Pergamon

Tetrahedron 57 (2001) 2485–2489

TETRAHEDRON

A catalytic enantioselective route to *cis*- and *trans*-3,4,4,5-tetrasubstituted cyclohexanones; remarkable chiral catalyst control in sequential catalytic 1,4-additions to cyclohexadienones

Rosalinde Imbos, Adriaan J. Minnaard and Ben L. Feringa*

Department of Organic and Molecular Inorganic Chemistry, Stratingh Institute, University of Groningen, Nijenborgh 4, 9747 AG Groningen, The Netherlands

Dedicated to Professor H. Kagan

Received 31 May 2000; revised 1 August 2000; accepted 3 August 2000

Abstract—Asymmetric copper-phosphoramidite catalysed conjugate addition of Et_2Zn to easily accessible, nearly enantiomerically pure cyclohexenones **2** and **4** was performed. Depending on the enantiomer of the chiral phosphoramidite used, the *cis*- or *trans*-3,4,4,5-tetrasubstituted cyclohexanones **5** and **6** could be formed selectively. Surprisingly, there is no directing effect of the 5-ethyl- or 4-alkoxy-substituents and the stereochemical outcome is only governed by the configuration of the chiral ligand. © 2001 Published by Elsevier Science Ltd.

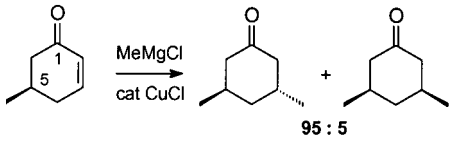
1. Introduction

Optically active multi-substituted cyclic alkanones are attractive chiral building blocks, as they contain structural features prominent in several classes of natural compounds.[1] These chiral cycloalkanones are generally synthesised from enantiomerically pure cycloalkenones, which in turn are usually obtained by either a classical or an enzymatic resolution[2] or multistep synthetic routes from chiral building blocks.[3] Formation of multiple stereocenters, by conjugate addition of organometallic reagents to chiral cyclic enones, is governed by kinetic control,[4] which has stereochemical consequences, i.e. products are mostly *trans*-disubstituted.[5]

As was already discovered in the 1960's, the conjugate addition of MeMgCl to (racemic) 5-methyl-2-cyclohexenone affords a mixture of two diastereomeric products in a *trans*/*cis* ratio of 95:5 (Scheme 1).[6] The diastereoselectivity has been explained not only in terms of steric hindrance but also in terms of difference in the energy of the transition state.[6]

For 3,5-disubstituted cyclohexanones the *trans*-product is higher in energy (one of the substituents is always axial) than the *cis* (all-equatorial), but nonetheless almost exclusively the *trans* product is formed.[7]

The stereochemistry of the conjugate addition of organocuprates to cyclic substituted enones has been studied intensively[8] and a possible transition state involving trihapto (d-π_3^*) coordination[9] has been proposed (Fig. 1). In the transition state leading to the *cis*-product an unfavourable interaction between the R and Me substituents takes place, resulting in predominant formation of the *trans*-adduct.



Scheme 1.

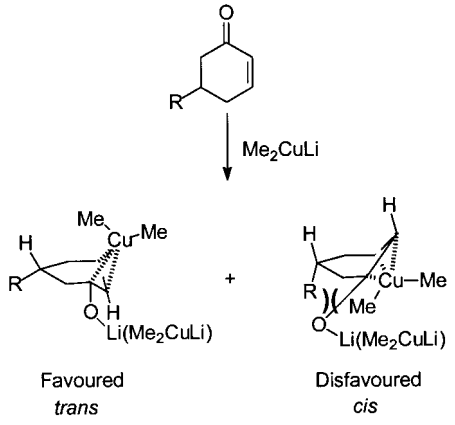
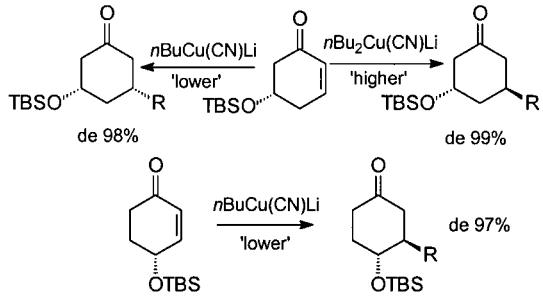


Figure 1.

Keywords: conjugate addition; phosphoramidites; chiral cyclohexanones; asymmetric catalysis.

* Corresponding author. Tel.: +31-50-3634278; fax: +31-50-3634296; e-mail: feringa@chem.rug.nl

0040–4020/01/$ - see front matter © 2001 Published by Elsevier Science Ltd.
PII: S0040-4020(01)00071-0

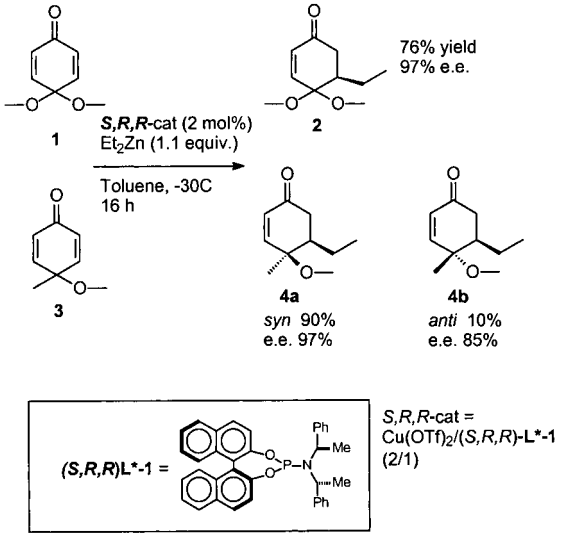


Scheme 2.

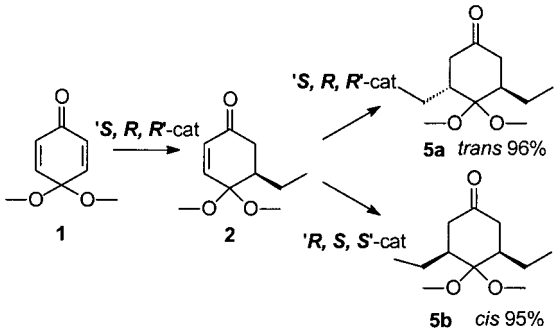
Recently, Sato et al. reported on the conjugate addition of cuprates to 5-(*tert*-butyldimethylsiloxy)-2-cyclohexenone (5-(TBSO)-2-cyclohexenone).[10] Conjugate addition of a higher order cyanocuprate yields the *trans*-product, whereas conjugate addition of a lower order cuprate affords the *cis*-product in a d.e. of 99% (Scheme 2). The unexpected *cis*-selectivity is proposed to be due to the ability of the alkoxy-moiety to coordinate to the lower-order cuprate. However, conjugate addition of a lower order cuprate to 4-TBSO-2-cyclohexenone afforded the *trans*-product in 97%, indicating that the selectivity is also highly dependent on the position of the alkoxy group on the cyclohexenone ring.

To the best of our knowledge, until now the work on conjugate additions to 5-substituted cyclohexenones to yield 3,5-disubstituted cyclohexanones has focussed on stoichiometric chemistry using various organometallic reagents. The challenge for us was to develop a catalytic version of these reactions and to obtain stereocontrol exclusively via the use of a chiral catalyst. In this way, possibly the *cis* and *trans* diastereoisomers can selectively be formed, simply by choosing the appropriate catalyst.

Recently, we developed a highly efficient catalytic route to enantiomerically pure cyclohexenones,[11] using the Cu-phosphoramidite catalysed asymmetric conjugate addition of dialkylzinc reagents to cyclohexadienones. For instance, 3-ethyl-4,4-dimethoxycyclohexenone **2** is obtained in 76%



Scheme 3.



Scheme 4.

yield and with an e.e. of 97%, using only 2 mol% of chiral catalyst and 1.1 equiv. of diethylzinc (Scheme 3). 3-Ethyl-4-methoxy-4-methylcyclohexenone **4** is formed as a *syn*/*anti* (90/10) mixture of both diastereoisomers, where the 3-ethyl group in the major isomer is *syn* to the alkoxy moiety. The excellent *syn*-selectivity was subscribed to a coordinating effect of the MeO-moiety. The *syn*-diastereoisomer can be obtained, after column chromatography, in 55% yield and with an e.e. of 97%.

Cyclohexenones **2** and **4** can be subjected to a second conjugate addition, using the same conditions as depicted in Scheme 3. In contrast to the planar and rigid cyclohexadienones the conjugate addition products (cyclohexenones) are flexible and are therefore expected to show different reactivity and selectivity in the second copper-phosphoramidite catalysed asymmetric 1,4-addition of Et_2Zn.

The key question was: is the stereochemistry of the second addition influenced by the presence of the asymmetric centre in the cyclohexenone or is it controlled by the chiral catalyst?[12] The results of these experiments might give us valuable information on the behaviour of the chiral phosphoramidite catalyst and the mechanism involved in our copper-catalysed conjugate additions.

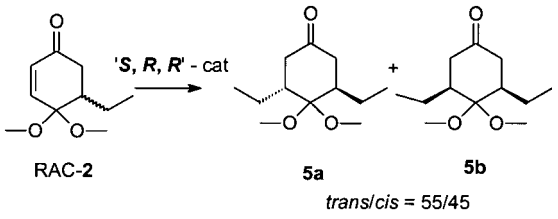
Furthermore, it is important to know whether the *cis*- and *trans*-disubstituted products can be formed selectively.

2. Results and discussion

2.1. Conjugate addition to ethyl-cyclohexenone-acetal 2

Conjugate addition of Et_2Zn to 4,4-dimethoxycyclohexadienone **1** using the in situ prepared catalyst from $Cu(OTf)_2$ and the (*S*,*R*,*R*) enantiomer of L*-**1** (1:2 ratio, 2 mol%) yielded the product **2** in 97% e.e. and 76% yield (Scheme 3). After work-up and purification, a second conjugate addition of Et_2Zn using the same enantiomer of the catalyst gave the 3,5-disubstituted cyclohexanone **5** in a *trans*/*cis* ratio of 96:4 in 77% isolated yield, which is in accordance with expectation (Scheme 4).[†] Using the same enantiomer of **2** as substrate and using *the enantiomer* of

[†] Unfortunately, we were not able to determine the e.e's of the diadducts. However, it may be deduced from the enantioselectivity in the first step that *trans*-**5a** will have an e.e. of 97% (*cis* is meso).



Scheme 5.

L*-**1** (e.g. *R*,*S*,*S*), the products were formed in a *trans*/*cis* ratio of 5:95 (yield 72%).

These results show that the chirality of the catalyst nearly completely governs the stereochemical outcome of the reaction and that there is apparently *no interaction* of the catalytically active species with the 5-substituent of the optically active cyclohexenone **2** (a 1,3-diaxial effect plays no significant role).

This leads to the pleasant feature that the optically active *trans*- and meso *cis*-di-adducts **5a** and **5b** can be made with high selectivity and independently, simply by changing the chirality of the ligand in the second conjugate addition step.

Conjugate addition of Et_2Zn on racemic 5-ethyl-4,4-dimethoxycyclohexenone using the (*S*,*R*,*R*)-enantiomer of the catalyst afforded the product in a *cis*/*trans* ratio of 55:45 (Scheme 5) which is nearly the expected 1:1 ratio. This provides additional support for the notion that the stereocontrol is mainly governed by the chirality of the catalyst and that the stereogenic centre already present plays only a minor role.

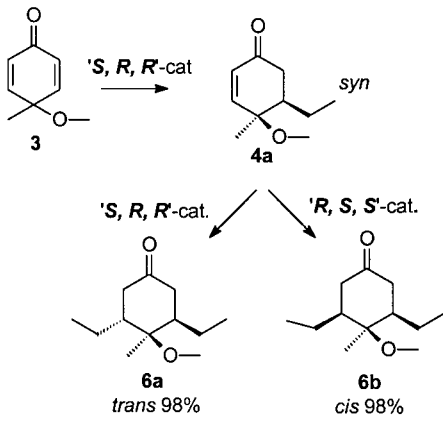
2.2. Conjugate addition to ethyl-cyclohexenone ether 4

We have shown that the copper-L*-**1** (*S*,*R*,*R*) catalysed conjugate addition of diethylzinc to 4-methoxy-4-methyl-cyclohexadienone **3** proceeds with a diastereomeric ratio of 90/10, where the major isomer is the *syn*-product **4**.[‡,11a] (Scheme 3) The e.e. of the major isomer was 97%. The diastereoselectivity was attributed to the *syn*-directing effect of the alkoxy moiety.[13]

Like **2**, mono-adduct **4** still contains an enone functionality and therefore may also be subjected to a second conjugate addition, resulting in cyclohexanones with 3 consecutive stereocenters. The question that arises in this case is: does the alkoxy-moiety have a directing effect in the second conjugate addition of diethylzinc or is it possible to synthesise the *trans*- and *cis*-adducts **6a** and **6b** selectively and independently?

In order to perform these reactions and examine the stereoselectivity in the second catalytic 1,4-addition the *syn*-mono-adduct **4a** was separated from its diastereoisomer by column chromatography and the single diastereoisomer (100% *syn*) **4a** was used as a starting material for the following experiments.

A conjugate addition of Et_2Zn to **4a** using the enantiomer of



Scheme 6.

L*-**1**, (i.e. *R*,*S*,*S*) afforded the *cis*-diadduct **6b** with >98% selectivity, as was expected. However, the conjugate addition using the *S*,*R*,*R* enantiomer of L*-**1** afforded the *trans*-diadduct **6a** selectively (98% *trans*, 2% *cis*)[†] (Scheme 6).

This means that in the second conjugate addition there is *no directing effect* of the alkoxy moiety or the ethyl group at the stereocenter at C-5. Again the stereocontrol in the second addition is governed by the chirality of the catalyst and the stereocenter already present in **4** as well as the alkoxy-substituent plays a negligible role. Therefore, both the *cis*- and *trans*-diadduct can be selectively made, depending on the enantiomer of the chiral ligand used.

2.3. Conjugate addition using a racemic ligand

To further test the hypothesis that the stereoselectivity in the conjugate addition depends only on the nature of the chiral catalyst and not on the stereochemistry of the chiral cyclohexenone, two more experiments were performed. Racemic dimethylamine-substituted phosphoramidite (L*-**2**) was used as the ligand and conjugate additions of Et_2Zn to both enantiomerically pure and racemic **2** were performed.

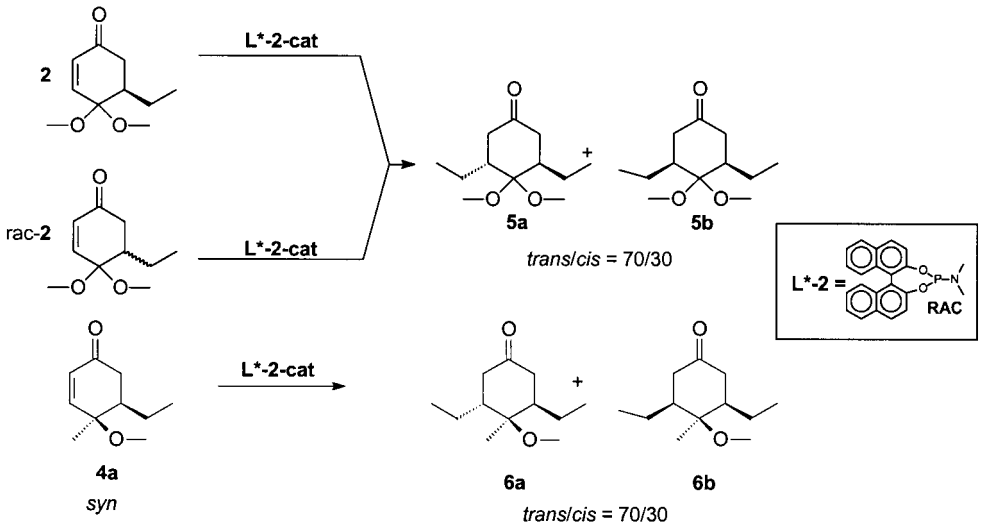
In both cases the diadduct **5** was obtained in a *trans*/*cis* ratio of 70:30. The fact that in both cases the ratio is the same also indicates that the 5-ethyl has no interaction with the catalytic active species (Scheme 7).

Finally, a conjugate addition experiment using enantiomerically pure *syn*-**4** and racemic L*-**2** was performed. The outcome was in accordance with expectation: the product **6** was formed in a *trans*/*cis* ratio of 70:30, so in this case an excess of *trans*-diadduct is formed. This means that there indeed is no directing effect of the methoxy moiety. Because the C-5 ethyl group in **4a** also has no directing effect (vide infra) and the racemic complexes are much less reactive, the ratio must be mainly due to the steric bulk of the methoxy group relative to the methyl group.

3. Conclusion

In the copper-L*-**1** catalysed conjugate addition of Et_2Zn to 4,4,5-trisubstituted cyclohexenones a C-5 ethyl substituent

[‡] This means *syn* with respect to the methoxy substituent.



Scheme 7.

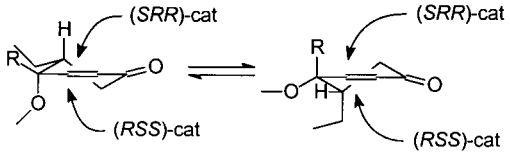


Figure 2.

has no effect on reactivity or selectivity. It also has been shown that in contrast to the first conjugate addition, there is no directing effect of a 4-methoxy moiety during the second conjugate addition. Therefore, only the stereochemistry of the chiral ligand is of importance for the stereochemical outcome of the reaction (Fig. 2).

The *cis*- or *trans*-diadducts can be synthesised in two steps with high diastereoselectivity starting from prochiral dienones, resulting in cyclohexanones with two or three stereocenters and with high enantiomeric purity (up to 97%). The sequential catalytic 1,4-addition provides flexible methodology that is of importance for the synthesis of natural products.

4. Experimental

4.1. General

Toluene was distilled from sodium and dichloromethane, Et_2O and hexane were distilled from P_2O_5. All solvents were stored under nitrogen. $Cu(OTf)_2$ and Et_2Zn (1.1 M in toluene) were purchased from Aldrich. Phosphoramidites and cyclohexenones **2** and **4** were synthesised analogously to a procedure previously reported.[11] All reactions were carried out under an argon atmosphere using dried glassware. Column chromatography was performed using: silica gel Merck Type 9385, 230–400 mesh, TLC was performed on silica gel 60, Merck, 0.25 mm. Mass spectra (HRMS) were obtained on an AEI MS-902. ^{1}H NMR and ^{13}C NMR ($CDCl_3$) (300 MHz): δ in ppm (δ=7.2 ppm) for protons and (δ=77 ppm) for carbon atoms.

4.2. General procedure for the conjugate addition of diethylzinc to 4,4-disubstituted-5-ethyl-cyclohex-2-enone employing a chiral catalyst derived from $Cu(OTf)_2$ and a phosphoramidite

A solution of $Cu(OTf)_2$ (0.010 mmol) and 0.023 mmol of a phosphoramidite in 5 mL of freshly distilled toluene was stirred under an argon atmosphere at ambient temperature for 1 h. The mono-adduct (0.5 mmol) was added, the mixture was cooled to −20°C and 1.1 equiv. of diethylzinc in toluene (1.1 M) was added. Stirring was continued at −20°C for 16 h. Conversion was determined by TLC. After complete conversion, the reaction mixture was poured in 25 mL of 1 M NaOH and extracted three times with diethyl ether (60 mL). The combined organic layers were dried with brine (25 mL) and Na_2SO_4, filtered and evaporated to yield the crude 1,4-adduct. The products were purified by column chromatography (hexane/EtOAc=9/1); the *cis*/*trans* ratios were determined by ^{1}H NMR.

4.2.1. *trans*-3,5-Diethyl-4,4-dimethoxycyclohexanone (5a). Isolated yield 77%. ^{1}H NMR δ 0.84 (t, J=7.3 Hz, 6H), 1.01 (m, 2H), 1.75 (m, 4H), 1.95 (m, 2H), 2.10 (dd, J=5, 1 Hz, 2H), 3.26 (s, 6H). ^{13}C NMR δ 12.69 (q), 22.48 (t), 42.06 (d), 43.89 (q), 49.80 (q),101.46 (s), 211.34 (s). HRMS calcd for $C_{12}H_{22}O_3$ 214.157, found 214.157.

4.2.2. *cis*-3,5-Diethyl-4,4-dimethoxycyclohexanone (5b). Isolated yield 72%. ^{1}H NMR δ 0.82 (t, J=7.5 Hz, 6H), 1.05 (m, 2H), 1.62 (m, 2H), 2.08 (m, 2H), 2.11 (d, J=10 Hz, 2H), 2.61 (dd, J=12, 4.5 Hz, 2H), 3.15 (s, 3H), 3.21 (s, 3H). ^{13}C NMR δ 13.32 (q), 22.07 (t), 41.38 (d), 43.92 (t), 47.66 (q), 49.78 (q), 101.77 (s), 211.87 (s). HRMS calcd for $C_{12}H_{22}O_3$ 214.157, found 214.154.

4.2.3. *trans*-3,5-Diethyl-4-methyl-4-methoxycyclohexanone (6a). Isolated yield 81%. ^{1}H NMR δ 0.80 (t, J=7.7 Hz, 3H), 0.86 (t, J=7.2 Hz, 3H), 0.91 (m, 2H), 1.21 (s, 3H), 1.38–1.55 (m, 3H), 1.95 (m, 1H), 2.07 (dd, J=15.1, 4.2 Hz, 1H), 2.54 (m, 2H), 2.55 (dd, J=15.1, 4.3 Hz, 1H), 3.16 (s, 3H). ^{13}C NMR δ 10.32 (q), 10.99 (q), 18.02 (t), 19.94 (t), 21.09 (q), 39.25 (d), 40.18 (d), 42.74 (t), 42.97

(t), 46.82 (q), 74.87 (s), 210.95 (s). HRMS calcd for $C_{12}H_{22}O_2$ 198.162, found 198.162.

4.2.4. *cis*-3,5-Diethyl-4-methyl-4-methoxycyclohexanone (6b). Isolated yield 76%. ^{1}H NMR δ 0.80 (t, J=7.3 Hz, 6H), 1.11 (m, 2H), 1.27 (s, 3H), 1.40 (m, 2H), 1.77 (m, 2H), 2.34 (m, 4H), 3.28 (s, 3H). ^{13}C NMR δ 10.92 (q), 16.33 (q), 21.66 (t), 40.42 (t), 48.96 (d), 51.51 (q), 74.52 (s), 211.82 (s). HRMS calcd for $C_{12}H_{22}O_2$ 198.162, found 198.163.

Acknowledgements

Financial support from The Netherlands Organisation for Scientific Research (NWO-CW) is gratefully acknowledged.

References

1. Mori, K. *Tetrahedron* **1989**, *45*, 3233–3298.
2. Drauz, K.; Waldmann, H. *Enzyme Catalysis in Organic Synthesis, A Comprehensive Handbook*, 1st ed.; Vol. 1; VCH: Weinheim, 1995.
3. Ogasawara, K. *J. Synth. Org. Chem.* **1999**, *57*, 957–969.
4. House, H. O.; Thompson, H. W. *J. Org. Chem.* **1963**, *28*, 360–365.
5. The conjugate addition of organometallic reagents to 5-substituted-2-cyclohexenones generally affords as the main product a *trans*-3,5-disubstituted cyclohexanone: (a) Kozlowski, J. A. *Comprehensive Organic Synthesis*, Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; pp 169–198. (b) Yamamoto, Y. *Methods in Organic Chemistry Stereoselective Synthesis*, Houben-Weyl, 4th ed.; Helmchen, G., Arend, M., Eds.; Thieme: Stuttgart, 1995; Vol. E21B, pp 2041–2067. (c) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*, Vol. 9; Pergamon: Oxford, 1992.
6. Allinger, N. L.; Riew, C. K. *Tetrahedron Lett.* **1966**, 1269–1272.
7. Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*, Wiley Interscience: New York, 1994.
8. (a) Blumenkopf, T. A.; Heathcock, C. H. *J. Am. Chem. Soc.* **1983**, *105*, 2355–2358. (b) Heathcock, C. H.; Germroth, T. C.; Graham, S. L. *J. Org. Chem.* **1979**, *44*, 4481–4487. (c) Yamamoto, Y.; Yamamoto, S.; Yatagai, H.; Ishihara, Y.; Maruyama, K. *J. Org. Chem.* **1982**, *47*, 119–126. (d) House, H.; Fischer, W. F. *J. Org. Chem.* **1968**, *33*, 949–956. (e) Asaoka, M.; Shima, K.; Takei, H. *J. Chem. Soc., Chem. Commun.* **1988**, 430–431.
9. (a) Krauss, S. R.; Smith, S. G. *J. Am. Chem. Soc.* **1981**, *103*, 141–148. (b) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1984**, *25*, 3063–3066. (c) Corey, E. J.; Hannon, F. J. *Tetrahedron Lett.* **1990**, *31*, 1393–1396.
10. Hareau-Vittini, G.; Hikicki, S.; Sato, F. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2099–2101.
11. (a) Imbos, R.; Brilman, M. H. G.; Pineschi, M.; Feringa, B. L. *Organic Lett.* **1999**, *1*, 623–626. (b) Feringa, B. L.; Pineschi, M.; Arnold, L. A.; Imbos, R.; de Vries, A. H. M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2621–2623.
12. The conjugate addition of Et_2Zn to 5,5-dimethylcyclohexenone catalyzed by the same chiral catalyst afforded the product in only 84% e.e. Naasz, R.; Arnold, L. A.; Pineschi, M.; Keller, E.; Feringa, B. L. *J. Am. Chem. Soc.* **1999**, *121*, 1104–1105.
13. A *syn*-directing effect of the methoxy-substituent in the organoaluminum mediated conjugate addition of RLi and RMgBr to quinol ethers has been observed; Stern, A. J.; Rhode, J. J.; Swenton, J. S. *J. Org. Chem.* **1989**, *54*, 4413–4418.