the results show in Table 1 (entries 1 and 2), the ligand **3** together with Ti(O*i*-Pr)$_4$ resulted in a better asymmetric induction in the addition of TMSCN to benzaldehyde. Having determined that ligand **3** was the preferred ligand, the amount of the catalyst and reaction solvent was then investigated. Among the solvents tested, acetonitrile was proved to be favorable to the reaction, a 66% ee was observed using catalyst prepared in situ at 0 °C for 24 h (Table 1, entry 10). When the corresponding Ti-complex of ligand **3** (Ti-**3**) was directly employed as a catalyst, a comparable result was achieved only in the presence of 3 mol % of complex Ti-**3** (Table 1, entry 12). Further reducing the amount of the catalyst led to a low yield (Table 1, entry 13). In general, the enantioselectivity of the asymmetric reaction could be improved by lowering the reaction temperature. To our delight, the silyl ether was obtained quantitatively in 70% ee, when the temperature was lowered to −20 °C. While the temperature was lowered to −40 °C, the product was formed in a nearly quantitative yield with an 81% ee (Table 1, entry 15).

Many papers have reported that using an additive could improve the enantiomeric excess and conversion, thus we tested a series of additives as mentioned above.[7] The results are summarized in Table 2. It should be noted that only *i*-PrOH or Ph_3PO gave similar ee values to those without an additive (Table 2, entries 1 and 2). With DMAP or DABCO as an additive, an excellent yield but racemic product was obtained (Table 2, entries 3 and 4). With CF_3COOH as an additive, only 5% yield of product was obtained (Table 2, entry 5). Moreover, C_6H_5COOH also showed a negative effect on the outcome of the reaction (Table 2, entry 6). All attempts to convert Ti-**3** into the corresponding bis-oxo-bridged bimetallic complex analogous according to the literature had no significant influence on the reaction outcome (Table 2, entry 7).[15] Based on the discussion above, we concluded that the optimized conditions involved an aldehyde that reacted with an excess (2 equiv) of TMSCN in the presence of (3 mol %) Ti-**3** complex as catalyst in acetonitrile at −40 °C for 48 h.

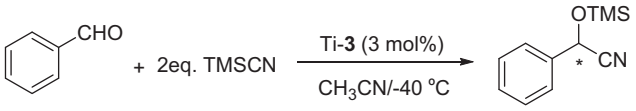
Table 1
The screening of reaction conditions for the addition of TMSCN to benzaldehyde[a]



Entry	Catalyst (mol %)	Solvent	Yield[b] (%)	ee[c] (%)
1	**3** + Ti(O*i*-Pr)$_4$ (15)	CH_2Cl_2	>99	60 (*S*)
2	**4** + Ti(O*i*-Pr)$_4$ (15)	CH_2Cl_2	32	10 (*S*)
3	**3** + Ti(O*i*-Pr)$_4$ (10)	CH_2Cl_2	>99	57 (*S*)
4	**3** + Ti(O*i*-Pr)$_4$ (5)	CH_2Cl_2	>99	59 (*S*)
5	**3** + Ti(O*i*-Pr)$_4$ (1)	CH_2Cl_2	46	44 (*S*)
6	**3** + Ti(O*i*-Pr)$_4$ (5)	Toluene	59	24 (*S*)
7	**3** + Ti(O*i*-Pr)$_4$ (5)	THF	35	13 (*S*)
8	**3** + Ti(O*i*-Pr)$_4$ (5)	Et_2O	51	6 (*S*)
9	**3** + Ti(O*i*-Pr)$_4$ (5)	$CHCl_3$	93	54 (*S*)
10	**3** + Ti(O*i*-Pr)$_4$ (5)	CH_3CN	92	66 (*S*)
11	Ti-**3** (5)	CH_3CN	99	64 (*S*)
12	Ti-**3** (3)	CH_3CN	99	66 (*S*)
13	Ti-**3** (1)	CH_3CN	50	64 (*S*)
14[d]	Ti-**3** (3)	CH_3CN	99	70 (*S*)
15[e]	Ti-**3** (3)	CH_3CN	99	81 (*S*)

[a] All reactions were carried out at 0 °C for 24 h.
[b] GC yield.
[c] Enantiomeric excess of the silyl ether determined by chiral GC with a CP-Chirasil-Dex CB column.
[d] The reaction was performed in CH_3CN at −20 °C for 24 h.
[e] The reaction was performed in CH_3CN at −40 °C for 48 h.

Table 2
Effect of varying the additives on the enantiomeric excess[a]



Entry	Additive	Yield[b] (%)	ee[c] (%)
1	*i*-PrOH	98	79 (*S*)
2[d]	Ph_3PO	98	82 (*S*)
3	DMAP	100	0
4	DABCO	100	5 (*S*)
5	CF_3COOH	5	43 (*S*)
6	C_6H_5COOH	76	65 (*S*)
7	H_2O	80	83 (*S*)

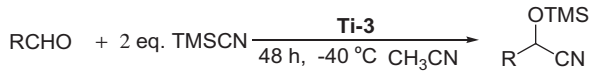
[a] All reactions were carried out with 3 mol % additive in CH_3CN at −40 °C for 48 h.
[b] GC yield.
[c] Enantiomeric excess of silyl ether determined by chiral GC with a CP-Chirasil-Dex CB column.
[d] 6 mol % of Ph_3PO.

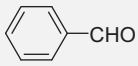
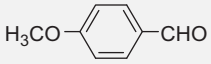
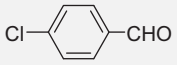
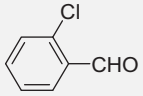
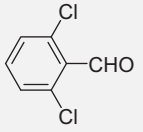
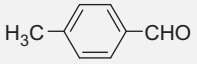
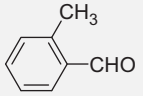
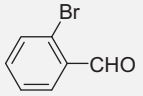
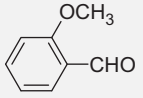
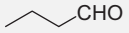
With the optimized reaction conditions in hand, the asymmetric addition of trimethylsilyl cyanide to a range of aldehydes catalyzed by Ti-**3** complex was investigated. The results shown in Table 3 indicate that excellent enantiomeric excesses are obtained with electron-rich aromatic aldehydes, while electron-deficient aromatic aldehydes give lower enantiomeric excesses (Table 3, entries 2, 3, 6). It is evident that the steric properties of the aromatic aldehyde have a great effect on the ee of the product in this reaction. The *ortho*-substituted aromatic aldehydes gave lower ee values than the *para*-substituted aromatic aldehydes (Table 3, entries 3, 4, 6, 7). No reaction occurred with two aliphatic aldehydes as substrates under the same conditions (Table 3, entries 10 and 11).

3. Conclusion

In summary, we have successfully designed and synthesized two novel chiral tetradentate ligands derived from salen ligands

Table 3
Cyanation of aldehydes or ketones with TMSCN catalyzed by Ti-**3**[a]



Entry	Aldehyde	Yield[b] (%)	ee[c] (%)
1		99 (95)[d]	81 (*S*)
2		99 (94)[d]	92 (*S*)
3		50	66 (*S*)
4		93	30 (*R*)
5		97	34
6		84 (80)[d]	90 (*S*)
7		50	37 (*R*)
8		98	29
9		96	33
10		–	–
11		–	–

[a] All reactions were carried out in CH_3CN for 48 h at −40 °C.
[b] GC yield.
[c] Enantiomeric excess of silyl ether determined by chiral GC with a CP-Chirasil-Dex CB column. The absolute configurations were determined by comparison of the sign of the specific rotations with the literature data.
[d] The isolated yield is indicated in parentheses.

and their titanium complexes are applied in the enantioselective cyanation of aldehydes that show moderate to good asymmetric induction. Further studies will focus on expanding the scope of these ligands in asymmetric reactions.

4. Experimental

4.1. General

The ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance III 400 MHz or a Varian Mercury Plus-300 spectrometer. The chemical shifts (δ) are reported in parts per million (ppm) and coupling constants (J) in Hertz. High resolution mass spectra (HRMS) were obtained on a Bruker Daltonics APEX II 47e FT-ICR mass spectrometer or on a Bruker Daltonics micrOTOF-Q^{II} mass spectrometer. Enantiomeric excesses (ee) were determined with an Agilent-6820 GC (column, CP-Chirasil-Dex CB coulmn 25 m × 0.32 mm). Optical rotations were measured on the Perkin–Elmer instruments, Model 341 LC polarimeter. Column chromatography was generally performed on silica gel (200–300 mesh).

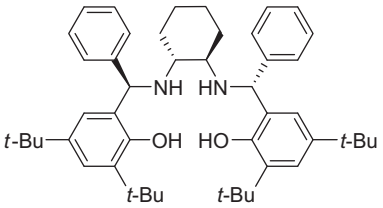
All reactions were carried out under argon in dried glassware. CH_2Cl_2, acetonitrile, and $CHCl_3$ were distilled from CaH_2 and stored under argon prior to use. Toluene was distilled from Na and stored under argon prior to use. THF and diethyl ether were freshly distilled from Na/benzophenone under argon. Ti(O^iPr)$_4$ (from Alfa) was distilled and diluted to 0.1 M in CH_2Cl_2 and stored under argon.

4.2. Synthesis of the desired ligands derived from chiral salen and the corresponding Ti-3 complex

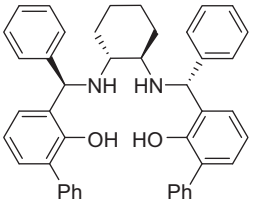
4.2.1. Preparation of chiral ligands 3 and 4

A solution of **1** (5 mmol) in Et_2O was added dropwise to a vigorously stirred Grignard reagent (50 mmol) in Et_2O (20 mL) at room temperature and the reaction mixture was stirred at same temperature for 24 h. Saturated NH_4Cl was added to quench the reaction. The organic phase was dried over anhydrous Na_2SO_4 and purified by column chromatography on silica gel (petroleum ether/EtOAc = 20:1) to afford the corresponding ligand **3** and **4**.

4.2.1.1. *N,N′*-bis[(*R*)-Phenyl(2-hydroxy-3,5-di-*tert*-butylbenzyl)] cyclohexane-(1*R*,2*R*)-diamine 3. Yield, 76%; $[\alpha]_D^{20} = -65.5$ (*c* 0.01, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): δ = 11.26 (s, 1H, OH), 7.61–7.18 (m, 7H, ArH), 6.60 (s, 1H, NH), 5.08 (s, 1H, CH), 2.41 (s, 1H, CH), 2.17 (s, 1H, CH_2), 1.64 (s, 1H, CH_2), 1.45 (s, 9H, CH_3), 1.19 (s, 9H, CH_3), 1.13–1.11 (m, 2H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.96, 140.74, 140.30, 136.34, 128.98, 128.73, 128.42, 127.71, 127.16, 125.56, 123.63, 123.08, 64.46, 57.58, 35.06, 34.12, 31.68, 29.66, 29.47, 23.66. HRMS (ESI-MS) calcd for $C_{48}H_{67}N_2O_2$ $[M+H]^+$: 703.5197, found: 703.5201.



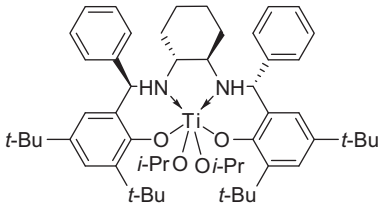
4.2.1.2. *N,N′*-bis[(*R*)-Phenyl (2-hydroxy-3-phenylbenzyl)] cyclohexane-(1*R*,2*R*)-diamine 4. Yield, 70%; $[\alpha]_D^{20} = -212.7$ (*c* 0.01, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$): δ = 7.60–6.72 (m, 13H, ArH), 5.08 (s, 1H, CH), 2.48 (s, 1H, CH), 2.11 (s, 1H, CH_2), 1.61 (s, 1H, CH_2), 1.26–1.17 (m, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.06, 140.81, 138.42, 129.83, 129.22, 129.50, 129.39, 129.04, 128.10, 127.92, 127.66, 126.85, 119.18, 115.22, 63.71, 57.66, 29.61, 23.43. HRMS (ESI-MS) calcd for $C_{44}H_{43}N_2O_2$ $[M+H]^+$: 631.3319, found: 631.3314.



4.2.2. Preparation of Ti-3 complex

The corresponding Ti-**3** complex was synthesized by the reaction of equimolar amounts of ligand **3** and Ti(O^iPr)$_4$ (0.1 M in CH_2Cl_2) in dry CH_2Cl_2 under an argon atmosphere at reflux for 12 h. Then the solvent was evaporated under vacuum to give the

product as a yellow solid. HRMS (ESI-MS; CH_2Cl_2/MeOH) calcd for $C_{49}H_{67}N_2O_3Ti$: $[M\text{-}2O^iPr\text{+}OMe]^+$, 779.4637, found: 779.4631.



4.3. General procedure for the asymmetric addition of trimethylsilylcyanide to aldehyde

The chiral Ti-**3** complex 0.0052 g (0.006 mmol) 3%, substrate (0.2 mmol), and nonane were added to the solvent of CH_3CN (1 mL) under an Ar atmosphere in the test tube and the solution was stirred for 70 min at −40 °C. Then 2 equiv of TMSCN (0.4 mmol) was added to the solution and the reaction was kept at −40 °C for 48 h. After that time, the ee and yields were analyzed by GC (CP-Chirasil-Dex CB column). Absolute configuration was assigned by comparison of the sign of the specific rotation with the literature.[9,16]

4.4. GC analysis for determination of the enantiomeric excesses

4.4.1. 2-Trimethylsilyloxy-2-phenylacetonitrile (Table 3, entry 1)

GC (CP-Chirasil-Dex CB coulmn 25 m × 0.32 mm, column temperature = 110 °C (isothermal), inject temperature = 230 °C, detector temperature = 250 °C): t_R (major) = 27.7 min, t_R(minor) = 28.5 min.

4.4.2. 2-Trimethylsilyloxy-2-(4-methoxyphenyl)acetonitrile (Table 3, entry 2)

GC (CP-Chirasil-Dex CB coulmn 25 m × 0.32 mm, column temperature = 125 °C (isothermal), inject temperature = 230 °C, detector temperature = 250 °C): t_R (minor) = 59.6 min, t_R (major) = 60.3 min.

4.4.3. 2-Trimethylsilyloxy-2-(4-chlorophenyl)acetonitrile (Table 3, entry 3)

GC (CP-Chirasil-Dex CB coulmn 25 m × 0.32 mm, column temperature = 120 °C (isothermal), inject temperature = 230 °C, detector temperature = 250 °C): t_R (minor) = 52.6 min, t_R (major) = 53.6 min.

4.4.4. 2-Trimethylsiloxy-2-(2-chlorophenyl)acetonitrile (Table 3, entry 4)

GC (CP-Chirasil-Dex CB coulmn 25 m × 0.32 mm, column temperature = 120 °C (isothermal), inject temperature = 230 °C, detector temperature = 250 °C): t_R (minor) = 29.5 min, t_R (major) = 30.2 min.

4.4.5. 2-Trimethylsiloxy-2-(2,6-dichlorophenyl)acetonitrile (Table 3, entry 5)

GC (CP-Chirasil-Dex CB coulmn 25 m × 0.32 mm, column temperature = 135 °C (isothermal), inject temperature = 230 °C, detector temperature = 250 °C): t_R (minor) = 34.3 min, t_R (major) = 35.1 min.

4.4.6. 2-Trimethylsilyloxy-2-(4-methylphenyl)acetonitrile (Table 3, entry 6)

GC (CP-Chirasil-Dex CB coulmn 25 m × 0.32 mm, column temperature = 115 °C (isothermal), inject temperature = 250 °C, detector temperature = 280 °C): t_R (minor) = 38.4 min, t_R (major) = 38.9 min.

4.4.7. 2-Trimethylsilyloxy-2-(2-methylphenyl)acetonitrile (Table 3, entry 7)

GC (CP-Chirasil-Dex CB coulmn 25 m × 0.32 mm, column temperature = 115 °C (isothermal), inject temperature = 250 °C, detector temperature = 280 °C): t_R (minor) = 29.1 min, t_R (major) = 30.1 min.

4.4.8. 2-Trimethylsilyloxy-2-(2-bromophenyl)acetonitrile (Table 3, entry 8)

GC (CP-Chirasil-Dex CB coulmn 25 m × 0.32 mm, column temperature = 125 °C (isothermal), inject temperature = 230 °C, detector temperature = 250 °C): t_R (minor) = 35.5 min, t_R (major) = 36.5 min.

4.4.9. 2-Trimethylsilyloxy-2-(2-methoxyphenyl)acetonitrile (Table 3, entry 9)

GC (CP-Chirasil-Dex CB coulmn 25 m × 0.32 mm, column temperature = 125 °C (isothermal), inject temperature = 230 °C, detector temperature = 250 °C): t_R (major) = 36.3 min, t_R (minor) = 38.2 min.

Acknowledgments

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References

1. (a) Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H.. In *Comprehensive Asymmetric Catalysis*; Springer: Berlin, 1999; Vol. II; (b) Ojima, I. *Catalytic Asymmetric Synthesis*, 2nd ed.; Wiley-VCH: New York, 2000; (c) Berkessel, A.; Groger, H. *Asymmetric Organocatalysis*; Wiley-VCH: Weinheim, 2005.
2. Venkataramanan, N. S.; Premsingh, S.; Rajagopal, S.; Pitchumani, K. *J. Org. Chem.* **2003**, *68*, 7460–7470.
3. (a) Canali, L.; Sherrington, D. C. *Chem. Soc. Rev.* **1999**, *28*, 85–93; (b) Katsuki, T. *Synlett* **2003**, 281–287; (c) Phan, N. T. S.; Khan, J.; Styring, P. *Tetrahedron* **2005**, *61*, 12065–12073; (d) Matsumoto, K.; Saito, B.; Katsuki, T. *Chem. Commun.* **2007**, 3619–3627; (e) Matsumoto, K.; Yamaguchi, T.; Katsuki, T. *Chem. Commun.* **2008**, 1704–1706; (f) Zulauf, A.; Mellah, M.; Schulz, E. *Chem. Commun.* **2009**, 6574–6576; (g) Kowalczyk, R.; Kwiatkowski, P.; Skarżewski, J.; Jurczak, J. *J. Org. Chem.* **2009**, *74*, 753–756; (h) Zhang, S.; Huang, Y. Z.; Jing, H. W.; Yao, W. X.; Yan, P. *Green Chem.* **2009**, *11*, 935–938; (i) Bianchini, G.; Cavarzan, A.; Scarso, A.; Strukul, G. *Green Chem.* **2009**, *11*, 1517–1520.
4. (a) Matsumoto, K.; Sawada, Y.; Saito, B.; Sakai, K.; Katsuki, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 4935–4939; (b) Saito, B.; Katsuki, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 4600–4602; (c) Sawada, Y.; Matsumoto, K.; Kondo, S.; Watanabe, H.; Ozawa, T.; Suzuki, K.; Saito, B.; Katsuki, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 3478–3480; (d) Sawada, Y.; Matsumoto, K.; Katsuki, T. *Angew. Chem., Int. Ed.* **2007**, *46*, 4559–4561; (e) Yamaguchi, T.; Matsumoto, K.; Saito, B.; Katsuki, T. *Angew. Chem., Int. Ed.* **2007**, *46*, 4729–4731; (f) Kondo, S.; Saruhashi, K.; Seki, K.; Matsubara, K.; Miyaji, K.; Kubo, T.; Matsumoto, K.; Katsuki, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 10195–10198; (g) Egami, H.; Katsuki, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 5171–5174; (h) Shitama, H.; Katsuki, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 2450–2453; (i) Matsumoto, K.; Oguma, T.; Katsuki, T. *Angew. Chem., Int. Ed.* **2009**, *48*, 7432–7435; (j) Suyama, K.; Sakai, Y.; Matsumoto, K.; Saito, B.; Katsuki, T. *Angew. Chem., Int. Ed.* **2010**, *49*, 797–799.
5. (a) Egami, H.; Katsuki, T. *J. Am. Chem. Soc.* **2007**, *129*, 8940–8941; (b) Saito, B.; Egami, H.; Katsuki, T. *J. Am. Chem. Soc.* **2007**, *129*, 1978–1986; (c) Egami, H.; Katsuki, T. *J. Am. Chem. Soc.* **2009**, *131*, 6082–6083.
6. (a) Irie, R.; Masutani, K.; Katsuki, T. *Synlett* **2000**, 1433–1436; (b) Matsumoto, K.; Sawada, Y.; Katsuki, T. *Synlett* **2006**, 3545–3547; (c) Shimada, Y.; Kondo, S.; Ohara, Y.; Matsumoto, K.; Katsuki, T. *Synlett* **2007**, 2445–2447; (d) Egami, H.; Katsuki, T. *Synlett* **2008**, 1543–1546; (e) Matsumoto, K.; Sawada, Y.; Katsuki, T. *Pure Appl. Chem.* **2008**, *80*, 1071–1077; (f) Matsumoto, K.; Yamaguchi, T.; Fujisaki, J.; Saito, B.; Katsuki, T. *Chem. Asian J.* **2008**, *3*, 351–358.
7. For recent reviews on the enantioselective synthesis of cyanohydrins and their derivatives, see: (a) Gregory, R. J. H. *Chem. Rev.* **1999**, *99*, 3649–3682; (b) North, M. *Tetrahedron: Asymmetry* **2003**, *14*, 147–176; (c) Brunel, J. M.; Holmes, I. P. *Angew. Chem., Int. Ed.* **2004**, *43*, 2752–2778; (d) Khan, N. H.; Kureshy, R. I.; Abdi, S. H. R.; Agrawal, S.; Jasra, R. V. *Coord. Chem. Rev.* **2008**, *252*, 593–623; (e) North, M.; Usanov, D. L.; Young, C. *Chem. Rev.* **2008**, *108*, 5146–5226.

8. (a) Hayashi, M.; Miyamoto, Y.; Inoue, T.; Oguni, N. *J. Chem. Soc., Chem. Commun.* **1991**, 1752–1753; (b) Hayashi, M.; Miyamoto, Y.; Inoue, T.; Oguni, N. *J. Org. Chem.* **1993**, *58*, 1515–1522; (c) Hayashi, M.; Inoue, T.; Miyamoto, Y.; Oguni, N. *Tetrahedron* **1994**, *50*, 4385–4398.
9. Yoshinaga, K.; Nagata, T. *Adv. Synth. Catal.* **2009**, *351*, 1495–1498.
10. Liu, J. M.; Peng, X. G.; Liu, J. H.; Zheng, S. Z.; Sun, W.; Xia, C. G. *Tetrahedron Lett.* **2007**, *48*, 929–932.
11. (a) Sun, W.; Wang, H. W.; Xia, C. G.; Li, J. W.; Zhao, P. Q. *Angew. Chem., Int. Ed.* **2003**, *42*, 1042–1044; (b) Cheng, Q. G.; Deng, F. G.; Xia, C. G.; Sun, W. *Tetrahedron: Asymmetry* **2008**, *19*, 2359–2362.
12. Xiong, D. L.; Wu, M.; Wang, S. F.; Li, F. W.; Xia, C. G.; Sun, W. *Tetrahedron: Asymmetry* **2010**, *21*, 374–378.
13. Wu, M.; Wang, B.; Wang, S. F.; Xia, C. G.; Sun, W. *Org. Lett.* **2009**, *11*, 3622–3625.
14. Unpublished results. The stereochemistry of ligand **4** was determined by X-ray crystallography of its corresponding Cu^{II}-complex (ligand **4**: *N*,*N*′-bis[(*R*)-phenyl (2-hydroxy-3-phenylbenzyl)] cyclohexane-(1*R*,2*R*)-diamine). The cif file of Cu-4 complex is available as Supplementary data. The stereochemistry of ligand **3** was assigned by analogy of ligand **4**.
15. Belokon, Y. N.; Caveda-Cepas, S.; Green, B.; Ikonnikov, N. S.; Khrustalev, V. N.; Larichev, V. S.; Moscalenko, M. A.; North, M.; Orizu, C.; Tararov, V. I.; Tasinazzo, M.; Timofeeva, G. I.; Yashkina, L. V. *J. Am. Chem. Soc.* **1999**, *121*, 3968–3973.
16. Kurono, N.; Arai, K.; Uemura, M.; Ohkuma, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 6643–6646.