Synthetic Communications®, 35: 751–759, 2005

ISSN 0039-7911 print/1532-2432 online
DOI: 10.1081/SCC-200050390

Taylor & Francis
Taylor & Francis Group

Asymmetric Cyanohydrin Synthesis Catalyzed by Mn(salen) Complex/ Triphenylphosphine Oxide

Sung Soo Kim and Sang Hyuck Lee
Department of Chemistry, Inha University, Incheon, South Korea

Abstract: Various aldehydes undergo enantioselective silylcyanation with $(CH_3)_3SiCN$ trimethylsilylcyanation (TMSCN) employing chiral Mn(salen) and achiral $POPh_3$ as the catalysts. This is the double activation where Mn(salen) plays the role of Lewis acid and $POPh_3$ Lewis base. Numerous aldehydes are subject to the enantioselective addition of TMSCN at 0°C. Hydrolysis of the adduct gave cyanohydrin with up to 96% yield and 62% ee.

Keywords: Aldehydes, $(CH_3)_3SiCN$, Mn(salen), $POPh_3$

INTRODUCTION

Chiral cyanohydrins are useful intermediates because the two functional groups could be easily transformed into various homochiral ones. These include α-hydroxy acids,[1,2] α-hydroxy aldehydes,[3] α-hydroxy ketones,[3] β-hydroxy amines,[2,3] and α-amino acid derivatives.[4] A number of catalysts for the asymmetric addition of cyanide to aldehydes[5] are known to include synthetic peptides and chiral transition metal complexes. Belokon,[6] Shibasaki,[7] Deng,[8] Hoveyda and Snapper,[9] and Bu[10] have made considerable contributions to development of the catalyst for the chiral silylcyanation. Achiral silylcyanation of aldehydes and ketones catalyzed by *N*-morpholine *N*-oxide and various alkali fluorides was

Received in Japan 15 October 2004
Address correspondence to Sung Soo Kim, Department of Chemistry, Inha University, Incheon 402-751, South Korea. E-mail: sungsoo@inha.ac.kr

investigated by us.[11] Salen structure was employed as a base into which numerous metal ions are combined to make effective catalysts. Belokon and North et al.[6] reported various Ti(IV) combined salen complexes for silylcyanation. [Ti(salen)(μ-O)]$_2$[6b] proved to be the best catalyst yielding 52∼92% enantiomeric excess (ee). The same authors[6e] used VO(salen) as the catalyst to give 68∼95% ee. Bu et al.[10] modified the substituents of the benzene ring of the salen legand (*tert*-pentyl group) that is combined with Ti(OPr-*i*)$_4$. The result indicated 84∼94% yield and 92∼97% ee.

RESULTS AND DISCUSSION

In this paper we would like to report the chiral silylcyanation of aldehydes utilizing Mn(salen)/$POPh_3$ as the catalyst. We have synthesized Mn(salen) **1** according to the known procedure.[12] The silylcyanation was then tried with **1** as catalyst under various conditions as shown in Table 1. CH_2Cl_2 proved to be the best solvent for the reaction (entry 1∼3). Addition of additive $POPh_3$ can further raise the % ee and shorten the reaction period. The yield and ee are not improved by decrease in amount of catalyst with longer reaction time (entries 4 and 5). Temperature decrease from rt to 0°C apparently increases the yield (entry 6). However, further temperature decreases could not obtain the favorable results (entries 7 and 8). Accordingly the condition of entry 6 is chosen as the optimal condition for the silylcyanation of various aldehydes.

Benzaldehydes with numerous substituents (entries 1∼6) undergo smooth enantioselective reactions with comparable outcome in terms of % yield and % ee. *p*-Chlorobenzaldehyde shows the best yield (96%) and ee (62%). It appears that electronic substituents effect may exert only a minor role in the reactions. *trans*-Cinnamaldehyde (entry 7) is easily converted into corresponding cyanohydrin for a relatively short reaction time. 2-Furaldehyde

Table 1. Silylcyanation of benzaldehyde under various conditions

Entry	Mn(salen)	Additive (10 mol%)	Solvent	Temp.	Time	Yield (%)	*ee* (%)
1	**1**, 5 mol%	—	$C_6H_5CH_3$	r.t	24 h	60	45
2	**1**, 5 mol%	—	CH_3CN	r.t	24 h	50	50
3	**1**, 5 mol%	—	CH_2Cl_2	r.t	10 h	97	48
4	**1**, 5 mol%	$POPh_3$	CH_2Cl_2	r.t	2 h	95	52
5	**1**, 1 mol%	$POPh_3$	CH_2Cl_2	r.t	15 h	92	53
6	**1**, 5 mol%	$POPh_3$	CH_2Cl_2	0°C	24 h	91	58
7	**1**, 1 mol%	$POPh_3$	CH_2Cl_2	0°C	30 h	90	58
8	**1**, 1 mol%	$POPh_3$	CH_2Cl_2	−10°C	5 days	88	59

(entry 8) requires the shortest time for the reaction. 3-Phenylpropanal (entry 9) reacts smoothly to give the cyanohydrin. Trimethylsilyl cyanide is readily added to citral for the silylcyanation in order to produce the cyanohydrin (Table 2).

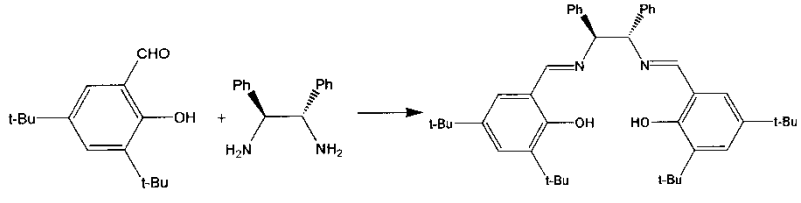
In the absence of $POPh_3$, reaction time is much longer and % ee is lower (compare entries 3 and 4 of Table 1). This may indicate the double activation process occurring through the catalysis of chiral Lewis acid and achiral Lewis base. Mn(salen) complex functions as a Lewis acid to activate the oxygen atom of aldehyde while $POPh_3$ works as a base for activation of TMSCN. The attack of N≡C would prefer *si* face of the aldehyde carbonyl to afford an *R*-cyanohydrin because *re* face is blocked by the bonding between carbonyl oxygen and the Mn atom of chiral Mn(salen) (Fig. 1).

CONCULSION

A double activation catalysis was developed for the enantioselective silylcyanation of various aldehydes. The Mn atom of chiral Mn(salen) is used to activate carbonyl oxygen for formation of the Si–O bond. $POPh_3$ functions for N≡C group to be transferred to the carbon atom of the carbonyl. The chirality of Mn(salen) controls the direction of approach of both groups to give the more *R* form of cyanohydrin.

EXPERIMENTAL

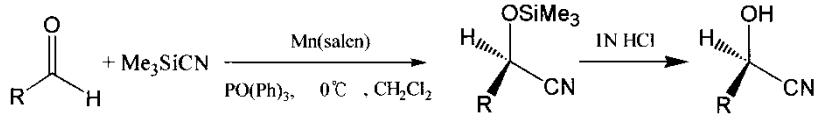
Synthesis of *(S,S)*-*N,N′*-Bis(3,5-di-*tert*-butylsalicylidene)-1, 2-diphenyl-ethylenediamine

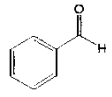
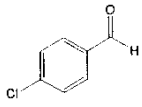
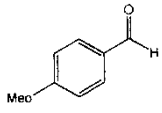
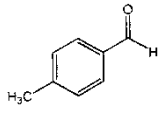
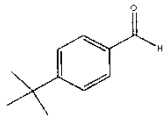
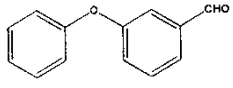
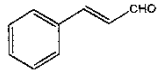
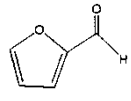
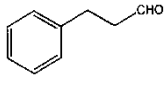
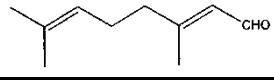


(S,S)-1,2-Diphenylethylenediamine (0.25 g, 1.18 mmol) and 3,5-di-*tert*-butyl-2-hydroxybenzaldehyde (0.55 g, 2.35 mmol) were refluxed in absolute ethanol (10 mL) for 3 h. A small amount of water was added to the reaction mixture, then it was allowed cool to 2°C and kept at that temperature for 2 h. The product was collected by suction filtration to afford a yellow powder, yield 0.53 g (70%) mp 197–198°C.

IR (KBr): 3087, 3062, 3030, 2958, 2909, 2869, 1626, 1598, 1469, 1454, 1442, 1362, 1250, 1174, 876, 776, 700 cm^{-1}.

Table 2. Silylcyanation of aldehydes catalyzed by Mn(salen) and $POPh_3$[a]



	Substrate	Temp.	Time	% Yield[b]	% *ee*[c] (*R* or *S*)
1		0°C	24 h	91	58 (*R*)
2		0°C	24 h	96	62 (*R*)
3		0°C	48 h	87	54 (*R*)
4		0°C	20 h	93	52 (*R*)
5		0°C	35 h	92	48 (*R*)
6		0°C	20 h	82	54 (*R*)
7		0°C	20 h	93	55 (*R*)
8		0°C	18 h	91	47 (*R*)
9		0°C	20 h	90	52 (*R*)
10		0°C	24 h	86	44 (*R*)

[a] 5 mol% of Mn(salen) and 10 mol% of $POPh_3$ were used.
[b] Isolated yield by weight.
[c] % ee determined by chiral HPLC column.

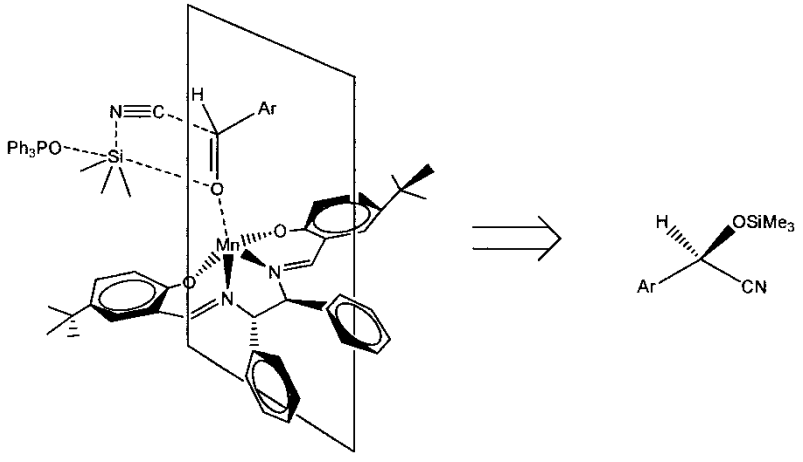


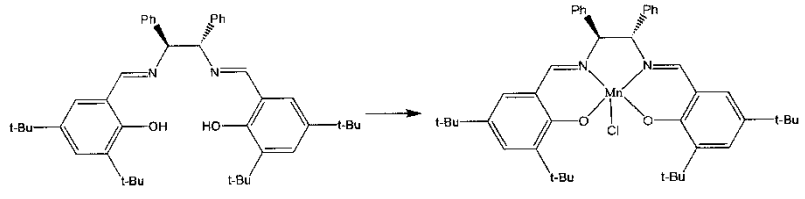
Figure 1. Transition state involved in the enantioselective cyanosilylation of aldehydes by double-activation catalysis.

^{1}H NMR: δ 1.22(18H, s, *t*-Bu), 1.42(18H, s, *t*-Bu), 4.72(2H, s, CH-N), 6.98(2H, d, $J = 2.4$ Hz, Ar-H), 7.18(10H, s, Ph), 7.31(2H, d, $J = 2.4$ Hz, Ar-H), 8.40(2H, s, CH═N), 13.59(2H, s, OH).

^{13}C NMR: δ 29.4, 31.4, 34.0, 34.9, 80.0, 117.7, 126.2, 127.0, 127.3, 127.9, 128.1, 136.2, 139.7, 139.9, 157.8, 167.1.

High resolution mass spectrometry (HRMS) (EI) m/z: calcd. for $C_{44}H_{56}N_2O_2$ 644.4342, found 644.4329.

Synthesis of [*(S,S)-N,N′*-Bis(3,5-di-*tert*-butylsalicylidene)-1, 2-diphenyl-ethylenediamine] chloromanganese(III)



Solid $Mn(OAc)_2 \cdot 4H_2O$ (0.40 g, 1.63 mmol) was added to a solution of *(S,S)-N,N′*-bis(3,5-di-*tert*-butyl-salicylidene)-1,2-diphenylethylenediamine (0.51 g, 0.79 mmol) in absolute ethanol (10 mL), and the dark brown mixture was refluxed for 2 h under air. Solid LiCl (0.11 g, 2.60 mmol) was then added and the mixture was refluxed for an additional 2 h and then stirred at 70°C overnight. The reaction mixture was cooled, and then water was added resulting in the precipitation of a brown powder that was collected by

suction filtration. The powder was redissolved in CH_2Cl_2 and extracted with water and brine. The organic phase was dried over anhydrous Na_2SO_4, and the solvent was evaporated to afford a brown powder, yield 0.54 g (93%), mp $>300^{\circ}C$.

IR (KBr): 3063, 3027, 2956, 2904, 2867, 1610, 1534, 1455, 1429, 1317, 1252, 1174, 857, 700, 579 cm^{-1}.

MS(FAB) m/z 697.6 $(M\text{-}Cl)^+$. Anal. Calcd. for $C_{44}H_{54}ClMnN_2O_2 \cdot 1/2H2O$: C, 71.19; H, 7.47; N, 3.77. Found: C, 71.36; H, 7.47; N, 3.66.

Silylcyanation of the Aldehydes Catalyzed by Mn(salen) and $POPh_3$

Aldehyde (2 mmol), TMSCN (3 mmol), Mn(salen) (5 mol%), and $POPh_3$ (10 mol%) were mixed and reacted at $0^{\circ}C$ for 18∼48 h. The solvent was evaporated. 1N HCl (30 mL) and ethyl acetate (30 mL) were added to the residue that underwent reaction for 4 h. The organic layer was extracted with ethyl acetate (2 × 20 mL) that was washed with brine and dried on anhydrous Na_2SO_4. The product was purified on Silica gel chromatography with petroleum ether/ethyl acetate (5:1) eluent. The sample was identified by ^1H, ^{13}C-NMR, HRMS; and ee % was determined by chiral high pressure liquid chromatography (HPLC) column (DAICEL CHIRALCEL OD and DAICEL CHIRALCEL AS).

2-Hydroxy-2-phenylacetonitrile

^1H NMR ($CDCl_3$) δ 7.44 (m, 5H), 6.15 (s, 1H), 4.22 (m, 2H), 1.27 (t, $J = 7.0$ Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 153.6, 131.3, 130.8, 129.4, 127.9, 115.6, 66.3, 65.6, 14.3. HRMS(M^+) cacld. for $C_{11}H_{11}NO_3$ 205.0739 found 205.0753. R enantiomer in 58% ee. HPLC (DAICEL CHIRALCEL OD) 11.5 min and 14.0 min. (The enantiomeric excess was determined by HPLC after conversion to ethylcarbonate.)

2-Hydroxy-2-(4-chlorophenyl)acetonitrile

^1H NMR ($CDCl_3$) δ 3.13 (s, 1H), 5.46 (s, 1H), 7.38 (d, 2H), 7.36 (d, 2H). ^{13}C NMR ($CDCl_3$) δ 63.35, 118.87, 128.46, 129.84, 134.08, 136.37. HRMS(M^+) cacld. for C_8H_6ClNO 167.0138 found 167.0143. R enantiomer in 62% ee. HPLC (DAICEL CHIRALCEL OD) 16.4 min and 19.9 min.

2-Hydroxy-2-(4-methoxyphenyl)acetonitrile

^1H NMR ($CDCl_3$) δ 2.8 (brs, 1H), 3.86 (s, 3H), 5.48 (s, 1H), 6.95 (d, $J = 8.5$ Hz, 2H), 7.46 (d, $J = 8.5$ Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 55.40, 63.27, 114.52, 118.93, 127.50, 128.29, 160.70. R enantiomer in 54% ee.

HPLC (DAICEL CHIRALCEL OD) 12.7 min and 14.8 min. (The enantiomeric excess was determined by HPLC after conversion to acetyl ester.)

2-Hydroxy-2-(4-methylphenyl)acetonitrile

^{1}H NMR ($CDCl_3$) δ 7.44 (d, $J = 8.25$ Hz, 2H), 7.25 (d, $J = 8.25$ Hz, 2H), 6.22 (s, 1H), 4.28 (m, 2H), 2.39 (s, 3H), 1.35 (t, $J = 7.3$ Hz. 3H). ^{13}C NMR ($CDCl_3$) δ 153.5, 140.7, 129.9, 128.6, 127.9, 115.9, 66.2, 65.3, 21.4, 14.1. HRMS(M^+) cacld. for $C_{12}H_{13}NO_3$ 219.0895 found 219.0889. R entiomer in 52% ee. HPLC (DAICEL CHIRALCEL OD) 17.4 min and 19.5 min. (The enantiomeric excess was determined by HPLC after conversion to ethylcarbonate.)

2-Hydroxy-2-(4-tert-butylphenyl)acetonitrile

^{1}H NMR ($CDCl_3$) δ 1.25 (s, 9H), 2.88 (s, 1H), 5.43 (s, 1H), 7.37 (m, 4H). ^{13}C NMR ($CDCl_3$) δ 31.64, 35.18, 63.77, 119.46, 126.56, 126.94, 132.79, 153.56. HRMS(M^+) cacld. for $C_{12}H_{15}NO$ 189.1154 found 189.1143. R enantiomer in 48% ee. HPLC (DAICEL CHIRALCEL OD) 21.5 min and 24.0 min.

2-Hydroxy-4-phenyl-3-butenenitrile

^{1}H NMR ($CDCl_3$) δ 7.43 (m, 5H), 6.98 (d, $J = 15.9$ Hz, 1H), 6.19 (dd, $J = 15.9$, 6.7 Hz. 1H), 6.03 (dd, $J = 6.7$, 0.9 Hz), 2.15 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 168.9, 137.9, 134.6, 129.6, 128.9, 127.1, 118.4, 115.7, 61.5, 20.5 HRMS(M^+) cacld. for $C_{12}H_{11}NO_2$ 201.0790 found 201.0782. R entiomer in 55% ee. HPLC (DAICEL CHIRALCEL OD) 18.1 min and 22.3 min. (The enantiomeric excess was determined by HPLC after conversion to acetylester.)

2-Hydroxy-2-(3-phenoxyphenyl)acetonitrile

^{1}H NMR ($CDCl_3$) δ 3.5 (brs, 1H), 5.46 (s, 1H), 7.5 (m, 9H). ^{13}C NMR ($CDCl_3$) δ 63.17, 116.63, 118.59, 119.65, 120.94, 123.94, 129.93, 130.52, 137.05, 156.34, 158.12. R entiomer in 54% ee. HPLC (DAICEL CHIRALCEL OD) 36.1 min and 40.7 min. (The enantiomeric excess was determined by HPLC after conversion to acetylester.)

2-(2-Furyl)-2-hydroxyethanenitrile

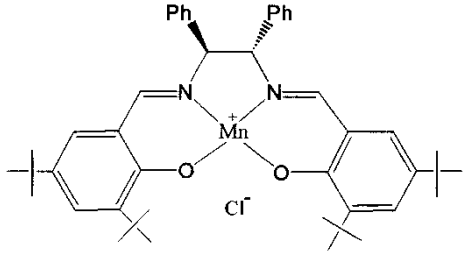
^{1}H NMR ($CDCl_3$) δ 7.50 (dt, $J = 1.8$ Hz, 1H), 6.65 (d, $J = 3.4$ Hz, 1H), 6.44 (s, 1H), 6.47 (dd, $J = 3.4$, 1.8 Hz, 1H), 2.15 (s, 3H). R entiomer in 47% ee. HPLC (DAICEL CHIRALCEL AS) 8.7 min and 9.7 min. (The enantiomeric excess was determined by HPLC after conversion to acetylester.)

2-Hydroxy-4-phenylbutanenitrile

^{1}H NMR ($CDCl_3$) δ 7.31 (m, 2H), 7.22 (m, 3H), 4.44 (t, $J = 6.4$ Hz, 1H), 2.80 (m, 2H), 2.15 (m, 2H), 0.92 (s, 9H), 0.18 (s, 3H), 0.12 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 140.0, 128.5, 128.4, 126.2, 119.9, 61.3, 37.9, 25.8, 18.1, 20.51, 25.3. R entiomer in 52% ee. HPLC (DAICEL CHIRALCEL OD) 8.7 min and 10.9 min. (The enantiomeric excess was determined by HPLC after conversion to TBDMSether.)

2-Hydroxy-4,8-dimethyl-nona-3,7-dienenitrile

^{1}H NMR ($CDCl_3$) δ 1.63 (s, 3H), 1.71 (s, 3H), 1.76 (s, 3H), 2.14 (m, 5H), 5.04 (t, $J = 7$ Hz, 1H), 5.13 (dd, $J = 7$ Hz, 6.5Hz, 1H), 5.44 (dd, $J = 6.5$ Hz, 7Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 16.83, 17.63, 25.88, 26.25, 39.17, 57.88, 118.83, 119.16, 122.91, 132.45, 145.11. R enantiomer in 44% ee. HPLC (DAICEL CHIRALCEL OD) 12.1 min and 14.0 min.



1

ACKNOWLEDGMENT

The authors warmly thank the Inha University for the financial support in 2005.

REFERENCES

1. Matthews, B. R.; Gountzos, H.; Jackson, W. R.; Watson, K. G. *Tetrahedron Letts.* **1989**, *30*, 5157.
2. Ziegler, T.; Horsch, B.; Effenberger, F. *Synthesis* **1990**, 575.
3. (a) Jackson, W. R.; Jacobs, H. A.; Jayatilake, G. S.; Matthews, B. R.; Watson, K. G. *Aust. J. Chem.* **1990**, *43*, 2045; (b) Jackson, W. R.; Jacobs, H. A.; Matthews, B. R.; Jayatilake, G. S.; Watson, K. G. *Tetrahedron Letts.* **1990**, *31*, 1447.
4. Effenberger, F.; Stelzer, U. *Angew. Chem. Int. Ed.* **1991**, *30*, 873.

5. North, M. *Comprehensive Organic Functional Group Transformations*; Katritzky, A. R., Meth-Comn, O., Rees, C., Pattenden, G., Eds.; Pergamon press: Oxford, 1995; Vol. 3, Chapter 18.
6. (a) Belokon, Y. N.; Green, B.; Ikonnikov, N. S.; North, M.; Tararov, V. I. *Tetrahedron Lett.* **1999**, *40*, 8147–8150; (b) 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; (c) Belokon, Y. N.; Green, B.; Ikonnikov, N. S.; North, M.; Tararov, V. I. *Tetrahedron Lett.* **1999**, *40*, 8147–8150; (d) Belokon, Y. N.; Green, B.; Ikonnikov, N. S.; Larichev, V. S.; Lokshin, B. V.; Moscalenko, M. A.; North, M.; Orizu, C.; Peregudov, A. S.; Timofeeva, G. I. *Eur. J. Org. Chem.* **2000**, 2655–2661; (e) Belokon, Y. N.; North, M.; Parsons, T. *Org. Lett.* **2000**, *2*, 1617; (f) Belokon, Y. N.; Green, B.; Ikonnikov, N. S.; North, M.; Parsons, T.; Tararov, V. I. *Tetrahedron* **2001**, *57*, 771–779.
7. (a) Hamashima, Y.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2000**, *122*, 7412–7213; (b) Hamashima, Y.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* **2001**, *42*, 691–694; (c) Yabu, K.; Masumoto, S.; Yamasaki, S.; Hamashima, Y.; Kanai, M.; Du, W.; Curran, D. P.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 9908–9909; (d) Yabu, K.; Masumoto, S.; Kanai, M.; Curran, D. P.; Shibasaki, M. *Tetrahedron Lett.* **2002**, *43*, 2923–2926; (e) Masumoto, S.; Suzuki, M.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* **2002**, *43*, 8647–8651.
8. (a) Tian, S.-K.; Deng, L. *J. Am. Chem. Soc.* **2001**, *123*, 6195–6196; (b) Tian, S.-K.; Hong, R.; Deng, L. *J. Am. Chem. Soc.* **2003**, *125*, 9900–9901.
9. Deng, H.-B.; Isler, M. P.; Snapper, M. L.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2002**, *41*, 1009–1012.
10. Liang, S.; Bu, X. R. *J. Org. Chem.* **2002**, *67*, 2702–2704.
11. (a) Kim, S. S.; Song, D. H. *Lett. Org. Chem.* **2004**, *1*, 93–98; (b) Kim, S. S.; Song, D. H. *J. Organometall. Chem.* **2004** in press; (c) Kim, S. S.; Rajagopal, G.; Kim, D. W.; Song, D. H. *Synthetic Commun.* **2004** in press; (d) Kim, S. S.; Song, D. H.; Rajagopal, G. *J. Organometall. Chem.* **2004**, *689*, 1734–1738; (e) Kim, S. S.; Kim, D. W.; Rajagopal, G. *Synthesis* **2004**, *2*, 213.
12. Pietikäinen, P. *Tetrahedron* **2000**, *56*, 417.