Organic LETTERS

Letter

pubs.acs.org/OrgLett

# Highly Diastereoselective Preparation of Aldol Products Using New Functionalized Allylic Aluminum Reagents

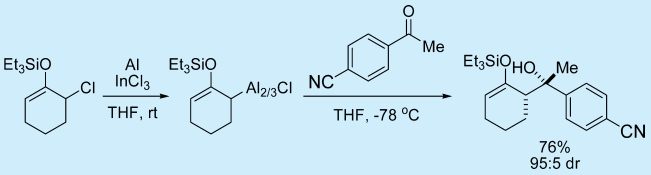
Zhi-Liang Shen,[†] Zhihua Peng,[†] Chun-Ming Yang,[†] Julian Helberg,[†] Peter Mayer,[†] Ilan Marek,[‡] and Paul Knochel*,[†]

[†]Department Chemie, Ludwig-Maximilians-Universität München, Butenandtstr. 5-13, 81377 München, Germany

[‡]The Mallat Family Laboratory of Organic Chemistry, Schulich Faculty of Chemistry and Lise Meitner-Minerva Center for Computational Quantum Chemistry, Technion-Israel Institute of Technology, Technion City, Haifa 32000, Israel

Supporting Information

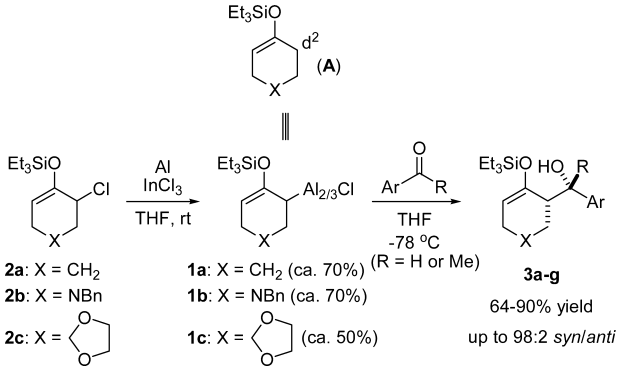
**ABSTRACT:** Chloro-substituted triethylsilyl enol ethers derived from cyclohexanone and related ketones are converted with aluminum powder in the presence of indium trichloride to functionalized allylic aluminum reagents which represent a new type of synthetic equivalent of metal enolates. These allylic organometallics undergo highly diastereoselective additions to aldehydes and methyl aryl ketones, giving aldol products with a $\beta$-quaternary center.




The aldol functional unit has a central position in organic chemistry since this structural unit is found in numerous natural products.[1] Substituted aldol derivatives bearing quaternary centers are sensitive organic molecules due to retro-aldol decomposition pathways.

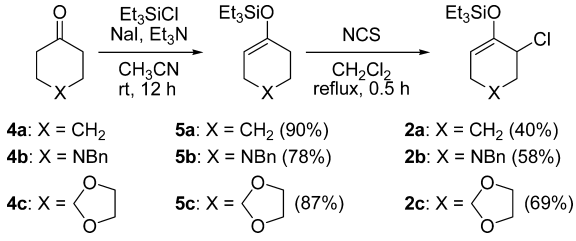
Extensive research efforts have been made to prepare such molecules in a stereoselective manner.[2] Aluminum organometallic chemistry has received in recent years renewed attention.[3] Recently, we have shown that functionalized allylic aluminum reagents bearing electron-attracting groups in position 2 such as a cyano or an ester group undergo highly diastereoselective additions to aldehydes and aryl methyl ketones.[4−6] Herein, we report the preparation of new functionalized allylic aluminum reagents of type **1** bearing a triethylsilyloxy substituent in position 2 and their diastereoselective additions to carbonyl derivatives (Scheme 1). These organometallic reagents were readily prepared from the corresponding allylic chloride of type **2** and represent a new type of d[2] enolate synthetic equivalents (**A**).[7] They underwent highly diastereoselective additions to aldehydes or ketones, leading in the last case to aldol products of type **3** bearing a $\beta$-quaternary carbon center.[8]

**Scheme 1. Preparation of Allylic Aluminum Reagents 1a−c and Their Additions to Aldehydes and Methyl Ketones**




The required chlorotriethylsilyl enol ethers **2a−c** were prepared in two steps from the corresponding ketones **4a−c** (Scheme 2). In the first step, the triethylsilyl enol ethers **5a−c** were obtained by the reaction of $Et_3SiCl$ (1.2 equiv), NaI (1.2 equiv), and $Et_3N$ (1.2 equiv) in $CH_3CN$ (25 °C, 12 h) with the corresponding ketones **4a−c** in 78−90% yields.[9] The allylic chlorination of **5a−c** proceeds best using NCS (1.0 equiv) in $CH_2Cl_2$ (reflux, 0.5 h), leading to the allylic chlorides **2a−c** in 40−69% yields.[10] These allylic chlorides can be stored at −70 °C for several months without decomposition. Using aluminum powder (3 equiv) in the presence of 5 mol % of $InCl_3$[11] in THF according to the method of Takai, the silyl enol ethers **2a−c** were converted into the corresponding allylic aluminum

**Scheme 2. Preparation of Allylic Chlorides 2a−c Bearing Silyl Enol Ether Functional Unit**




**Received:** December 20, 2013
**Published:** January 30, 2014

 © 2014 American Chemical Society  dx.doi.org/10.1021/ol403692k | Org. Lett. 2014, 16, 956−959

reagents **1** in ca. 70% yield for **1a**,**b** and ca. 50% yield for **1c** as determined by GC analysis of hydrolyzed reaction aliquots (Scheme 1).

The treatment of various aldehydes and methyl ketones (0.5 equiv) with these allylic aluminum reagents **1a**–**c** at −78 °C produced the expected aldol adducts of type **3** in 64–90% yields and high diastereoselectivities in favor of the *syn* diastereomer (Table 1).[12] The stereochemistry of products **3**

**Table 1. Diastereoselective Preparation of Homoallylic Alcohols 3 Using Allylic Aluminum Reagents 1a–c**

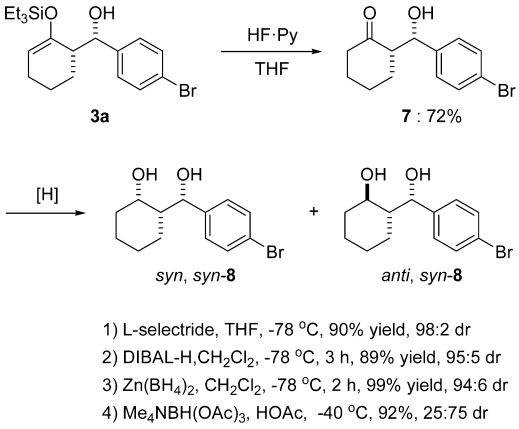
| entry | aluminum reagent[a] | carbonyl electrophile[b] | product[c,d] |
|---|---|---|---|
| 1 | **1a** | **6a** | **3a**: 85%; 95:5 |
| 2 | **1a** | **6b** | **3b**: 90%; 92:8 |
| 3 | **1a** | **6c** | **3c**: 76%; 95:5 |
| 4 | **1a** | **6d** | **3d**: 79%; 98:2 |
| 5 | **1b** | **6e** | **3e**: 69%; 95:5 |
| 6 | **1b** | **6f** | **3f**: 72%; 96:4 |
| 7 | **1c** | **6g** | **3g**: 64%; 95:5 |

[a]All reactions were carried out on a 2 mmol scale. [b]With 0.5 equiv of electrophiles. [c]Yield of isolated, analytically pure product. [d]Diastereoselectivities were determined by $^1$H NMR spectroscopy.

was established by treating the aldol product **3a** with HF·Py in THF (−20 to 0 °C, 2 h). This afforded the *β*-hydroxy ketone **7** in 72% yield as only one diastereoisomer (Scheme 3). Comparison of the $^1$H and $^{13}$C NMR data of ketone **7** with the literature indicated that the diastereomer produced was the *syn* isomer.[13] The *syn* selectivity of the addition reaction can be rationalized by the proposed transition state shown in Figure 1.[14]

The diastereoselective reduction of aldol product **7** was examined in some detail (Scheme 3), and the use of L-selectride[15] (THF, −78 °C) provided *syn*,*syn*-1,3-diol **8** as major diastereomer (90% yield, dr = 98:2) with three contiguous chiral centers. Also, the use of DIBAL-H[16] and

**Scheme 3. Conversion of Alcohol 3a to *β*-Hydroxy Ketone 7 by Desilylation and Diastereoselective Preparation of 1,3-Diol 8 Bearing Three Contiguous Stereogenic Centers Starting from *β*-Hydroxy Ketone 7**



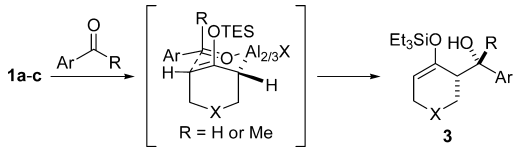




**Figure 1.** Proposed transition state for the diastereoselective additions of **1a**–**c** to aldehydes and methyl ketones.

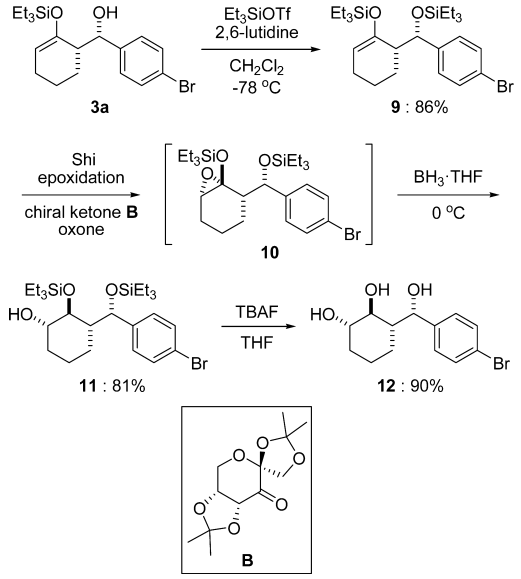
$Zn(BH_4)_2$[17] as reducing agents gave satisfactory diastereoselectivities via chelation control. Interestingly, the opposite diastereomer *anti*,*syn*-1,3-diol **8** was predominantly obtained by using $Me_4NBH(OAc)_3$[18] as reductive reagent. The stereochemistry of the two diastereomers of product **8** was determined by comparison with the already reported NMR data of similar 1,3-diol compounds.[19]

To functionalize the alcohols of type **3** further, we have used the method developed by Myers involving a Shi epoxidation of the silyl enol ether followed by a reductive opening of the epoxide by $BH_3$·THF,[20] as shown in Scheme 4. Protection of the alcohol **3a** with $Et_3SiOTf$ resulted in the formation of disilyl compound **9** (86% yield).[21] A subsequent Shi epoxidation of **9** with oxone in the presence of chiral ketone **B**[22] produced the intermediate epoxide **10**, which was in situ opened with $BH_3$·THF according to Myers' procedure, leading to the selectively protected triol **11** in 81% yield. The use of cyclohexanone as a catalyst instead of Shi's chiral ketone **B** produced the same product **11** but in 66–70% yield. After desilylation of product **11** with TBAF, triol **12** with four contiguous chiral centers was formed in 90% yield. The stereochemistry of triol **12** was ambiguously determined by X-ray diffraction analysis. This further confirmed the stereochemistry of the previous aldol product **3a** as being the *syn* diastereomer (Figure 2). By applying the same sequence to the lactone **3d** obtained previously (Table 1, entry 4), we have prepared the selectively protected disilyloxy lactone **13** bearing four contiguous stereogenic centers in 68% yield as a single diastereomer (Scheme 5).

In summary, we have reported a new approach to aldol products bearing a *β*-quaternary center with high diastereoselectivities using novel functionalized allylic aluminum reagents bearing a silyloxy substituent in position 2. Extension of this reaction is currently underway in our laboratory.


dx.doi.org/10.1021/ol403692k | *Org. Lett.* 2014, 16, 956–959

**Scheme 4. Diastereoselective Preparation of Triol 12 with Four Contiguous Chiral Centers Starting from Aldol Product 3a**



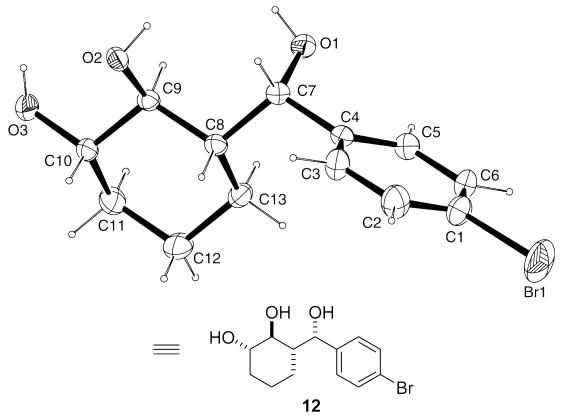
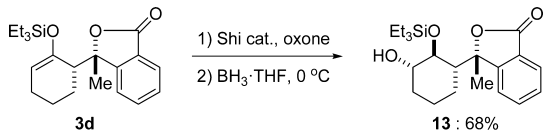




**Figure 2.** X-ray crystal structure of triol **12**.

**Scheme 5. Preparation of Lactone 13 with Four Contiguous Chiral Centers Starting from Aldol Product 3d**




## ■ ASSOCIATED CONTENT

### Supporting Information

Experimental procedures, characterization data of products, and copies of $^{1}H$ and $^{13}C$ NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

## ■ AUTHOR INFORMATION

### Corresponding Author

*E-mail: paul.knochel@cup.uni-muenchen.de.

### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

We thank the German–Israel Project Cooperation (DIP) for financial support. We also thank BASF SE (Ludwigshafen), W.C. Heraeus GmbH (Hanau), and Rockwood Lithium GmbH (Höchst) for the gift of chemicals.

## ■ REFERENCES

(1) *Modern Aldol Reactions*; Mahrwald, R., Ed.; Wiley-VCH: Weinheim, Germany, 2004.

(2) For selected examples, see: (a) List, B.; Lerner, R. A.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2000**, *122*, 2395–2396. (b) Notz, W.; List, B. *J. Am. Chem. Soc.* **2000**, *122*, 7386–7387. (c) Mase, N.; Tanaka, F.; Barbas, C. F., III. *Angew. Chem., Int. Ed.* **2004**, *43*, 2420–2423. (d) Hayashi, Y.; Sumiya, T.; Takahashi, J.; Gotoh, H.; Urushima, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 958–961. (e) Denmark, S. E.; Wilson, T. W.; Burk, M. T.; Heemstra, J. R., Jr. *J. Am. Chem. Soc.* **2007**, *129*, 14864–14865. (f) Huddleston, R. R.; Cauble, D. F.; Krische, M. J. *J. Org. Chem.* **2003**, *68*, 11–14. (g) Das, J. P.; Chechik, H.; Marek, I. *Nat. Chem.* **2009**, *1*, 128–132. (h) Minko, Y.; Pasco, M.; Lercher, L.; Botoshansky, M.; Marek, I. *Nature* **2012**, *490*, 522–526. (i) Simaan, S.; Marek, I. *J. Am. Chem. Soc.* **2010**, *132*, 4066–4067. (j) Sklute, G.; Marek, I. *J. Am. Chem. Soc.* **2006**, *128*, 4642–4649. (k) Zheng, C.; Wu, Y.; Wang, X.; Zhao, G. *Adv. Synth. Catal* **2008**, *350*, 2690–2694 and references cited therein.

(3) For reviews, see: (a) *Modern Organoaluminum Reagents: Preparation, Structure, Reactivity and Use*; Woodward, S., Dagorne, S., Eds.; Springer-Verlag: Berlin, 2013. For recent examples, see: (b) Jackowski, O.; Lecourt, T.; Micouin, L. *Org. Lett.* **2011**, *13*, 5664–5667. (c) Zhou, Y.; Lecourt, T.; Micouin, L. *Angew. Chem., Int. Ed.* **2010**, *49*, 2607–2610. (d) Palais, L.; Bournaud, C.; Micouin, L.; Alexakis, A. *Chem.—Eur. J.* **2010**, *16*, 2567–2573. (e) Ooi, T.; Ohmatsu, K.; Maruoka, K. *J. Am. Chem. Soc.* **2007**, *129*, 2410–2411. (f) Hashimoto, T.; Naganawa, Y.; Maruoka, K. *J. Am. Chem. Soc.* **2011**, *133*, 8834–8837. (g) Welker, M.; Woodward, S.; Alexakis, A. *Org. Lett.* **2010**, *12*, 576–579. (h) Bleschke, C.; Tissot, M.; Müller, D.; Alexakis, A. *Org. Lett.* **2013**, *15*, 2152–2155. (i) Hawner, C.; Li, K.; Cirriez, V.; Alexakis, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 8211–8214. (j) Gremaud, L.; Alexakis, A. *Angew. Chem., Int. Ed.* **2012**, *51*, 794–797. (k) Mata, Y.; Diéguez, M.; Pàmies, O.; Woodward, S. *J. Org. Chem.* **2006**, *71*, 8159–8165. (l) Hawner, C.; Müller, D.; Gremaud, L.; Felouat, A.; Woodward, S.; Alexakis, A. *Angew. Chem., Int. Ed.* **2010**, *49*, 7769–7772. (m) Kolb, A.; Hirner, S.; Harms, K.; von Zezschwitz, P. *Org. Lett.* **2012**, *14*, 1978–1981. (n) Shojaei, H.; Li-Böhmer, Z.; von Zezschwitz, P. *J. Org. Chem.* **2007**, *72*, 5091–5097. (o) Siewert, J.; Sandmann, R.; von Zezschwitz, P. *Angew. Chem., Int. Ed.* **2007**, *46*, 7122–7124. (p) Raluy, E.; Diéguez, M.; Pàmies, O. *Tetrahedron Lett.* **2009**, *50*, 4495–4497.

(4) Peng, Z.; Blümke, T. D.; Mayer, P.; Knochel, P. *Angew. Chem., Int. Ed.* **2010**, *49*, 8516–8519.

(5) For the preparation of analogous allylic zinc reagents, see: Ren, H.; Dunet, G.; Mayer, P.; Knochel, P. *J. Am. Chem. Soc.* **2012**, *134*, 613–622.

(6) For the preparations of other organoaluminum reagents through aluminum insertion, see: (a) Blümke, T. D.; Chen, Y.-H.; Peng, Z.; Knochel, P. *Nat. Chem.* **2010**, *2*, 313–318. (b) Guo, L.-N.; Gao, H.; Mayer, P.; Knochel, P. *Chem.—Eur. J.* **2010**, *16*, 9829–9834. (c) Blümke, T. D.; Groll, K.; Karaghiosoff, K.; Knochel, P. *Org. Lett.* **2011**, *13*, 6440–6443. (d) Blümke, T. D.; Klatt, T.; Koszinowski, K.; Knochel, P. *Angew. Chem., Int. Ed.* **2012**, *51*, 9926–9930.

(7) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 239–336.

(8) For reviews on the construction of quaternary carbon centers, see: (a) Fuji, K. *Chem. Rev.* **1993**, *93*, 2037–2066. (b) Trost, B. M.; Jiang, C. *Synthesis* **2006**, 369–396. (c) Christoffers, J.; Baro, A. *Adv. Synth. Catal.* **2005**, *347*, 1473–1482. (d) *Quaternary Stereocenters: Challenges and Solutions for Organic Synthesis*; Christoffers, J., Baro, A., Eds. Wiley-VCH: Weinheim, Germany, 2005. (e) Douglas, C. J.; Overman, L. E. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5363–5367. (f) Peterson, E. A.; Overman, L. E. *Proc. Natl. Acad. Sci. U.S.A.* **2004**,

*101*, 11943−11948. (g) Das, J. P.; Marek, I. *Chem. Commun.* **2011**, *47*, 4593−4623. (h) Wang, B.; Tu, Y. Q. *Acc. Chem. Res.* **2011**, *44*, 1207−1222.

(9) (a) Saraber, F. C. E.; Dratch, S.; Bosselaar, G.; Jansen, B. J. M.; de Groot, A. *Tetrahedron* **2006**, *62*, 1717−1725. (b) Hong, A. Y.; Krout, M. R.; Jensen, T.; Bennett, N. B.; Harned, A. M.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2011**, *50*, 2756−2760. (c) Cui, L.-Q.; Liu, K.; Zhang, C. *Org. Biomol. Chem.* **2011**, *9*, 2258−2265. (d) Huang, L.; Zhang, X.; Zhang, Y. *Org. Lett.* **2009**, *11*, 3730−3733.

(10) Hambly, G. F.; Chan, T. H. *Tetrahedron Lett.* **1986**, *27*, 2563−2566. It should be noted that 20 and 5% regioisomers were obtained for allylic chlorides **2a** and **2c**, respectively (see the Supporting Information for detail). In addition, the TMS enol ethers were not suited for the chlorination step and the subsequent reactions due to relative instability. Also for the TBS enol ethers, low yields of chlorinated products were obtained. Furthermore, the synthesis of unsymmetrical allylic chlorides is complicated and is currently studied in our laboratories.

(11) Takai, K.; Ikawa, Y. *Org. Lett.* **2002**, *4*, 1727−1729.

(12) By using aliphatic aldehydes such as isobutylaldehyde, we have observed a *syn*/*anti* diastereoselectivity of 90:10. Although the yield was acceptable (ca. 72%), the product could not be obtained in a pure form.

(13) Yanagisawa, A.; Asakawa, K.; Yamamoto, H. *Chirality* **2000**, *12*, 421−424.

(14) (a) Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 1920. (b) Heathcock, C. H. *Science* **1981**, *214*, 395.

(15) (a) Brown, H. C.; Krishnamurthy, S. *J. Am. Chem. Soc.* **1972**, *94*, 7159−7161. (b) Krishnamurthy, S.; Brown, H. C. *J. Am. Chem. Soc.* **1976**, *98*, 3383−3384. (c) Chun, J.; Byun, H.-S.; Arthur, G.; Bittman, R. *J. Org. Chem.* **2003**, *68*, 355−359.

(16) (a) Kiyooka, S.-i.; Kuroda, H.; Shimasaki, Y. *Tetrahedron Lett.* **1986**, *27*, 3009−3012. (b) Evans, D. A.; Starr, J. T. *J. Am. Chem. Soc.* **2003**, *125*, 13531−13540.

(17) (a) Narasimhan, S.; Balakumar, R. *Aldrichimica Acta* **1998**, *31*, 19−27. (b) Hoyveda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307−1370. (c) Evans, D. A.; Kim, A. S.; Metternich, R.; Novack, V. J. *J. Am. Chem. Soc.* **1998**, *120*, 5921−5942. (d) Dakin, L. A.; Panek, J. S. *Org. Lett.* **2003**, *5*, 3995−3998.

(18) (a) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560−3578. (b) Paterson, I.; Delgado, O.; Florence, G. J.; Lyothier, I.; O'Brien, M.; Scott, J. P.; Sereinig, N. *J. Org. Chem.* **2005**, *70*, 150−160.

(19) (a) Acetti, D.; Brenna, E.; Fuganti, C.; Gatti, F. G.; Serra, S. *Eur. J. Org. Chem.* **2010**, 142−151. (b) Thompson, S. H. J.; Mahon, M. F.; Molloy, K. C.; Hadley, M. S.; Gallagher, T. *J. Chem. Soc., Perkin Trans. 1* **1995**, 379−383.

(20) Lim, S. M.; Hill, N.; Myers, A. G. *J. Am. Chem. Soc.* **2009**, *131*, 5763−5765.

(21) (a) Corey, E. J.; Cho, H.; Rücker, C.; Hua, D. H. *Tetrahedron Lett.* **1981**, *22*, 3455−3458. (b) Paterson, I.; Norcross, R. D.; Ward, R. A.; Romea, P.; Lister, M. A. *J. Am. Chem. Soc.* **1994**, *116*, 11287−11314. (c) Lister, T.; Perkins, M. V. *Org. Lett.* **2006**, *8*, 1827−1830.

(22) For a review on organocatalytic asymmetric epoxidation of olefins by chiral ketones, see: Shi, Y. *Acc. Chem. Res.* **2004**, *37*, 488−496.