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TETRAHEDRON: *ASYMMETRY*

Catalytic asymmetric ring opening of epoxides to chlorohydrins with mild chloride donors and enantiopure titanium complexes

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Abstract

The ring opening of symmetric and racemic epoxides with dilithium tetrachlorocuprate or trimethylsilyl chloride in the presence of titanium (*R*,*R*)-(+)-TADDOLates or a titanium (*R*)-(+)-BINOL complex gave vicinal chlorohydrins or their TMS ethers with maximum 36% enantiomeric excess.

1. Introduction

Enantioselective ring opening of *meso*- or racemic epoxides by nucleophilic reagents is one of the most powerful methods in the asymmetric synthesis of 1,2-disubstituted compounds.[1] This type of reaction has been successfully accomplished with carbon nucleophiles,[2] thiols,[3–5] phenols,[6,7] carboxylic acids,[8] aromatic amines,[9–11] azide,[1,9,12–14] and cyanide[15] as nucleophiles. In contrast, no example of the catalytic formation of optically active halohydrins existed until very recently, when Denmark et al.[16] reported an asymmetric ring opening of epoxides with silicon tetrachloride in the presence of an enantiopure Lewis base, and Nugent et al.[17] synthesized TMS ethers of bromo and iodohydrins by enantioselective ring opening of *meso*-epoxides in the presence of a chiral zirconium complex. These papers led us to publish our results on ring opening with mild chloride donors and enantiopure titanium complexes. The classical reagents for halohydrin syntheses from epoxides are Lewis-acidic metal halides[18] or hydrohalic acids, which provide powerful electrophilic activation of oxiranes. Previous methods for the asymmetric synthesis of halohydrins by enantioselective ring opening of epoxides required stoichiometric amounts of chiral reagents.[19,20]

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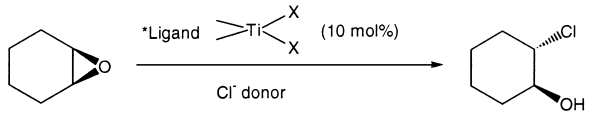
2. Results and discussion

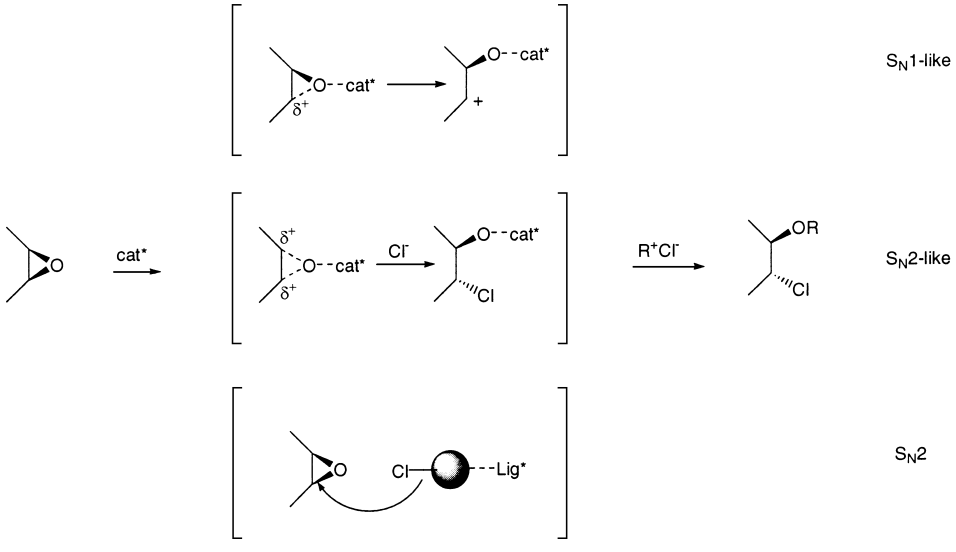
As a model reaction cyclohexene oxide **2** was treated with various combinations of readily available chiral Lewis-acidic titanium complexes and different Cl^- donors to give (*S*,*S*)-(+)-2-chlorocyclohexanol or its TMS ether, respectively (Scheme 1).



Scheme 1.

Reactions with strong acids gave only racemates, even at low temperatures, and frequently oligomerization and/or catalyst decomposition was observed. Mild Cl^- donors, on the other hand, transformed the epoxides only at rather high temperatures, and again racemic products were isolated.

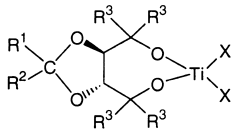
Asymmetric ring opening of epoxides in the presence of Lewis acids in general can proceed via different mechanisms (Scheme 2). In an S_N1-like reaction, complexation of the enantiopure Lewis acid leads to a non-symmetrical charge distribution in the transition state providing an intermediate carbenium ion in which the catalyst is still complexed during attack of the nucleophile. Due to the long distance to the electrophilic center, the influence of the chiral catalyst is low and a high enantiomeric excess cannot be expected. In cases when Lewis acid activation and nucleophilic attack are concerted (S_N2-like), there is generally a good chance for efficient asymmetric induction since the coordinated enantiopure catalyst can steer the halogenide to one preferred position. Alternatively, direct delivery of the nucleophile from the metal center may occur.[21] Just as in the previous case, this S_N2 transmission can lead to high enantiomeric excess.

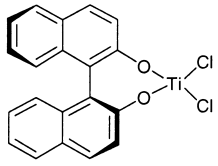


Scheme 2.

Our attempts to find matching combinations of a stable catalyst having good Lewis acid activity even at low temperature and a chloride donor which opens epoxides in an S_N2-like or an S_N2 way under these conditions lead us finally to a couple of (*R*,*R*)-(+)-tartrate-based titanium complexes such as Seebach's systems[22,23] and to titanium (*R*)-(+)-BINOL catalysts[24,25] (Scheme 3) in combination with dilithium

tetrachlorocuprate (Li_2CuCl_4)[26] serving as chloride donor. Moreover, trimethylsilyl chloride (TMSCl) was tested as a Cl^- donor to obtain the TMS ethers of chlorohydrins (Table 1).





I $R^1 = R^2$ = Me; **(a)** X = Cl; **(b)** X = F
II $R^1 = R^2$ = Me; R^3 = Biphenyl; **(a)** X = Cl; **(b)** X = F
III R^1 = Ph; R^2 = Me; R^3 = Ph; **(a)** X = Cl; **(b)** X = F
IV R^1 = H; R^2 = Naphthyl; R^3 = Ph; X = Cl
V R^1 = H; R^2 = *tert.*-Butyl; R^3 = Ph; X = Cl

VII

Scheme 3.

Initial experiments with TMSCl showed that the latter reaction is extremely moisture-sensitive. Traces of HCl easily open the epoxides to the corresponding racemic chlorohydrins without participation of the metal catalyst. Thus, it is essential to use freshly distilled (argon atmosphere, pyridine) TMSCl free of HCl.

The epoxides **1**–**6** (Scheme 4) were treated under the conditions shown in Table 1 with the corresponding chloride donor in the presence of one of the enantiopure Lewis acidic catalysts (Scheme 3) at low temperature for 1 to 10 days in the case of dilithium tetrachlorocuprate or 1.5 to 4 h in the case of TMSCl.

All catalysts were prepared in situ mixing the enantiopure diol and $TiCl_2(O^iPr)_2$ in dry toluene at room temperature to obtain the dichloro titanium compounds[22,23,28] except for catalyst **IV**, which was prepared according to a literature procedure.[24]

Our ring opening experiments of **2** with enantiopure Ti-complexes show that chloride can be delivered directly from the catalyst to the substrate. The reaction of **2** with an equimolar amount of the Ti-complex **Ia** (without Li_2CuCl_4) gave (*S*,*S*)-(+)-2-chlorocyclohexanol in quantitative yield and with 17–20% ee after 65 h at −20°C which is not significantly higher compared to the catalytic reaction (12–17% ee). Thus, in the latter case the catalyst **Ia** can be regenerated from Li_2CuCl_4 which on its own is unable to open the epoxide with any noticeable rate under these conditions. However, the alternative chloride transfer from the cuprate to the activated epoxide cannot be ruled out.

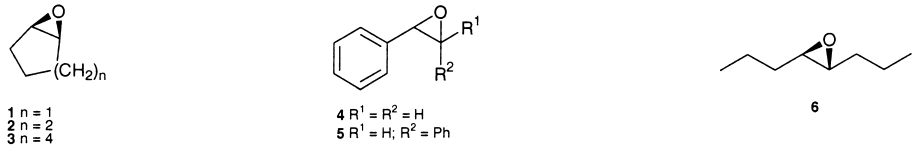
The reactions of **2** with TMSCl/pyridine and the Ti-catalysts occurred much faster at −20°C. Since the ring opening of **2** with TMSCl/pyridine in the absence of the catalysts is significantly slower (no reaction after 2 h at +15°C, 100% conversion after 15 h at +25°C), there is an effective activation of the epoxide by the Ti-complexes. Stereodifferentiation during ring opening, according to an S_N2-type process similar to those mentioned above to give the TMS ether of the chlorohydrin, is more efficient with TMSCl (Table 1). Working at an even lower temperature (−78°C) did not enhance the ee.

For further experiments the catalysts **Ia**–**IIIa** were transformed to **Ib**–**IIIb** by chloride with fluoride exchange applying trimethyltin fluoride in toluene under the conditions Roesky et al. used for titanocene complexes.[29] Using these catalysts, reactions with Li_2CuCl_4 proceeded at lower temperatures giving higher ees (Table 1). This indicates that chloride is transferred from the cuprate to the activated epoxide in these cases. In contrast, reactions with TMSCl/pyridine in the presence of the latter catalysts was less effective and gave the TMS ethers in low yield and with <5% ee.

Table 1
Asymmetric ring opening of epoxides with mild chloride donors and enantiopure titanium complexes (10 mol%)

Epoxide	*Cat	Source of Cl^-	Solvent	Temperature [°C]	Time [h]	Yield (GC) of Chlorohydrin [%]	ee of Chlorohydrin[a] [%]
1	**Ia**	Me_3SiCl	toluene	-40→r.t.	24	80[b]	15[b]
2	**Ia**	Li_2CuCl_4	THF/toluene	-20	90	90	12 - 17
2	**Ib**	Li_2CuCl_4	THF/toluene	-60→-20	40	51	27 - 32
2	**Ia**	Me_3SiCl	toluene	-60→-20	4	100[b]	36[b]
2	**IIa**	Li_2CuCl_4	THF/toluene	-30→-20	20	83	6
2	**IIb**	Li_2CuCl_4	THF/toluene	-40→-30	70	58	20 - 25
2	**IIa**	Me_3SiCl	toluene	-60→-20	4	100[b]	23[b]
2	**IIIa**	Me_3SiCl	toluene	-60→-30	3	100[b]	31[b]
2	**IIIb**	Li_2CuCl_4	THF/toluene	-40→-20	90	80	6 - 8
2	**IV**	Me_3SiCl	toluene	-60→-30	3	100[b]	23[b]
2	**V**	Me_3SiCl	toluene	-60→-30	3	100[b]	30[b]
2	**VII**	Li_2CuCl_4	THF/toluene	-40	70	100	8 - 10
3	**Ia**	Li_2CuCl_4	THF/toluene	-40→r.t.	140	22	< 1
3	**Ia**	Me_3SiCl	toluene	r.t.	240	30[b]	4[b]
4	**Ia**	Li_2CuCl_4	THF/toluene	-30→-20	20	10 / 40[c]	9 / 10
4	**Ib**	Li_2CuCl_4	THF/toluene	-40→-30	40	17 / 33[c]	7 / 10 - 15
4	**Ia**	Me_3SiCl	toluene	-60→-20	4	13 / 37[b,c]	8[b]
4	**IIa**	Li_2CuCl_4	THF/toluene	-30→-20	20	9 / 41[c]	3 / 6
4	**IIb**	Li_2CuCl_4	THF/toluene	-40→-30	40	3 / 47[c]	9 / 6 - 10
4	**V**	Me_3SiCl	toluene	-60→-40	3	15 / 35[b,c]	5[b]
4	**VII**	Me_3SiCl	CH_2Cl_2	-60 - -40	1,5	1 / 49[b,c]	13[b]
5	**Ia**	Me_3SiCl	toluene	-20→r.t.	19	100[b]	18[b,d]
5	**IIa**	Me_3SiCl	toluene	-20→r.t.	3	100[b]	9[b,d]
5	**III**	Me_3SiCl	toluene	-20→r.t.	3	100[b]	5[b,d]
5	**IV**	Me_3SiCl	toluene	-20→r.t.	3	100[b]	12[b,d]
6	**Ia**	Me_3SiCl	toluene	-20→r.t.	24	50[b]	3[b]

[a] determined by chiral GC (beta-cyclodextrin column)
[b] corresponding TMS ether,
[c] 50% conversion; ratio of 2-chloro-1-phenylethanol/(*R*)-(-)-2-chloro-2-phenylethanol
[d] determined after hydrolysis with trifluoroacetic acid in methanol by comparison of the $[\alpha]_D$ with that of the enantiopure chlorohydrin.[27]



Scheme 4.

3. Experimental

^{1}H NMR (300.13 MHz) and ^{13}C NMR (75.5 MHz) were recorded in $CDCl_3$ on a Bruker WM 300 apparatus with TMS for ^{1}H and $CDCl_3$ for ^{13}C NMR as internal standards. Mass spectra (70 eV) were obtained by GLC–MS using a Varian GC 3400 (quartz capillary column HP1 (0.33 μm) dimensions: 25 m, ∅ 0.2 mm). Other GLC experiments were performed on Hewlett–Packard 5890 II gas chromatographs

(HP1 (0.25 μm) dimensions: 25 m, Ø 0.2 mm). The enantiomeric excess was determined by chiral GLC (beta-cyclodextrin column, Supelco, Beta-Dex™ 120 (0.25 μm), dimensions: 30 m, Ø 0.25 mm).

3.1. General procedure for Ti-catalyzed ring opening of epoxides with Li_2CuCl_4

In a dried Schlenk vessel with a rubber septum 84.8 mg (2 mmol) of anhydrous LiCl and 134 mg (1 mmol) of anhydrous $CuCl_2$ were dissolved in 10 ml of dry THF under argon. The reddish-brown solution was stirred at room temperature for 1 h. Using a syringe this solution was added to a solution of the chiral titanium catalyst, prepared in situ from 23.7 mg (0.1 mmol) of $TiCl_2(O^iPr)_2$ and 0.1 mmol of the corresponding enantiopure ligand in 10 ml of toluene in a second Schlenk vessel. The mixture was cooled down to the starting temperature (Table 1) and 1 mmol of the corresponding epoxide was added with stirring at this temperature. The mixture was allowed to warm up to the reaction temperature and stirred for the time given in Table 1. Then the mixture was hydrolyzed with 10 ml of water and extracted with methylene chloride (4×10 ml). The combined organic layers were dried over magnesium sulfate and the solvent was removed under reduced pressure. The crude product was analyzed by GC and the product separated by column chromatography (silica gel, cyclohexane/ethylactetate, 5:1 to 20:1).

3.2. General procedure for Ti-catalyzed ring opening of epoxides with trimethylsilyl chloride

In a dried Schlenk vessel with a rubber septum the toluene solution of 0.1 mmol of the catalyst (prepared as described above) was treated with 1 mmol of the epoxide and immediately cooled down to the starting temperature (Table 1). Then 0.8 ml (1 mmol) of dry pyridine and 0.22 ml (2 mmol) of distilled, fresh TMSCl were added with a syringe at this temperature. The mixture was allowed to warm up to the reaction temperature and was stirred for the time given in Table 1. Then the reaction mixture was filtered over 5 cm of basic alumina and purified by column chromatography (silica gel, cyclohexane/ethylacetate).

3.3. (S,S)-(+)-2-Chlorocyclohexanol[30,31]

$[\alpha]_D^{20}$=+4.0 (*c* 1.0 in $CHCl_3$), 32% ee (chiral GC after silylation with BSA), ($[\alpha]_D^{20}$=+27.7 (*c* 4.7 in $CHCl_3$) for the enantiopure compound),[32] $[\alpha]_D^{20}$=+8.3 (*c* 2.2 in $CHCl_3$, TMS ether), 36% ee (chiral GC); ^{1}H NMR: δ 1.28 (m, 3H, CH_2), 1.68 (m, 3H, CH_2), 2.11 (m, 2H, CH_2), 2.62 (br s, 1H, OH), 3.48 (m, 1H, CHCl), 3.69 (ddd, 1H, $^3J_{HH}$=4.3 Hz, $^3J_{HH}$=9.1 Hz, $^3J_{HH}$=11.45 Hz, C*H*OH); ^{13}C NMR: δ 24.0 (t, CH_2), 25.8 (t, CH_2), 33.1 (t, CH_2), 35.2 (t, CH_2), 67.6 (d, CHCl), 75.3 (d, CHOH); GC–MS (70 eV): m/z (%) 134/135/136 (21) [M^+], 116/118 (3) [M^+–H_2O], 98 (14) [M^+–HCl], 88 (18), 81 (22) [$C_6H_9^+$], 80 (34) [$C_6H_8^{+\cdot}$], 69 (10), 57 (100) [$C_4H_9^+$], 44 (14), 43 (10), 39 (7).

3.4. (R)-(−)-2-Chloro-2-phenylethanol[26,31]

$[\alpha]_D^{20}$=−16.1 (*c* 1.0 in $CHCl_3$), 15% ee (chiral GC, after silylation with BSA), ($[\alpha]_D^{22}$=+162.4 ($CHCl_3$) for the enantiopure (*S*)-isomer);[27] ^{1}H NMR: δ 2.13 (m, 1H), 3.92 (m, 2H, C*H*OH), 4.98 (dd, 1H, $^3J_{HH}$=6.0 Hz, $^3J_{HH}$=7.1 Hz, CHCl), 7.02–7.44 (m, 6H, H_{arom}); ^{13}C NMR: δ 65.0 (d, CHCl), 68.0 (t, CH_2OH), 127.4 (d), 128.8 (d), 128.9 (d), 137.9 (s, C_q); GC–MS (70 eV): m/z (%) 156/157/158 (26) [M^+], 128 (23), 125/127 (100) [M^+–CH_2OH], 91 (82) [$C_7H_7^+$], 77 (9) [$C_6H_6^+$], 65 (9), 63 (8), 51 (12) [$C_4H_3^+$], 39 (9) [$C_4H_3^+$].

3.5. 2-Chloro-1-phenylethanol[26,31]

^{1}H NMR: δ 2.69 (br, 1H), 3.67 (dd, 1H, $^3J_{HH}$=7.9 Hz, $^2J_{HH}$=11.2 Hz, CH_2Cl), 3.72 (dd, 1H, $^3J_{HH}$=4.4 Hz, $^2J_{HH}$=11.2 Hz, CH_2Cl), 4.88 (dd, 1H, $^3J_{HH}$=4.4 Hz, $^3J_{HH}$=7.9 Hz, C*H*OH), 7.02–7.44 (m, 5H, H_{arom}); ^{13}C NMR: δ 50.8 (t, CH_2Cl), 74.1 (d, CHOH), 126.0 (d, 2CH), 128.4 (d, CH), 128.6 (d, 2CH), 139.9 (s, C_q); GC–MS (70 eV): m/z (%) 156/158 (0) [M^+], 138/140 (8) [M^+–H_2O], 107 (100) [M^+–CH_2Cl], 91 (9) [$C_7H_7^+$], 77 (49) [$C_6H_6^+$], 51 (28) [$C_4H_3^+$], 39 (9) [$C_3H_3^+$].

3.6. 2-Chloro-1,2-diphenylethanol

^{1}H NMR: δ 2.99 (br s, 1H, OH), 4.93 (d, 1H, $^3J_{HH}$=8.1 Hz, CHCl), 5.00 (d, 1H, $^3J_{HH}$=8.1 Hz, C*H*OH), 7.04–7.29 (m, 10H, H_{arom}); ^{13}C NMR: δ 70.7 (d, CHCl), 78.8 (d, CHOH), 127.0 (d, 2C), 128.0 (d, 2C), 128.1 (d, 2C), 128.2 (d, 2C), 128.5 (d, 2C), 134.6 (s, 1C), 137.6 (s, 1C); GC–MS (70 eV): m/z (%) 232/234 (0.25) [M^+], 196 (1.5), [M^+–HCl], 180 (8) [$(Ph)_2C_2H_2^+$], 167 (14), 107 (100) [$PhCH_2O^+$], 91 (13) [$C_7H_7^+$], 89 (9), 77 (25) [$C_6H_6^+$], 65 (9), 51 (6) [$C_4H_3^+$], 39 (5) [$C_3H_3^+$].

3.7. 5-Chloro-4-(trimethylsilyloxy)octane

GC–MS (70 eV): m/z (%) 236 (0) [M^+], 221/223 (3.5) [M^+–CH_3], 193/195 (6.5) [M^+–C_3H_7], 145 (100) [M^+–C_4H_8Cl], 103 (8), 93 (9), 75 (12) [$C_2H_7OSi^+$], 73 (74) [TMS^+], 69 (16), 55 (12), 43 (11).

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References

1. Hodgson, D. M.; Gibbs, A. R.; Lee, G. P. *Tetrahedron* **1996**, *52*, 14361 and references cited therein.
2. Mizuno, M.; Kanai, M.; Iida, A.; Tomioka, K. *Tetrahedron: Asymmetry* **1996**, *7*, 2483.
3. Yamashita, H.; Mukaiyama, T. *Chem. Lett*. **1985**, 1643.
4. Yamashita, H. *Bull. Chem. Soc. Jpn*. **1988**, *61*, 1213.
5. Iida, T.; Yamamoto, N.; Sasaki, H.; Shibasaki, M. *J. Am. Chem. Soc*. **1997**, *118*, 4783.
6. Iida, T.; Yamamoto, N.; Matsunaga, S.; Woo, H.-G.; Shibasaki, M. *Angew. Chem*. **1998**, *110*, 2383; *Angew. Chem., Int. Ed. Engl*. **1998**, *37*, 2223.
7. Vogl, E. M.; Matsunaga, S.; Kanai, M.; Iida, T.; Shibasaki, M. *Tetrahedron Lett*. **1998**, *39*, 7917.
8. Jacobsen, E. N.; Kakiuchi, F.; Konsler, R. G.; Larrow, J. F.; Tokunaga, M. *Tetrahedron Lett*. **1997**, *38*, 773.
9. Yamashita, H. *Chem. Lett*. **1987**, 525.
10. Fu, X. L.; Wu, S. H. *Synth. Commun*. **1997**, *27*, 1677.
11. Hou, X.-L.; Wu, J.; Dai, L.-X.; Xia, L.-J.; Tang, M.-H. *Tetrahedron: Asymmetry* **1998**, *9*, 1747.
12. Hansen, K. B.; Leighton, J. L.; Jacobsen, E. N. *J. Am. Chem. Soc*. **1996**, *118*, 10924.
13. Schaus, S. E.; Larrow, J. F.; Jacobsen, E. N. *J. Org. Chem*. **1997**, *62*, 4197.
14. Annis, A. D.; Helluin, O.; Jacobsen, E. N. *Angew. Chem*. **1998**, *110*, 2010; *Angew. Chem., Int. Ed. Engl*. **1998**, *37*, 1907.
15. Cole, B. M.; Shimizu, K. D.; Krueger, C. A.; Harrity, J. P. A.; Snapper, M. L.; Hoveyda, A. H. *Angew. Chem*. **1996**, *108*, 1776; *Angew. Chem., Int. Ed. Engl*. **1996**, *35*, 1668.
16. Denmark, S. E.; Barsanti, P. A.; Wong, K.-T.; Stavenger, R. A. *J. Org. Chem*. **1998**, *63*, 2428.
17. Nugent, W. A.; Licini, G.; Boncio, M.; Bortolini, O.; Finn, M. G.; McCleland, W. *Pure Appl. Chem*. **1998**, *70*, 1041; Nugent, W. A. *J. Amer. Chem. Soc*. **1998**, *120*, 7139.

18. Bonini, C.; Righi, G. *Synthesis* **1994**, 225.
19. Joshi, N. N.; Srebnik, M.; Brown, H. C. *J. Am. Chem. Soc*. **1988**, *110*, 6246.
20. Naruse, Y.; Esaki, T.; Yamamoto, H. *Tetrahedron* **1988**, *44*, 4747.
21. Martinez, L. E.; Leighton, J. L.; Carsten, D. H.; Jacobsen, E. N. *J. Am. Chem. Soc*. **1995**, *117*, 5897.
22. Beck, A. K.; Bastani, B.; Plattner, D. A.; Petter, W.; Seebach, D.; Braunschweiger, H.; Gysi, P.; La Vecchia, L. *Chimia* **1991**, *45*, 238.
23. Seebach, D.; Plattner, D. A.; Beck, A. K.; Wang, Y. M.; Hunziker, D.; Petter, W. *Helv. Chim. Acta* **1992**, *75*, 2171.
24. Reetz, M. T.; Kyung, S.-H.; Bolm, C.; Zierke, T. *Chem. Ind*. **1986**, 824.
25. Terada, M.; Matsumoto, Y.; Nakamura, Y.; Mikami, K. *J. Chem. Soc., Chem. Comm*. **1997**, 281.
26. Ciaccio, J. A.; Addess, K. J.; Bell, T. W. *Tetrahedron Lett*. **1986**, *27*, 3697.
27. Berti, G.; Bottari, F.; Ferrarini, P. L.; Macchia, B. *J. Org. Chem*. **1965**, *30*, 4091.
28. Seebach, D.; Weidmann, B.; Widler, L. *Modern Synthetic Methods*, Vol. 3; Sheffold, R., Ed.; Salle & Sauerländer: Aarau, 1983; p. 217.
29. Herzog, A.; Liu, F.-Q.; Roesky, H. W.; Demsar, A.; Keller, K.; Noltemeyer, M.; Pauer, F. *Organometallics* **1994**, *13*, 1251.
30. Coleman, G. H.; Johnstone, H. F. *Org. Synth*. **1941**, *Coll. Vol. I*, 158.
31. Kotsuki, H.; Shimanouchi, T.; Ohshima, R.; Fujiwara, S. *Tetrahedron* **1998**, *54*, 2709.
32. Sadozai, S. V.; Merckx, E. M.; Van de Wal, A. J.; Lemière, S. L.; Esmans, E. L.; Alderweireldt, F. C. *Bull. Soc. Chim. Belg.* **1982**, *91*, 163.