An Alternative Route to Protected Aldols: Cobalt-Catalyzed Hydroformylation of Epoxides and in situ Protection of β-Hydroxyaldehydes by $HC(OMe)_3$

Koji Nakano,[a] Masaya Katayama,[a] Shinjiro Ishihara,[b] Tamejiro Hiyama,[b] Kyoko Nozaki*[a]

[a] Department of Chemistry and Biotechnology, Graduate School of Engineering, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113-8656, Japan
Fax +81(3)58417261; E-mail: nozaki@chembio.t.u-tokyo.ac.jp

[b] Department of Material Chemistry, Graduate School of Engineering, Kyoto University, Nishikyo-ku, Kyoto 615-8510, Japan

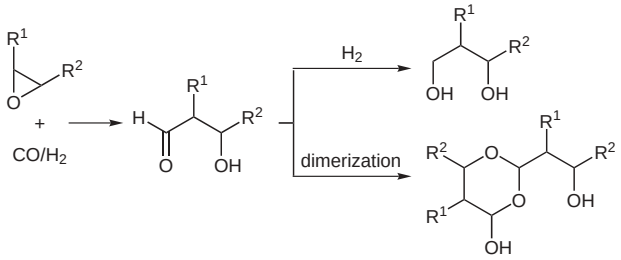
Received 27 February 2004

Abstract: A wide range of epoxides were efficiently converted to protected aldols by hydroformylation-acetalization using $Co_2(CO)_8$ as a catalyst in trimethyl orthoformate. The formylation of terminal epoxides was regioselective for the terminal position, and (*S*)-1-benzyloxy-2,3-epoxypropane was transformed into (*R*)-1-benzyloxy-4,4-dimethoxybutan-2-ol with retention of the configuration.

Key words: acetals, hydroformylations, epoxides, cobalt, aldols

The aldol addition is one of the most useful C-C bond forming reaction for the synthesis of β-hydroxy carbonyl compounds, and the extensive work on this subject has been devoted to develop the stereoselective and catalytic variants.[1] In general, a control of the reaction between the different aliphatic aldehydes has been understood to be difficult because of some accompanying problems: (1) each aldehyde possibly reacts as an electrophilic acceptor and a nucleophilic donor to give a mixture of aldol products (β-hydroxyaldehydes), (2) the reaction of an aldol product with an aldehyde monomer or with itself gives the aldehyde trimer or aldol product dimer, respectively, and (3) dehydration of an aldol product yields α,β-unsaturated aldehyde which allows Michael-type reaction.[2] Recent advances have overcome these undesired reactions and demonstrated the catalytic and selective condensation between different aliphatic aldehydes.[3]

Transition-metal catalyzed hydroformylation of epoxides is also an effective method to give β-hydroxyaldehydes.[4,5] Similar to the aldol reaction above mentioned, the reactive aldehyde function potentially causes some unwanted side reactions such as dimerization of products or reduction of carbonyl function under the hydroformylation condition (Scheme 1). Accordingly, in order to establish the synthetic utility of epoxide hydroformylation, it is required to protect the functional groups (hydroxy and/or formyl group) in situ. A successful example for protection of hydroxyl group is the rhodium-catalyzed silylformylation of epoxides reported by Murai et al. where $HSiR_3$ is used instead of H_2.[6] On the other hand, for the protection of formyl group, Orchin et al. attempted the cobalt-catalyzed hydroformylation of cyclohexene oxide in the presence of ethylene glycol which would have trapped the hydroformylation product as an acetal.[7] However, in fact, ethylene glycol coordinated to the cobalt center to retard the reaction. For the purpose of efficient hydroformylation followed by a transformation into acetal, we focused on transacetalization reaction. The use of orthoformate [$HC(OEt)_3$] or acetal [$H_2C(OMe)_2$] in combination with acid catalyst such as $SnCl_2$ or PPTS (pyridinium *p*-toluenesulfonate) was shown to be effective for the in situ acetalization of a formyl group in the rhodium-catalyzed hydroformylation of olefins.[8] Here, we report the cobalt-catalyzed hydroformylation–acetalization of epoxides by using $HC(OMe)_3$. Dimethyl acetals of β-hydroxyaldehydes were obtained as a stable protected monomer form. In this system, acidic $HCo(CO)_4$, derived from $Co_2(CO)_8$ under the reaction condition, operated not only as formylation catalyst but also acetalization catalyst.



Scheme 1 Hydroformylation of epoxides and the accompanying side reactions

Hydroformylation of cyclohexene oxide (**1**) was carried out using $Co_2(CO)_8$ (2.5 mol%) in the presence of acetalization reagent in toluene at 90 °C for 21 hours. The use of $Me_2C(OMe)_2$ or $H_2C(OMe)_2$ (1 equiv to epoxide) as an acetalization reagent resulted in production of a mixture of the unprotected and protected hydroformylation products **2** and **3**. In contrast, when $HC(OMe)_3$ was employed, the product β-hydroxyaldehyde was efficiently converted to β-hydroxydimethylacetal **3** (13%) and its formate **4** (31%), which was probably given by transesterification of **3** with in situ generated methyl formate (Table 1, run 1).[9] Formation of only *trans* isomer demonstrates that ring-opening event proceeded with inversion at one of the chiral centers.[10] The increase of the amount of $HC(OMe)_3$ accelerated the reaction: the hydroformylation in $HC(OMe)_3$ (ca. 20 equiv to epoxide) instead of toluene

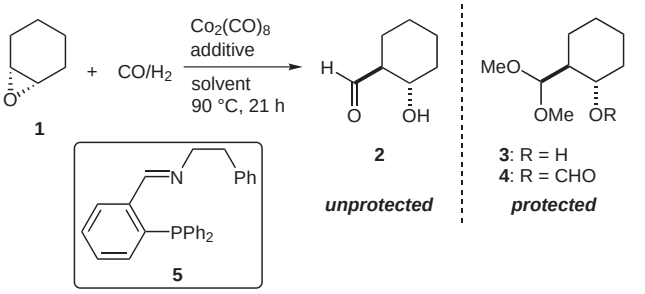
SYNLETT 2004, No. 8, pp 1367–1370
Advanced online publication: 04.06.2004
DOI: 10.1055/s-2004-825620; Art ID: Y00904ST

gave **3** and **4** in 48% and 27% yield, respectively.[12] Addition of phosphine and/or nitrogen-containing ligand also elevated the yield, and the highest yield of the hydroformylation–acetalization products were achieved by using iminophosphine ligand **5** (1 equiv to Co) to afford **3** (20%) and **4** (60%). The formate **4** can be transformed to **3** by treating the crude reaction mixture with methanol. Thus, cyclohexene oxide was converted to **3** in 70% isolated yield under the optimized hydroformylation–acetalization conditions [epoxide (5.0 mmol), CO/H_2 (80 atm), $Co_2(CO)_8$ (0.125 mmol) and **5**(0.25 mmol) in $HC(OMe)_3$ (10 mL) at 90 °C for 21 h].

To study the scope and limitation of this reaction, we investigated the reaction with various epoxides under the optimum conditions as shown in Table 2.[13] Cyclopentene oxide (**6a**) was efficiently converted to the *trans*-hydroxyl acetals, while the use of cyclooctene oxide or *trans*-4-octene oxide (**6b**) resulted in low conversion. When terminal epoxides were used, less hindered carbon was selectively carbonylated to give the linear product as the major isomer, which is the same as a cross-aldol product between acetaldehyde and another aldehyde. For example, the reaction with 1,2-epoxyoctene (**6c**) produced a mixture of linear- and branched-**7c** (linear/branched = 4.5) in 69% isolated yield. Functionalized terminal epoxides, epichlorohydrin (**6d**) and 1-benzyloxy-2,3-epoxypropane (**6e**), gave the corresponding acetals in 33% (**7d**) and 57% (**7e**) yield, respectively. It is noteworthy that neither branched-**7d** nor branched-**7e** was detected. An optically pure (*S*)-**6e** was converted to linear-(*R*)-**7e** in 52% yield with retention of the configuration.[14] This compound can be easily transformed into protected 3,4-dihydroxybutanal, which is known to react with *t*-butyl acetate enolate to give the standard intermediate for HMG-CoA reductase inhibitors.[15]

Our experiments indicate the nucleophilic attack of cobalt carbonyl anion to the epoxide activated by proton as shown in Scheme 2.[16] The preferable formation of linear

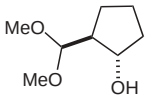
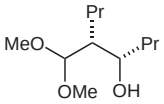
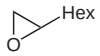
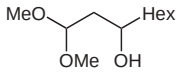
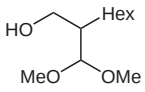
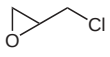
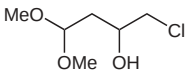
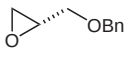
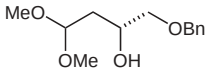
Table 1 Cobalt-Catalyzed Hydroformylation of Cyclohexene Oxide in the Presence of $HC(OMe)_3$[a]



Run	Solvent	Additive (mmol)		Yield (%)[b]	
				3	**4**
1	Toluene	$HC(OMe)_3$	(5)	13	31
2	$HC(OMe)_3$	–		48	27
3	$HC(OMe)_3$	**5**	(0.25)	20 (70)[c]	60

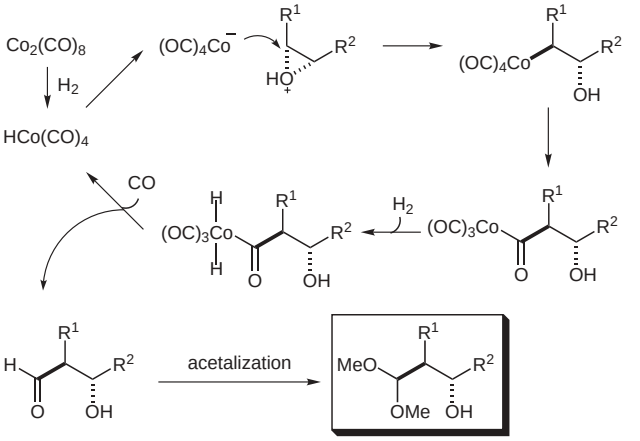
[a] Reaction condition: cyclohexene oxide (5.0 mmol), CO (40 atm), H_2 (40 atm), $Co_2(CO)_8$ (0.125 mmol) and a desirable amount of additive in toluene (5 mL) or $HC(OMe)_3$ (10 mL) at 90 °C for 21 h.
[b] GC yield.
[c] Isolated yield after treatment of the crude product with MeOH.

Table 2 Hydroformylation–Acetalization of Epoxides in $HC(OMe)_3$[a]

Run	Epoxide	Product		Yield (%)[b]
1	 **6a**	 **7a**		(74)
2	 **6b**	 **7b**		(13)
3	 **6c**	 *linear*-**7c**	 *branched*-**7c**	(69) l/b = 4.5
4	 **6d**	 *linear*-**7d**		(33)
5	 (*S*)-**6e**	 (*R*)-*linear*-**7e**		(52)

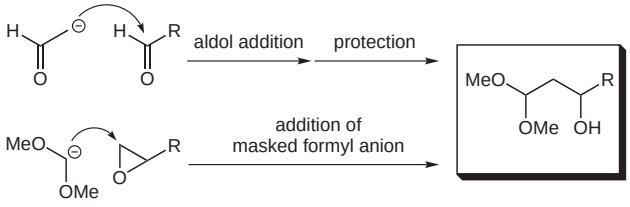
[a] Reaction condition: epoxide (5.0 mmol), CO/H_2 (80 atm), $Co_2(CO)_8$ (0.125 mmol) and **5** (0.25 mmol) in $HC(OMe)_3$ (10 mL) at 90 °C for 21 h.
[b] Isolated yield after treatment of the crude product with MeOH.

β-hydroxyacetals from terminal epoxides (**6c**, **6d**, **6e**) is a sign of susceptibility of the nucleophilic attack to the steric hindrance. This is consistent with the low reactivity of 1,2-disubsutituted internal epoxide such as cyclooctene oxide and *trans*-4-octene oxide (**6b**). The higher reactivity of cyclohexene oxide (**1**) and cyclopentene oxide (**6a**), in spite of their 1,2-disubstituted patterns, is probably due to their ring-strain for overcoming the steric hindrance. Production of *trans* isomer in the reaction of **1** and **6a** supports that the nucleophilic ring-opening is likely S_N2 mechanism rather than S_N1.



Scheme 2 A plausible catalytic cycle in the hydroformylation–acetalization of epoxide with $Co_2(CO)_8$

In conclusion, we established the cobalt-catalyzed hydroformylation of epoxides followed by in situ acetalization with $HC(OMe)_3$. A variety of internal and terminal epoxides was transformed into β-hydroxyaldehyde equivalents, useful for organic synthesis. Particularly, this process produces optically active β-hydroxyaldehyde from optically active terminal epoxides, which can be easily prepared by the asymmetric epoxidation of olefins,[17] or hydrolytic kinetic resolution of terminal epoxides.[18] From the viewpoint of the product structure, this reaction is a substitute to the aldol addition; and from the viewpoint of the reaction pathway, this reaction can be considered as a nucleophilic addition of a masked formyl anion to epoxide, providing a new variant of an umpolung of carbonyl function (Scheme 3).[19]



Scheme 3

Acknowledgment

One of the authors (K. N.) is grateful to The Asahi Glass Foundation for financial support.

References

(1) (a) Heathcock, C. H. In *Asymmetric Synthesis*, Part B, Vol. 3; Morrison, J. D., Ed.; Academic Press: New York, **1984**, Chap. 2. (b) Alcaide, B.; Almendros, P. *Eur. J. Org. Chem.* **2002**, 1595. (c) Machajewski, T. D.; Wong, C. H. *Angew. Chem. Int. Ed.* **2000**, *39*, 1352. (d) Denmark, S. E.; Stavenger, R. A. *Acc. Chem. Res.* **2000**, *33*, 432. (e) Nelson, S. G. *Tetrahedron: Asymmetry* **1998**, *9*, 357. (f) Shibasaki, M.; Sasai, H.; Arai, T.; Iida, T. *Pure Appl. Chem.* **1998**, *70*, 1027.

(2) Heathcock, C. H. In *Comprehensive Organic Synthesis*, Vol. 2; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: New York, **1991**, Chap. 1.5.

(3) (a) Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 6798. (b) Denmark, S. E.; Ghosh, S. K. *Angew. Chem. Int. Ed.* **2001**, *40*, 4759. (c) Han, Z.; Yorimitsu, H.; Shinokubo, K.; Oshima, K. *Tetrahedron Lett.* **2000**, *41*, 4415. (d) Mahrwald, R.; Costisella, B.; Gündogan, B. *Synthesis* **1998**, 262. (e) Heathcock, C. H.; Buse, C. T.; Kleschick, W. A.; Pirrung, M. C.; Sohn, J. E.; Lampe, J. *J. Org. Chem.* **1980**, *45*, 1066.

(4) (a) Powell, J. B.; Weider, P. R.; Knifton, J. F.; Allen, K. D.; Slaugh, L. H.; Arhancet, J. P. U.S. Patent 6,660,892, **2003**. (b) Lee, B. N.; Yang, D. J.; Byun, Y. H. U.S. Patent 6,348,611, **2002**. (c) Weber, R.; Englert, U.; Ganter, B.; Keim, W.; Möthrath, M. *Chem. Commun.* **2000**, 1419.

(5) Recent reports on carbonylation reaction of epoxides. Carbonylative ring expansion, see: (a) Schmidt, J. A. R.; Mahadevan, V.; Getzler, Y. D. Y. L.; Coates, G. W. *Org. Lett.* **2004**, *6*, 373. (b) Mahadevan, V.; Getzler, Y. D. Y. L.; Coates, G. W. *Angew. Chem. Int. Ed.* **2002**, *41*, 2781. (c) Lee, J. T.; Thomas, P. J.; Alper, H. J. *J. Org. Chem.* **2001**, *66*, 5424. (d) Hydroesterification, see: Hinterding, K.; Jacobsen, E. N. *J. Org. Chem.* **1999**, *64*, 2164. (e) Silylamidation, see: Goodman, S. N.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2002**, *41*, 4703. (f) Alternating copolymerization, see: Allmendinger, M.; Eberhardt, R.; Luinstra, G.; Rieger, B. *J. Am. Chem. Soc.* **2002**, *124*, 5646. (g) Takeuchi, D.; Sakaguchi, Y.; Osakada, K. *J. Polym. Sci., Part A: Polym. Chem.* **2002**, *40*, 4530.

(6) (a) Chatani, N.; Murai, S. *Synlett* **1996**, 414. (b) Fukumoto, Y.; Chatani, N.; Murai, S. *J. Org. Chem.* **1993**, *58*, 4187.

(7) Roos, L.; Goetz, R. W.; Orchin, M. *J. Org. Chem.* **1965**, *30*, 3203.

(8) (a) Fernández, E.; Castillón, S. *Tetrahedron Lett.* **1994**, *35*, 2361. (b) Stille, J. K.; Su, H.; Brechot, P.; Parrinello, G.; Hegedus, L. S. *Organometallics* **1991**, *10*, 1183. (c) Parrinello, G.; Stille, J. K. *J. Am. Chem. Soc.* **1987**, *109*, 7122.

(9) A typical procedure is as follows: A mixture of cyclohexene oxide (0.50 mL, 5.0 mmol), $Co_2(CO)_8$ (43 mg, 0.125 mmol) and **5** (98 mg, 0.25 mmol) in trimethyl orthoformate (10 mL) was placed in a 20 mL Schlenk tube and degassed by freeze-thaw cycles. Then, the solution was transferred into a 50 mL autoclave. After carbon monoxide (40 atm) and hydrogen (40 atm) were pressurized, the resulting mixture was stirred at 90 °C for 21 h. The reaction mixture was cooled down to the ambient temperature, and the carbon monoxide and hydrogen pressure were slowly released. The volatile materials were evaporated and the resulting crude residue was treated with MeOH (10 mL) under refluxing overnight. The solvent was removed off by evaporation, and then the residue was purified by silica gel chromatography (hexane–EtOAc = 10:1) to give **3** in 70% yield. ^1H NMR ($CDCl_3$): δ = 4.28 (d, *J* = 6.9 Hz, 1 H), 4.12 (s, 1 H), 3.53–3.46 (m, 1 H), 3.45 (s, 3 H), 3.35 (s, 3 H), 2.04–1.97 (m, 1 H), 1.79–1.61 (m, 4 H), 1.25–1.12 (m, 3 H), 1.05–0.96 (m, 1 H). ^{13}C NMR

($CDCl_3$): δ = 108.97, 71.22, 55.26, 52.32, 45.78, 34.24, 26.37, 24.99, 24.39. Anal. Calcd for $C_9H_{18}O_3$: C, 62.04; H, 10.41. Found: C, 61.86; H, 10.35.

(10) The configuration was assigned by comparing the ^{1}H NMR signals of the diol given by reduction of **3** (60% yield) with those reported.[11]

(11) Kakuchi, T.; Narumi, A.; Kaga, H.; Ishibashi, T.; Obata, M.; Yokota, K. *Macromolecules* **2000**, *33*, 3964.

(12) During the reaction, we observed more amount of gas absorption than the expected amount for the reaction with epoxide. This phenomenon is probably due to the reaction of $HC(OMe)_3$ with CO/H_2 to yield $CH_3CH(OMe)_2$, MeOH and HCO_2Me, see: Piacenti, F.; Cioni, C.; Pino, P. *Chem. Ind. (London)* **1960**, 1240.

(13) Spectral data for new compounds. Compound **7a**: ^{1}H NMR ($CDCl_3$): δ = 4.26 (d, *J* = 8.3 Hz, 1 H), 3.99–3.94 (m, 1 H), 3.42 (s, 3 H), 3.32 (s, 3 H), 2.68 (br s, 1 H), 2.10–2.03 (m, 1 H), 2.01–1.92 (m, 1 H), 1.88–1.81 (m, 1 H), 1.77–1.65 (m, 1 H), 1.63–1.53 (m, 1 H), 1.41–1.33 (m, 1 H). ^{13}C NMR ($CDCl_3$): δ = 108.02, 75.59, 54.83, 51.56, 49.26, 33.49, 25.56, 21.27. Anal. Calcd for $C_8H_{16}O_3$: C, 59.97; H, 10.07. Found: C, 60.11; H, 9.85. Compound **7b**: ^{1}H NMR ($CDCl_3$): δ = 4.33 (d, *J* = 5.5 Hz, 1 H), 3.89–3.82 (m, 1 H), 3.44 (s, 3 H), 3.37 (s, 3 H), 2.95 (d, *J* = 5.1 Hz, 1 H), 1.76–1.71 (m, 1 H), 1.59–1.50 (m, 1 H), 1.45–1.27 (m, 7 H), 0.97–0.90 (m, 6 H). ^{13}C NMR ($CDCl_3$): δ = 108.32, 70.51, 56.16, 53.88, 44.91, 35.78, 27.05, 21.46, 19.75, 14.44, 14.13. Anal. Calcd for $C_{11}H_{24}O_3$: C, 64.67; H, 11.84. Found: C, 64.63; H, 11.94. Compound linear-**7c**: ^{1}H NMR ($CDCl_3$): δ = 4.29 (d, *J* = 6.0 Hz, 1 H), 3.70–3.64 (m, 1 H), 3.61–3.56 (m, 1 H), 3.45 (s, 3 H), 3.37 (s, 3 H), 2.85 (dd, *J* = 7.8, 4.1 Hz, 1 H), 1.87–1.81 (m, 1 H), 1.42–1.20 (m, 10 H), 0.88 (t, *J* = 6.9 Hz, 3 H). ^{13}C NMR ($CDCl_3$): δ = 108.89, 62.62, 55.85, 53.48, 42.73, 31.72, 29.56, 27.06, 26.61, 22.60, 14.05. Anal. Calcd for $C_{11}H_{24}O_3$: C, 64.67; H, 11.84. Found: C, 64.56; H, 11.92. Compound linear-**7d**: ^{1}H NMR ($CDCl_3$): δ = 4.61 (t, *J* = 5.5 Hz, 1 H), 4.05–3.99 (m, 1 H), 3.55 (qd, $J_{H\text{-}Cl}$ = 11 Hz, $J_{H\text{-}H}$ = 6.0 Hz, 2 H), 3.39 (s, 3 H), 3.38 (s, 3 H), 3.07 (br s, 1 H), 1.93–1.84 (m, 2 H). ^{13}C NMR ($CDCl_3$): δ = 103.16, 68.33, 53.87, 53.43, 49.34, 36.72. Anal. Calcd for $C_6H_{13}O_3Cl$: C, 42.74; H, 7.77. Found: C, 42.56; H, 7.88. Compound linear-**7e**: ^{1}H NMR ($CDCl_3$): δ = 7.37–7.27 (m, 5 H), 4.60 (t, *J* = 5.5 Hz, 1 H), 4.56 (s, 2 H), 4.02–3.95 (m, 1 H), 3.49–3.46 (m, 1 H), 3.43–3.40 (m, 1 H), 3.36 (s, 3 H), 3.36 (s, 3 H), 2.87 (s, 1 H), 1.81–1.78 (m, 2 H). ^{13}C NMR ($CDCl_3$): δ = 138.00, 128.41, 127.70, 103.17, 74.09, 73.32, 67.33, 53.51, 53.32, 36.23. Anal. Calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 64.80; H, 8.35. $[\alpha]_D^{26}$ for linear-(*R*)-**7e** = 1.7° (*c* 3.0, $CHCl_3$).

(14) No racemization was confirmed by HPLC analysis (DAICEL CHIRALCEL OD-H, Hexane–*i*-PrOH = 95:5). The absolute configuration was determined based on the optical rotation of 2-hydroxy-1,4-butanediol which was prepared from linear-(*R*)-**7e** in 4 steps.

(15) Rosen, T.; Heathcock, C. H. *Tetrahedron* **1986**, *42*, 4909.

(16) Heck, R. F. *J. Am. Chem. Soc.* **1963**, *85*, 1460.

(17) (a) Johnson, R. A.; Sharpless, K. B. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley: New York, **2000**, Chap. 6A. (b) Katsuki, T. In *Comprehensive Asymmetric Catalysis*, Vol. II; Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H., Eds.; Springer: New York, **1999**, Chap. 18.1.

(18) (a) Schaus, S. E.; Brandes, B. D.; Larrow, J. F.; Tokunaga, M.; Hansen, K. B.; Gould, A. E.; Furrow, M. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 1307. (b) Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, *277*, 936.

(19) (a) Stork, G.; Ozorio, A. A.; Leong, Y. W. *Tetrahedron Lett.* **1978**, *52*, 5175. (b) Possel, O.; van Leusen, A. M. *Tetrahedron Lett.* **1977**, *18*, 4229.