Synthesis of Optically Active 5-(*tert*-Butyldimethylsiloxy)-2-cyclohexenone and Its 6-Substituted Derivatives as Useful Chiral Building Blocks for the Synthesis of Cyclohexane Rings. Syntheses of Carvone, Penienone, and Penihydrone

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Abstract: Optically active 5-(*tert*-butyldimethylsiloxy)-2-cyclohexenone (**1**) and its 6-substituted derivatives **2a**,**b** were synthesized from the readily available optically active ethyl 3-(*tert*-butyldimethylsiloxy)-5-hexenoate (**4**), where the Ti(II)-mediated intramolecular nucleophilic acyl substitution reaction and the $FeCl_3$-mediated ring expansion reaction of a 1-hydroxybicyclo[3.1.0]hexane are the key reactions. The enone **1** reacted with higher-order cyanocuprates with excellent diastereoselectivity to afford the *trans*-addition products, *trans*-**13**, in excellent yields. The reaction of **1** with lower-order cyanocuprates proceeded with moderate to excellent *syn*-selectivity to afford *cis*-**13**. Treatment of *trans*- and *cis*-**13** with DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) or catalyst *p*-TSA (*p*-toluenesulfonic acid) resulted in a β-elimination reaction to furnish the corresponding optically active 5-substituted-2-cyclohexenones **14**. The 1,4-addition reaction of **2a** and **2b** with organocyanocuprates followed by treatment of the resulting **20** with DBU provided the 2,5-disubstituted-2-cyclohexenones **19** with excellent ee. The conversion of **14** into the 3,5-disubstituted-2-cyclohexenone **22** has also been carried out via 1,2-addition of alkyllithium onto the carbonyl group and the following oxidation with PCC (pyridinium chlorochromate). Similarly, the conversion of **19** into 2,3,5-trisubstituted-2-cyclohexenones **24** has been carried out. A highly efficient, first total synthesis of penienone **25** and penihydrone **26** has been accomplished. Thus, the 1,4-addition reaction of **1** with the (*E*,*E*)-1,3-heptadienyl cyanocuprate and consecutive trap of the resulting copper enolate with formaldehyde gave **28,** which upon treatment with DBU or Pyr·HF yielded **25** and **26**, respectively. An efficient synthesis of both enantiomers of carvone starting from (*S*)-**20ab** has been also accomplished.

Introduction

Many biologically important compounds have a chiral cyclohexane ring in their structure as the main or a subunit. One attractive method to synthesize these skeletons involves the use of a chiral 2-cyclohexenone derivative as the starting material, taking advantage of its versatile reactivity. Chiral 2-cyclohexenones also have been widely used as building blocks for the preparation of a variety of acyclic chiral compounds. The easily accessible naturally occurring 2-cyclohexenones used for this purpose are, however, restricted to only a few such as carvone and pulegone.[1] Therefore, considerable efforts have been made to develop an efficient method to prepare chiral 2-cyclohexenones[2−4] as well as to introduce new 2-cyclohexenone chiral building blocks.[5]

Optically active 2-cyclohexenone having an alkoxyl group at the 5-position seems to be an attractive chiral building block for the preparation of a variety of cyclohexanone as well as

(1) For some recent synthetic implications of carvone in organic synthesis, see: Srikrishna, A.; Reddy, T. J.; Kumar, P. P. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3143−3144 and references therein. For pulegone, see: Chen, C. Y.; Nagumo, S.; Akita, H. *Chem. Pharm. Bull.* **1996**, *44*, 2153−2156.

(2) Chiral cyclohexenones can be obtained by derivatization of optically active natural products according to multistep sequences. (a) From sugars, see: Ferrier, R. J.; Middleton, S. *Chem. Rev.* **1993**, *93*, 2779−2831 and references therein. (b) From pinene, see: Chapuis, C.; Brauchli, R.; Thommen, W. *Helv. Chim. Acta* **1993**, *76*, 535−544 and references therein. (c) From quinic acid, see: Barros, M. T.; Maycock, C. D.; Ventura, M. R. *J. Org. Chem.* **1997**, *62*, 3984−3988 and references therein. (d) From quebrachitol, see: Barton, D. H. R.; Bath, S.; Billington, D. C.; Gero, S. D.; Quiclet-Sire, B.; Samadi, M. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1551−1558 and references therein.

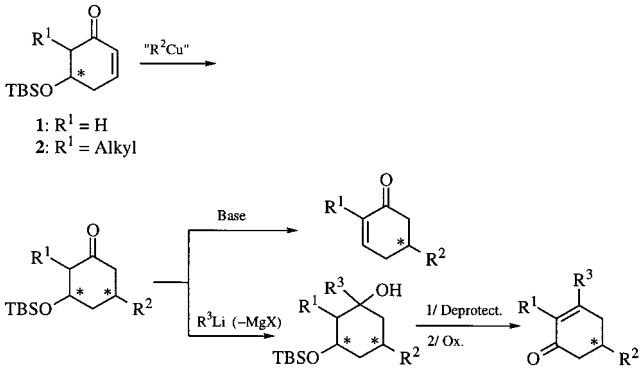
(3) Another approach is the kinetic resolution of a racemic mixture of starting materials where enzymes have been the mostly used see: (a) Polla, M.; Frejd, T. *Tetrahedron* **1991**, *47*, 5883−5894. (b) Miyaoka, H.; Sagawa, S.; Inoue, T.; Nagaoka, H.; Yamada, Y. *Chem. Pharm. Bull.* **1994**, *42*, 405−407. (c) Weissfloch, A. N. E.; Kazlauskas, R. J. *J. Org. Chem.* **1995**, *60*, 6959−6969 and references therein. Resolution can be also achieved by using organometallics species: (d) Trost, B. M.; Organ, M. G. *J. Am. Chem. Soc.* **1994**, *116*, 10320−10321. (e) Hashiguchi, S.; Fujii, A.; Haack, K. J.; Matsumura, K.; Ikariya, T.; Noyori, R. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 288−290. For other examples of resolution see: (f) Gorthey, L. A.; Vairamani, M.; Djerassi, C. *J. Org. Chem.* **1985**, *50*, 4173−4182 and references therein.

(4) Enantioselective syntheses of 2-cyclohexenones have been reported: (a) Based on an asymmetric Diels−Alder reaction: Wada, E.; Yasuoka, H.; Kanemasa, S. *Chem. Lett.* **1994**, 1637−1640; Kozmin, S. A.; Rawal, V. H. *J. Am. Chem. Soc.* **1997**, *119*, 7165−7166 and references therein. (b) Based on amino acid-catalysed aldolization: Fuji, K. *Chem. Rev.* **1993**, *93*, 2037−2066 and references therein. (c) Enantioselective deprotonation: O'Brien, P.; Poumellec, P. *Tetrahedron Lett.* **1996**, *37*, 8057−8058. (d) The most efficient and general up-to-date method for synthesizing optically active 2-cyclohexenones has been developed by Meyers using optically active bicyclic lactams, see: Romo, D.; Meyers, A. I. *Tetrahedron* **1991**, *47*, 9503−9569. Schwarz, J. B.; Devine, P. N.; Meyers, A. I. *Tetrahedron* **1997**, *53*, 8795−8806 and references therein.

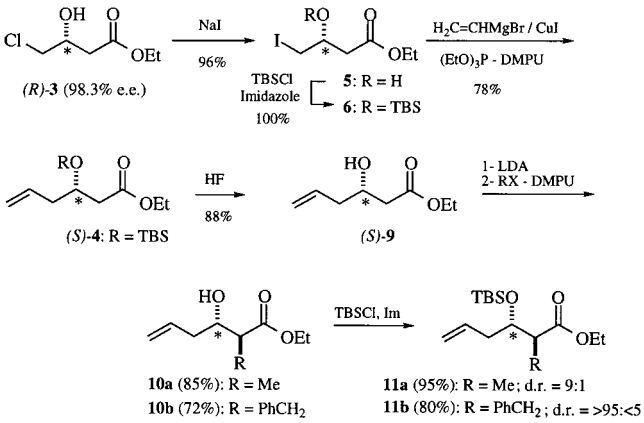
(5) (a) Asaoka, M.; Shima, K.; Takei, H. *Tetrahedron Lett.* **1987**, *28*, 5669−5672. Asaoka, M.; Takei, H. *J. Synth. Org. Chem. Jpn.* **1990**, *48*, 216−228 (review in Japanese). (b) Takano, S.; Higashi, Y.; Kamikubo, T.; Moriya, M.; Ogasawara, K. *Synthesis* **1993**, 948−950. Ogasawara, K. *Pure Appl. Chem.* **1994**, *66*, 2119−2122.

10.1021/ja9843122 CCC: $18.00
Published on Web 04/06/1999

Scheme 1



Scheme 2



cyclohexenone derivatives, since the transformations shown in Scheme 1 are easily conceivable.

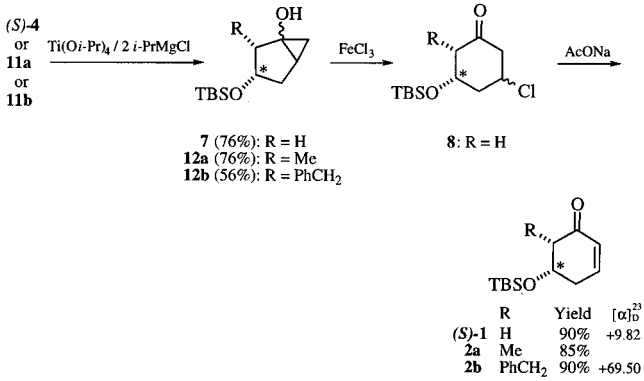
Two research groups[6,7] have independently synthesized the optically active 5-(benzyloxy)-2-cyclohexenone according to the porcine β-liver esterase-catalyzed asymmetric hydrolysis of *meso*-1,3-diacetoxy-5-(benzyloxy)cyclohexane and oxidation of the resulting hydroxy monoacetate. However, the enantiomeric excess (ee) of the enone thus prepared was 85−87% and the method only opens an access to the enantiomer with (*S*)-configuration. To the best of our knowledge, the compound has not been utilized for the synthesis of cyclohexane derivatives.

Herein, we report an efficient and practical synthesis of the optically active 5-(*tert*-butyldimethylsiloxy)-2-cyclohexenone (**1**) and its 6-substituted derivative **2**, which readily undergo the transformations shown in Scheme 1 highly selectively.[8]

Results and Discussion

Synthesis of Optically Active 5-(*tert*-Butyldimethylsiloxy)-2-cyclohexenone (1) and Its 6-Substituted Derivative 2. The synthesis of nonracemic **1** has been readily carried out starting from the optically active ethyl 3-hydroxy-4-chlorobutyrate (**3**). First, (*R*)-**3** (98.3% ee) was converted into the (*S*)-ethyl 3-(*tert*-butyldimethylsiloxy)-5-hexenoate (**4**) in 75% overall yield according to the procedure shown in Scheme 2. The conversion of (*S*)-**4** into (*S*)-**1** was smoothly carried out as illustrated in Scheme 3. Thus, the reaction of (*S*)-**4** with a Ti(O*i*-Pr)$_4$/2*i*-PrMgCl reagent resulted in a tandem reaction of intramolecular

Scheme 3



nucleophilic acyl substitution and intramolecular carbonyl addition to afford **7** in 76% yield.[9] The reaction of **7** with $FeCl_3$ in the presence of pyridine yielded the ring expansion product **8**, which was treated in turn, without purification, with NaOAc in CH_3OH to furnish (*S*)-**1** in 90% overall yield from **7**.[10]

5-(*tert*-Butyldimethylsiloxy)-2-cyclohexenones **2** having a substituent at the 6-position can also be readily synthesized from **3**. Thus, the introduction of a methyl or benzyl group at the 2-position of (*S*)-**9**, prepared by desilylation of (*S*)-**4**, according to the reported protocol,[11] gave, after silylation, **11a** and **11b**, respectively (Scheme 2). Following the reaction sequence of **4** → **1**, the compounds **11a,b** yielded **2a,b**, which consisted of two diastereomers in a ratio of 9:1 for **2a** and >95:<5 for **2b** (Scheme 3, where only the major diastereoisomer is shown).

Since both (*R*)- and (*S*)-**3** are commercially available in excellent optical purity or can be readily prepared by enantioselective hydrogenation of ethyl 4-chloro-3-oxobutyrate with a BINAP−Ru catalyst,[12] the present method allows the preparation of both enantiomers of **1** and **2**, and we indeed prepared (*R*)-**1** starting from (*S*)-**3**. In addition, as the reagents used for the transformation of **3** into **1** or **2** are nontoxic and inexpensive, the overall yield is high, and all the reaction procedures being operationally simple, the synthesis of **1** and **2** is practical. The compounds **1** and **2** thus obtained are found to be stable: no racemization or degradation has been detected on storage.

Synthetic Utility of 1 as Masked Chiral Synthetic Equivalent of 2,5-Cyclohexadienone. The Gilman butylcuprate reagent (Bu_2CuLi) and the higher-order butylcyanocuprate ($Bu_2Cu(CN)Li_2$) reacted with **1** via an *anti*-addition pathway, as expected, with selectivities of 89:11 and 98.5:1.5, respectively, to afford *trans*-**13** (R = Bu) in excellent yield.[13] Meanwhile, to our surprise, the reaction with the lower-order butylcyanocuprate

(6) Suemune, M.; Takahashi, M.; Maeda, S.; Xie, Z.-F.; Sakai, K. *Tetrahedron: Asymmetry* **1990**, *1*, 425−428.

(7) Dumortier, L.; Carda, J.; Van der Eycken, J.; Snatzke, G.; Vandewalle, M. *Tetrahedron: Asymmetry* **1991**, *2*, 789−792.

(8) Portions of this work have been communicated: Hikichi, S.; Hareau, G. P-J.; Sato, F. *Tetrahedron Lett.* **1997**, *38*, 8299−8302. Hareau, G. P-J.; Hikichi, S.; Sato, F. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2099−2101.

(9) Kasatkin, A.; Sato, F. *Tetrahedron Lett.* **1995**, *36*, 6079−6082. Kasatkin, A.; Kobayashi, K.; Okamoto, S.; Sato, F. *Tetrahedron Lett.* **1996**, *37*, 1849−1852. Lee, J.; Kang, C. H.; Kim, H.; Cha, J. K. *J. Am. Chem. Soc.* **1996**, *118*, 291−292. Sun U, J.; Lee, J.; Cha, J. K. *Tetrahedron Lett.* **1997**, *38*, 5233−5236.

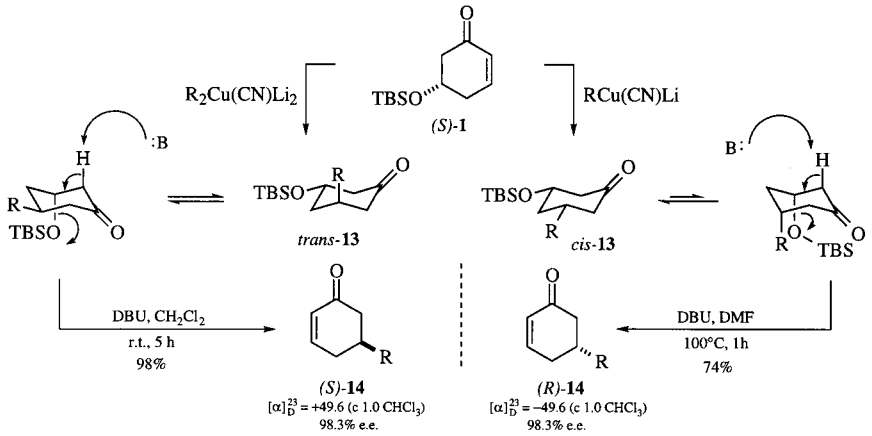
(10) Ito, Y.; Fujii, S.; Saegusa, T. *J. Org. Chem.* **1976**, *41*, 2073−2074. Ito, Y.; Fujii, S.; Nakatsuka, M.; Kawamoto, F.; Saegusa, T. *Org. Synth.* **1988** (Collect. Vol. 6), 327−333.

(11) Seebach, D.; Wasmuth, D. *Helv. Chim. Acta* **1980**, *63*, 197−200. Frater, G.; Müller, U.; Günther, W. *Tetrahedron* **1984**, *40*, 1269−1277.

(12) Kitamura, M.; Ohkuma, T.; Takaya, H.; Noyori, R. *Tetrahedron Lett.* **1988**, *29*, 1555−1556.

(13) The conjugate addition of organocuprates onto 5-substituted-2-cyclohexenones yields generally a very high proportion of the *trans*-adduct; see the following reviews and references therein: Yamamoto, Y. *Methoden Org. Chem. (Houben-Weyl), Engl. Ed.* **1995**, *E21b*, 2041−2067 (Helmchen, G., Hoffman, R. W., Mulzer, J., Shauman, E., Eds.). Lipshutz, B. H. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Tokyo, 1991; Vol. 1, pp 107−138. Kozlowski, J. A. *Ibid.* Vol. 4, pp 169−198. Lipshutz, B. H.; Sengupta, S. *Org. React.* **1992**, *41*, 135−631.

Scheme 4. Conjugate Addition of Higher- and Lower-Order Cyanocuprates onto **1** Followed by Desiloxylation Yielding the Chiral 5-Substituted-2-cyclohexenone **14** (R = Bu)

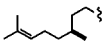


(BuCu(CN)Li)[14] proceeded via the *syn*-addition pathway providing *cis*-**13** almost exclusively.[15] The treatment with DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) of *trans*- and *cis*-**13** thus prepared gave, respectively, the (*S*)- and (*R*)-5-butyl-2-cyclohexenone (**14**) in good yield (Scheme 4). The ee values of both enantiomers of **14** were almost identical to that of the starting **3** (98.3% ee),[16] suggesting that no racemization occurred during the whole process including the conversion of **3** into **1**. Noteworthy here is the fact that the desiloxylation of *cis*-**13** (R = Bu) requires harsher conditions than those needed for *trans*-**13** (R = Bu);[17] this can be explained by assuming that the reaction occurs through an antiperiplanar pathway, and for *cis*-**13**, a large 1,3-diaxial interaction between the OTBS and the R group appears to make the antiperiplanar transition state higher in energy (Scheme 4).

Since $Bu_2Cu(CN)Li_2$ gave better selectivity than Bu_2CuLi, the 1,4-addition reactions of **1** using a variety of higher- and lower-order cyanocuprates were carried out. The yield and diastereomeric ratio of the resulting 1,4-addition products **13** as well as their desiloxylation into 5-substituted-cyclohexenones **14** in several representative cases are summarized in Tables 1 and 2, respectively.

As can be seen from Table 1, a variety of $R_2Cu(CN)Li_2$ where R is methyl, primary-, secondary-, and tertiary-alkyl, phenyl, and vinyl gave the corresponding *trans*-**13** highly predominantly and in excellent yields. The mixed higher-order cyanocuprate[19] [RCu(2-thienyl)(CN)Li_2] can also be used for the production of *trans*-**13** (entry 3). In contrast, as revealed from Table 2, the reaction of **1** with a variety of lower-order cyanocuprates, except for the vinyl derivative, proceeds mainly via the *syn*-addition pathway, although the yield with the phenylcyanocuprate is moderate. Especially noteworthy is the excellent *cis*-selectivity observed with methyl and primary- and secondary-alkyl derivatives. The tertiary-alkyl and phenyl derivatives (Table 2, entries 9 and 10), however, proceeded with lower *cis*-selectivity of 75−80% dr (diastereomeric ratio). It can also be found that, even if the selectivity was somewhat diminished, the lower-order cyanocuprates RCu(CN)MgX derived from Grignard reagents also yielded the *cis*-addition product mainly (entries 4 and 7). Noteworthy also is the fact that, although the reaction of RCu(CN)Li proceeded with excellent *cis*-selectivity either in Et_2O or in THF, the yield appeared to be better in Et_2O (entries 1 vs 2 and 3 vs 5).[20] The only exception to the *cis*-selective addition reaction of lower-order cyanocuprates to **1** is the vinyl derivative

Table 1. 1,4-Addition of Higher-Order Cyanocuprates onto (*S*)-**1**[a]

Entry	$R_2Cu(CN)Li_2$	1,4-adduct (**13**)		Elimination Product (*S*)-**14**[b,c]	
		cis : *trans*[d]	Yield (%)[e]	Yield (%)[f]	$[\alpha]_D$[g]
1	Me	3 : 97	83	92	+88.1 (c 0.5)
2	Bu	1.5 : 98.5	92	93	+49.6 (c 0.5)
3	 [h]	<2 : >98 [i]	60[j]		
4	*sec*-Bu	2 : 98	92[j]		
5	*tert*-Bu	2 : 98	92[j]		
6	Ph	7 : 93	80	94	+43.5 (c 0.5)
7	H_2C=CH	5 : 95	75[j]		

[a] The reactions were run in THF. [b] Elimination performed in CH_2Cl_2 with DBU (3 equiv) at r.t. for 5 h. [c] Reported $[\alpha]_D$ for the (*R*)-**14**: −90.2 (R = Me); −51.2 (R = Bu); −46.4 (R = Ph); see ref 18. [d] GC measurement. [e] Isolated yield unless otherwise noted. [f] Isolated yield from **13**. [g] In $CHCl_3$ at 23 °C. [h] R(2-thienyl)Cu(CN)Li_2 was used. [i] NMR measurement. [j] NMR yield.

(14) RCu(CN)Li (lower-order) and $R_2Cu(CN)Li_2$ (higher-order) indicate that the reagents have been prepared stoichiometrically by mixing CuCN and RLi in the 1:1 and 1:2 ratios, respectively, see: Kronenburg, C. M. P.; Jastrzebski, J. T. B. H.; Spek, A. L.; van Koten, G. *J. Am. Chem. Soc.* **1998**, *120*, 9688−9689 and references therein. See also: *Organocopper Reagents: A Practical Approach*; Taylor, R. J. K., Ed.; Oxford University Press: Oxford, U.K., 1994. The terms "1:1 cyanocuprates" and "1:2 cyanocuprates" are now preferred to "lower-" and "higher-order cyanocuprates" nevertheless, for convenience, we have conserved the old terminology.

(15) A selectivity of 92:8 in favor of the cis isomer has been reported on a 4-oxy-substituted spirocyclohexenone: Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1985**, *26*, 6015−6018. *cis*-Michael-type addition has been observed on 4-oxy-substituted-2-cyclohexenone: Jeroncic, L. O.; Cabal, M. P.; Danishefsky, S. J. *J. Org. Chem.* **1991**, *56*, 387−395.

(16) ee calculated from chiral GC or HPLC: chiral GC (Chirasil-DEX/Chrompack, 0.25 mm × 25 m, DF = 0.25); chiral HPLC (Daicel Chiralcel OB−H).

(17) The reductive elimination of the *cis*-adduct of **13** does not proceed easily at r.t. so that the treatment at r.t. with DBU of a *cis/trans* mixture of **13** can result in a kinetic resolution of the starting material, thus affording the eliminated product **14** with high ee.

(18) (*R*)-(−)-5-Butyl-2-cyclohexenone: $[\alpha]_D$ = −51.2 (*c* 1.40; $CHCl_3$): Asaoka, M.; Takenouchi, K.; Takei, H. *Chem. Lett.* **1988**, 921−922. (*R*)-(−)-5-Methyl-2-cyclohexenone: $[\alpha]_D$ = − 90.2 (*c* 0.8; $CHCl_3$): Allinger, N. L.; Riew, C. K. *J. Org. Chem.* **1975**, *40*, 1316−1321 and ref 3f. (*R*)-(−)-5-Phenyl-2-cyclohexenone: $[\alpha]_D$ = − 46.4 (*c* 5.0; $CHCl_3$): Asaoka, M.; Shima, K.; Fujii, N.; Takei, H. *Tetrahedron* **1988**, *44*, 4757−4766.

(19) Lipshutz, B. H.; Koerner, M.; Parker, D. A. *Tetrahedron Lett.* **1987**, *28*, 945−948.

(20) For the solvent effect in the conjugate addition of lower-order cyanocuprates onto 2-cyclohexenones, see: Bertz, S. H.; Dabbagh, G. *Tetrahedron* **1989**, *45*, 425−434.

Table 2. 1,4-Addition of Lower-Order Cyanocuprates onto *rac*-**1**[a]

Entry	RCu(CN)M R	RCu(CN)M M	1,4-adduct (**13**) *cis* : *trans* [c]	1,4-adduct (**13**) Yield (%) [d]	Elimination Product **14** [b] Yield (%) [d]
1	Me	Li	>99 : <1 [e]	77 [f]	80
2 [g]	Me	Li	>95 : <5 [e]	35 [f]	
3 [h]	Bu	Li	>99.5 : <0.5 [e]	91 [f]	74 [f]
4	Bu	Mg	90 : 10	73	
5 [g]	Bu	Li	>99 : <1	80	
6		Li	98 : 2	87 [f]	
7		Mg	70 : 30		
8	*sec*-Bu	Li	>98 : <2	84 [f]	75 [i]
9	*tert*-Bu	Li	80 : 20	78	
10	Ph	Li	75 : 25	25	
11	H_2C=CH	Li	25 : 75	45	

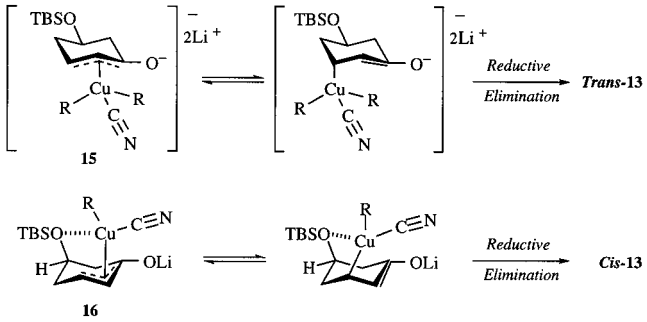
[a] The reactions were run in Et_2O, unless otherwise noted, at −78 °C (entries 3−7) or from −78 to 0 °C (entries 1, 2, 8−11). [b] With DBU (3 equiv) at 100 °C, DMF, 1 h. The elimination with DBU at r.t. in CH_2Cl_2 (or DMF) for 5 h gave **14** < 10% yield. [c] NMR measurement unless otherwise noted. [d] NMR yield unless otherwise noted. [e] GC measurement. [f] Isolated yield. [g] THF was used. [h] (*S*)-**1** was used (see Scheme 4). [i] The elimination was carried out with cat. *p*-TSA in CH_2Cl_2 at r.t. for 3 h, under treatment with DBU (3 equiv), 100 °C, DMF, 1 h, **14** has been produced in 30% yield. [j] NMR yield.

(entry 11) which gave the *trans*-adduct as the major product, and the explanation underlying this exception must await further study.

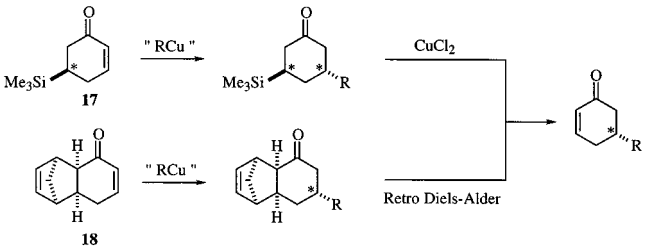
The results shown in Tables 1 and 2 are significant from the synthetic viewpoint since, by simply choosing the lower- or higher-order alkyl cyanocuprate,[21] both diastereomers of **13** can be readily prepared, thus opening up an easy and practical access to both enantiomers of 5-alkyl-2-cyclohexenones **14** starting from a single enantiomer of **1**.[22]

The unprecedented *syn*-selective 1,4-addition reaction of lower-order cyanocuprates onto 5-substituted-2-cyclohexenones was also significant from the viewpoint of the organocopper chemistry;[13] thus, we devoted our efforts to reveal whether this phenomenon was characteristic of **1** or not. The reaction of BuCu(CN)Li with the 5-methyl- and 5-(trimethylsilyl)-2-cyclohexenone[5] yielded almost exclusively the corresponding *trans*-addition products. This result strongly indicated that the alkoxy functionality in the substrate **1** plays a crucial role in the control of the stereochemistry of the conjugate addition reaction to the *cis*-product. We confirmed this assumption by carrying out the reaction of BuCu(CN)Li with the 5-(benzyloxy)-2-cyclohexenone,[6,7] which provided the corresponding *cis*-adduct exclusively with 98% dr. We then carried out the reaction of BuCu(CN)Li with 4-(*tert*-butyldimethylsiloxy)-2-cyclohexenone[23] to examine the effect of the position of the alkoxy group on the diastereoselectivity of the addition. The reaction furnished the *trans*-addition product as a single diastereomer, suggesting

Scheme 5. Proposed Intermediates for the Reaction of **1** with Higher- or Lower-Order Cyanocuprates



Scheme 6. Chiral 2,5-Cyclohexadienone Synthons Reported So Far



that the selectivity is also highly dependent on the positioning of the alkoxy group on the cyclohexane ring. Thus, in conclusion, the *syn*-selective conjugate addition is a characteristic of the 5-alkoxy-2-cyclohexenone.

The stereochemical outcome of the reaction shown in Tables 1 and 2 seems to be explained by assuming that the reaction of **1** with organocopper compounds proceeds via the intermediacy of a d,π* complex as suggested by Corey.[24] Thus, the reaction with $R_2Cu(CN)Li_2$ proceeds via the d,π* complex **15** having an alkoxy group at a *pseudo*-equatorial position, while the reaction with RCu(CN)Li proceeds *via* **16**, where the copper atom is coordinated by the oxygen of the alkoxy group (Scheme 5).[25]

The result that **1** can be readily converted into a variety of optically active **14**, which also has a chiral 2-cyclohexenone moiety, indicates that **1** acts as a masked chiral synthetic equivalent of the 2,5-cyclohexadienone. Two chiral 2,5-cyclohexadienone synthons have already been developed: Asaoka and Takei have introduced the optically active 5-(trimethylsilyl)-2-cyclohexenone (**17**),[5a] and Takano and Ogasawara have developed the optically active tricyclic dienone **18** (Scheme 6).[5b] Both compounds **17** and **18** allow highly stereoselective 1,4-addition reactions of organocopper compounds, and the resulting 1,4-adducts are converted into the 5-substituted-2-cyclohexenones by removal of the group masking the double bond. However, the step for the removal of the masking group sometimes results in rather low yields for **17** or requires severe reaction conditions for **18**. The compound **1** developed here has the advantage that the reductive elimination can be readily carried out under milder reaction conditions and in good yields; moreover, **1** alone allows the highly selective synthesis of both

(21) Taking advantage of one of the reviewer's comments, we include the following note: the reaction of $R_2Cu(CN)Li_2$ onto an enone produces, after transfer of the R group, RCu(CN)Li, which, however, seems to be kinetically less reactive than $R_2Cu(CN)Li_2$. We have indeed observed that, in the case where the reaction with $R_2Cu(CN)Li_2$ (R = Bu) in THF actually was complete after few minutes at −78 °C, the reaction of RCu(CN)Li (R = Bu) in Et_2O required 1 h at −78 °C and in some cases, such as R = Me, *s*-Bu, *t*-Bu and Ph, a gradual elevation of the temperature to 0 °C (see Table 2) to go to completion.

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(23) Danishefsky, S. J.; Simoneau, B. *J. Am. Chem. Soc.* **1989**, *111*, 2599−2604.

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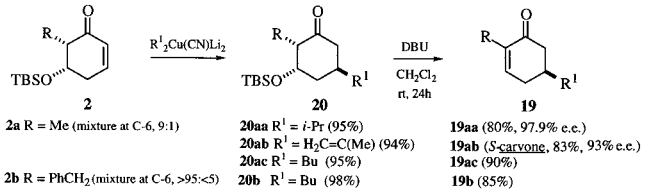
(25) For some recent progress on the mechanism of the 1,4-addition of cuprates on enones, see: Krauze, N. *J. Org. Chem.* **1992**, *57*, 3509−3512. Vellekoop, A. S.; Smith, R. A. J. *J. Am. Chem. Soc.* **1994**, *116*, 2902−2913. Snyder, J. P. *J. Am. Chem. Soc.* **1995**, *117*, 11025−11026. Nilsson, K.; Ullenius, C.; Krause, N. *J. Am. Chem. Soc.* **1996**, *118*, 4194−4195. Nakamura, E.; Mori, S.; Morokuma K. *J. Am. Chem. Soc.* **1997**, *119*, 4900−4910 and references therein.

Scheme 7. Synthesis of 2,5-Disubstituted-2-cyclohexenones (**19**) from **2** via **20**



enantiomers of the 5-substituted-2-cyclohexenones which might be difficult to attain using **17** or **18**.

Synthesis of Optically Active 2,5- and 3,5-Disubstituted- and 2,3,5-Trisubstituted-2-Cyclohexenones from 1 and/or 2. With a highly efficient method enabling the synthesis of chiral 5-substituted-2-cyclohexenones (**14**) from **1** in hand, we anticipated that the optically active 2,5-disubstituted-2-cyclohexenones (**19**) might be obtained from the enone **2**. Although **2** consists of a mixture of two diastereomers in a ratio 9:1 for **2a** and >95:<5 for **2b** with respect to the stereogenic center at C-6, we expected that the stereochemistry of the conjugate addition of cuprate reagents onto **2** might be controlled essentially by the siloxy group at C-5, thus providing, after reductive elimination, the enones **19** with excellent enantiomeric excess.

The reaction of **2a** with $i\text{-Pr}_2Cu(CN)Li_2$ gave the corresponding 1,4-addition products **20aa** in 95% yield (the diastereomeric ratio being not determined) which upon treatment with DBU gave **19aa** with 97.9% ee[16] in 80% yield.[26] Similarly, with $(2\text{-propenyl})_2Cu(CN)Li_2$,[27] **19ab**, i.e. (*S*)-carvone, was obtained in 93.0% ee[16] and in excellent yield. The reaction with $Bu_2Cu(CN)Li_2$ yielded **20ac**, which upon treatment with DBU gave **19ac**. Similarly, the reaction of **2b** with $Bu_2Cu(CN)Li_2$ followed by desiloxylation of the resulting **20b** yielded **19b**. Although our attempts to determine the ee values of **19ac** and **19b** were unsuccessful, the results obtained for **19aa** and **19ab**, together with the proton and carbon NMR data of **20ac** and **20b** which showed the presence of two diastereoisomers for the former and essentially a single one for the latter, strongly suggest that **19ac** and **19b**, with excellent ee, had been produced with the absolute configuration shown in Scheme 7. These results strongly indicated that the conjugate addition of higher-order cyanocuprates on **2** was mainly controlled, as expected, by the substituent at the C-5 position to furnish the *anti*-addition product highly selectively.

The NMR data of the reaction product of the lower-order BuCu(CN)Li with **2a** strongly indicated that, as is the case for **1**, the reaction proceeded via the *syn*-pathway with the *cis*-selectivity diminished to *cis*:*trans* = 85:15 (determined by the characteristic signals of the proton NMR: $\delta_{cis} = 3.95$ ppm, $\delta_{trans} = 4.19$ ppm). The lowered *cis*-selectivity can be explained by the steric interaction between the OTBS group and the methyl at C-6 in the transition state of the conjugate addition intermediate; thus, the coordination of the copper atom by the oxygen does not occur smoothly (Figure 1).

The ketones **14** obtained from **1** and organocopper reagents (Table 1) can be also readily converted into 3,5-disubstituted-2-cyclohexenones (**22**) as exemplified in Scheme 8. Thus, the reaction of **14** (R = Bu) with MeLi and the following manipulation of the resulting 1,2-addition product **21** by a conventional reaction sequence provided **22** (97.9% ee).[16] The

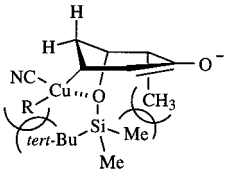
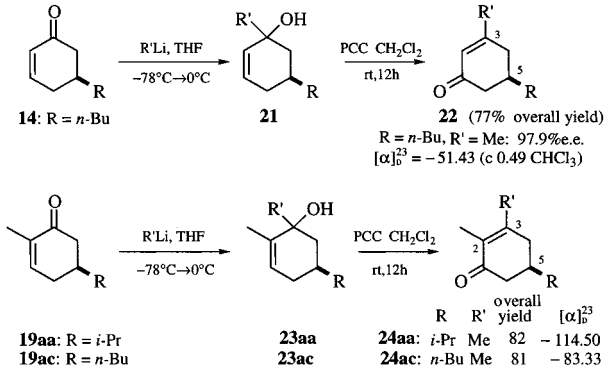


Figure 1.

Scheme 8. Synthesis of 3,5- and 2,3,5-Substituted-2-cyclohexenones



2,3,5-trisubstituted-2-cyclohexenones **24aa** and **24ac** can be similarly synthesized via **23** starting from the ketones **19** (R = *i*-Pr, Bu) (Scheme 8).

Chiral 2,5-, 3,5-, and 2,3,5-substituted-2-cyclohexenones are generally derived from naturally available carvones or pulegones.[1] To the best of our knowledge, only a very few methods for their asymmetric syntheses appear in the literature which include the use of the enantiomerically pure 5-trimethylsilyl-2-cyclohexenone **17** as the starting material for the 2,5-disubstituted-2-cyclohexenones[5a] and for the 3,5-substituted-2-cyclohexenones, through an asymmetric aldolisation of 1,5-diketones induced by the (*S*)-proline,[28] a Diels−Alder condensation of enantiomerically pure vinylketenes with the appropriate dienophiles,[29] or an enantioselective deprotonation.[30] The approach we have developed here for the synthesis of 2,5-, 3,5- and 2,3,5-substituted-2-cyclohexenones has the advantage of being very efficient and general.

Asymmetric Synthesis of Penienone, Penihydrone, and Carvone. In this section, we describe an efficient synthesis of three natural products starting from the enones **1** or **2** by taking advantage of their highly selective conjugate addition reactions with cyanocuprates.

Penienone (**25**) and penihydrone (**26**) have been isolated recently from the metabolite of the fungus *Penicillium* sp. No13 as new plant growth regulators, and their structures have been elucidated on the basis of NMR and CD spectra studies.[31] A short synthesis of both **25** and **26** starting from (*R*)-**1** was accomplished according to the reaction sequence shown in Scheme 9. It was clearly apparent that, with (*R*)-**1** in hand, the preparation of the higher-order (*E*,*E*)-dienylcyanocuprate was the main problem to tackle. For this purpose, we applied the higher-order cyanocuprates derived from the dienylzirconium species.[32] Thus, hydrozirconation of the enyne **27**[33] followed

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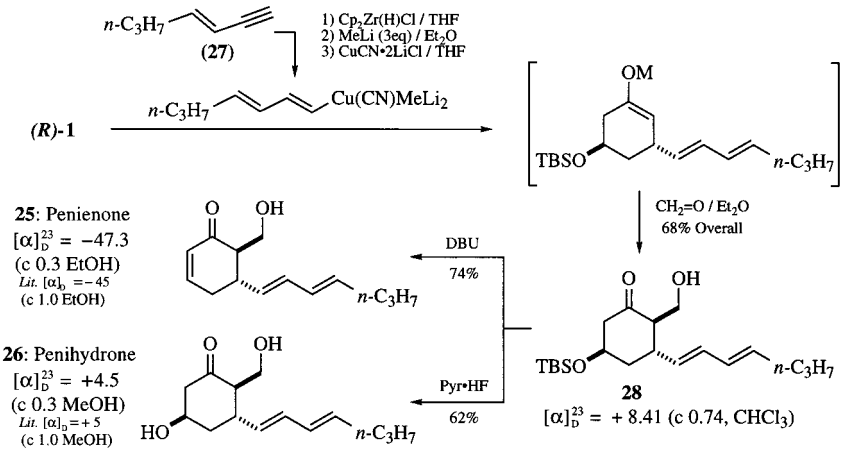
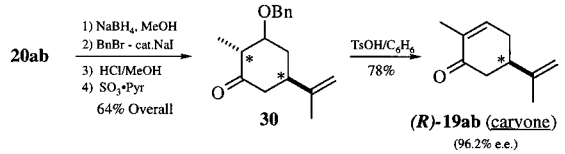
Scheme 9. Synthesis of (−)-Penienone and (+)-Penihydrone



Scheme 10. Synthesis of (*R*)-Carvone



by transmetalation with $Me_2Cu(CN)Li_2$ generated in situ gave the mixed higher-order (*E*,*E*)-dienylcyanocuprate which reacted highly selectively with (*R*)-**1** to give, after trap of the resulting copper enolate[34] with formaldehyde, the key intermediate **28** as a single diastereoisomer in a good 68% overall yield. The treatment of **28** with DBU in dichloromethane yielded penienone (**25**) in 74% yield. The protodesilylation of **28** proved to be troublesome: treatment with Bu_4NF gave a complex mixture of unidentified products and the reaction with an acidic reagent resulted in the β-elimination product **25**. However, the reaction of **28** with Pyr·HF in acetonitrile gave, to our satisfaction, penihydrone (**26**) in a moderate 62% yield. Both of the compounds **25** and **26** thus synthesized showed identical spectroscopic data as those reported for the products isolated from nature, therefore certifying the validity of the characterization.

We have already described the synthesis of (*S*)-carvone [(*S*)-**19ab**] by the reaction of **2a** with $(2\text{-propenyl})_2Cu(CN)Li_2$[27] (Scheme 7). We also readily succeeded in synthesizing (*R*)-carvone [(*R*)-**19ab**] from the same enantiomer of **2a** according to the procedures shown in Scheme 10. The (*R*)-carvone [(*R*)-**19ab**] thus obtained in 50% overall yield from **20ab** has an ee of 96.2%.[16]

Conclusion

A highly efficient and practical method for synthesizing the optically active 5-(*tert*-butyldimethylsiloxy)-2-cyclohexenone (**1**) and its 6-substituted derivatives **2** from the commercially available, optically active ethyl 3-hydroxy-4-chlorobutyrate has been developed. The cyclohexenones thus prepared are found to act as useful chiral building blocks for preparing both enantiomers of the 5-monosubstituted-2-cyclohexenones, and the 2,5- and 3,5-disubstituted- and 2,3,5-trisubstituted-2-cyclohexenones. The synthetic utility of the reaction has been demonstrated by the syntheses of several naturally occurring compounds such as penienone, penihydrone, and carvone.

Experimental Section

General Procedure. All reactions were carried out under an argon atmosphere, using flame-dried glassware and were monitored by TLC (Merck, Kieselgel 60 F254); visualization was done with UV light (254 nm)/$KMnO_4$ or CAN. ^1H and ^{13}C NMR were recorded at 300 and 75 MHz, respectively; chemical shifts (δ) are reported in parts per million with reference at 0.0 ppm (Me_4Si) or 7.26 ppm ($CHCl_3$) for the proton and at 77.0 ppm (centered on the signal of $CDCl_3$) for the carbon. Enantiomeric excess (ee) values have been determined by chiral GC (Chirasil-DEX/Chrompack, 0.25 mm × 25 m, DF = 0.25) or chiral HPLC (Daicel Chiralcel OB-H).

Materials. CuCN was purchased from Koso Chemical Co., Ltd. (Tokyo, Japan) and used without further purification. CuI was purified in a soxlet apparatus with refluxing THF. MeLi, BuLi, *s*-BuLi, *t*-BuLi, PhLi, and CH_2=CHMgBr were purchased from Aldrich; the citronellyllithium was prepared from citronellyl bromide and lithium metal in hexane at 60 °C; the vinyllithium was prepared from tetravinylstannane and BuLi. The concentrations of Grignard and organolithium reagents were determined according to an acid/base titration. (*R*)- and (*S*)-Ethyl 3-hydroxy-4-chlorobutyrate (**3**) are available from DAISO Co., Ltd (Japan).

Preparation of Enones 1 and 2. (*R*)-Ethyl 3-Hydroxy-4-iodobutyrate (5). To a solution of ethyl 3-hydroxy-4-chlorobutyrate (16.65 g, 100 mmol) in dry acetone (200 mL) was added dry NaI (60 g, 400 mmol). The mixture was stirred energetically under gentle reflux for 3 days. The acetone was mainly evaporated in vacuo, the residue diluted with water (100 mL). A usual extraction with Et_2O followed by washing with saturated $Na_2S_2O_3$ gave, after drying ($MgSO_4$) and evaporation of the solvent, a pale yellow oil which was passed through a pad of silica (elution hexane:Et_2O = 1:1) to give after concentration in vacuo **5**[35] (25.5 g, 98%).^1H NMR: δ 4.14 (q, J = 7.2 Hz, 2H), 3.98 (m, 1H), 3.34 (dd, J = 10.2 and 5.1 Hz, 1H), 3.28 (dd, J = 10.2 and 5.7 Hz, 1H), 3.22 (br s, 1H), 2.66 (dd, J = 16.5 and 4.2 Hz, 1H), 2.58 (dd, J = 16.5 and 7.8 Hz, 1H), 1.27 (t, J = 7.2 Hz, 3H). ^{13}C NMR: δ 171.7, 67.3, 60.8, 40.7, 13.8, 12.0.

(*R*)-Ethyl 3-(*tert*-Butyldimethylsiloxy)-4-iodobutyrate (6). To a solution of **5** (25.5 g, 98 mmol) in dry DMF (200 mL) were added imidazole (13.3 g, 196 mmol) and NaI (29.4 g, 196 mmol). Portionwise addition of TBSCl (22.3 g, 148 mmol) at 0 °C followed by stirring for 12 h from 0 °C to room temperature (rt) gave, after dilution with H_2O and usual workup with Et_2O, drying ($MgSO_4$), and evaporation, an oil which was purified by flash chromatography (SiO_2; hexanes−Et_2O gradient) to yield **6** (36.56 g, 99%) as a colorless oil. ^1H NMR: δ 4.14 (qd, J = 7.2 and 2.4 Hz, 2H), 4.03 (m, 1H), 3.30 (dd, J = 10.1 and 4.4 Hz, 1H), 3.25 (dd, J = 10.1 and 5.9 Hz, 1H), 2.68 (dd, J = 15.3 and 4.8 Hz, 1H), 2.53 (dd, J = 15.3 and 7.4 Hz, 1H), 1.27 (t, J = 7.2 Hz,

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3H), 0.88 (s, 9H), 0.12 (s, 3H), 0.07 (s, 3H). ^{13}C NMR: δ 170.8, 68.2, 60.3, 42.3, 25.4, 17.6, 13.9, 12.7, −4.8, −5.2. IR (neat): 2956, 2929, 2856, 1736, 1375, 1307, 1255, 1194, 1099, 837, 779 cm^{-1}. Anal. Calcd for $C_{12}H_{25}IO_3Si$: C, 38.71; H, 6.77. Found: C, 38.77; H, 6.80.

(*S*)-Ethyl 3-(*tert*-Butyldimethylsiloxy)-5-hexenoate (4). To a suspension of CuI (5.7 g, 30 mmol) in freshly distilled THF (60 mL) was slowly added, at −35 °C and under efficient magnetic stirring, vinylmagnesium bromide (1.0 M in THF, 60 mL, 60 mmol). The resulting brown slurry was stirred for 15 min, and DMPU (7.3 mL, 60 mmol)[36] was added at −35 °C followed by $(EtO)_3P$ (10.3 mL, 60 mmol).[37] The resulting mixture was stirred for 5 min and a THF (20 mL) solution of **6** (11.17 g, 30 mmol) was slowly added at −35 °C. The stirring was continued for 1 h at −35 °C before allowing the mixture to warm to r,.t. over a period of 2−3 h. The reaction was quenched at 0 °C (saturated NH_4Cl) and stirred at r.t. for 30 min. The product was extracted with Et_2O and dried ($MgSO_4$), and evaporation of the solvent gave a yellow residue which was purified by flash chromatography (SiO_2; hexanes−Et_2O) to give **4** (6.36 g, 78%) as a pale yellow oil. ^{1}H NMR: δ 5.81 (ddt, J = 17.9, 9.5 and 7.1 Hz, 1H), 5.11−5.03 (m, 2H), 4.21 (quint., J = 6.5 Hz, 1H), 4.12 (qt, J = 7.2 and 1.5 Hz, 2H), 2.43 (d, J = 6.9 Hz, 1H), 2.43 (d, J = 5.7 Hz, 1H), 2.31−2.25 (m, 2H), 1.26 (t, J = 7.2 Hz, 3H), 0.87 (s, 9H), 0.07 (s, 3H), 0.04 (s, 3H). ^{13}C NMR: δ 171.9, 134.2, 117.7, 68.9, 60.2, 42.1, 42.0, 25.6, 17.8, 14.0, −4.7, −5.1. IR (neat), 2929, 2858, 1737, 1471, 1375, 1309, 1255, 1176, 1093, 1034, 1004, 916, 837, 809, 777. Anal. Calcd for $C_{14}H_{28}O_3Si$: C, 61.72; H, 10.36. Found: C, 61.66; H, 10.38.

(1*RS*,3*S*)-1-Hydroxy-3-(*tert*-butyldimethylsiloxy)bicyclo[3.1.0]-hexane [(*S*)-7]. To a solution of (*S*)-**4** (6.36 g, 23.4 mmol) in freshly distilled Et_2O (120 mL) was added at r.t. Ti(O*i*-Pr)$_4$ (13.80 mL; 46.8 mmol); the resulting colorless mixture was cooled to −45 °C and *i*-PrMgCl (1.48 M in Et_2O, 63.2 mL, 93.6 mmol) was added dropwise. The clear yellow solution, which turned slowly to dark orange, was stirred for 1 h between −45 and −40 °C; then, the temperature was allowed to rise to r.t. over a period of 90 min and stirring was continued for another 2 h. The reaction was hydrolyzed at 0 °C with saturated NH_4Cl (25 mL); the resulting heterogeneous gray mixture was vigorously stirred for 30 min at r.t., whereupon a white suspension appeared. Extraction with Et_2O and drying ($MgSO_4$) gave, after evaporation of the solvent, a pale yellow oil which was purified by flash chromatography (SiO_2; hexanes−Et_2O gradient) to yield a colorless oil (*S*)-**7** (4.05 g, 76%) as a mixture of two diastereoisomers in a 1:1 ratio. ^{1}H NMR: δ 4.28−4.21 (m, 1H), 3.83−3.71 (m, 1H), 2.50−2.30 (br s, 2H), 2.35 (dd, J = 12.0 and 7.0 Hz, 1H), 2.26−2.13 (m, 2H), 2.04 (d, J = 13.5 Hz, 1H), 2.00−1.76 (m, 3H), 1.48 (d, J = 13.5 Hz, 1H), 1.38−1.27 (m, 2H), 1.06 (dd, J = 4.5 and 4.5 Hz, 1H), 0.94−0.74 (m, 2H), 0.85 (s, 9H), 0.84 (s, 9H), 0.38 (dd, J = 5.5 and 4.5 Hz, 1H), 0.01 (s, 3H), 0.00 (s, 3H), −0.01 (s, 3H), −0.02 (s, 3H). ^{13}C NMR: δ 71.9, 70.7, 63.7, 60.8, 44.2, 42.7, 37.8, 36.5, 25.70, 25.66, 23.7, 22.5, 18.9, 17.9, 17.7, 16.7, −5.00, −5.06. IR (neat) 3307, 2929, 2858, 1255, 1115, 1093, 1053, 1003, 837, 775. Anal. Calcd for $C_{12}H_{24}O_2Si$: C, 63.10; H, 10.59. Found: C, 63.01; H, 10.69.

(*S*)-5-(*tert*-Butyldimethylsiloxy)-2-cyclohexenone [(*S*)-1]. Into a flame-dried round-bottom flask flushed with argon was introduced $FeCl_3$ (6.34 g, 39.12 mmol); the flask was cooled to −5 °C and dry DMF (20 mL) was slowly added under vigorous magnetic stirring. The ice bath was removed, and pyridine (1.4 mL, 17.8 mmol) and then (*S*)-**7** (4.05 g, 17.78 mmol) in solution in DMF (2 mL) were added. The resulting mixture was stirred for 30 min at r.t. and diluted with water (20 mL). Extraction with Et_2O, drying ($MgSO_4$), and evaporation of the solvent gave a pale brown oil which was diluted with MeOH (20 mL) and treated at r.t. with NaOAc (7.38 g, 90 mmol) added in one portion under efficient stirring. The resulting mixture was stirred for 1 h before dilution with water (100 mL). Extraction with CH_2Cl_2, drying ($MgSO_4$), and concentration in vacuo gave a colorless oil which was rapidly purified by flash chromatography (SiO_2; hexanes−Et_2O gradient) to yield (*S*)-**1** as a colorless oil (3.61 g, 90%) stored over CaH_2 at r.t. $[\alpha]^{23}_D$ = + 9.82 (*c* 1.0, $CHCl_3$). ^{1}H NMR: δ 6.88 (ddd, J = 10.2, 5.1 and 3.3 Hz, 1H), 6.06 (br d, J = 10.2 Hz, 1H), 4.23 (dddd, J = 9.7, 7.6, 4.5 and 4.5 Hz, 1H), 2.66 (dd, J = 15.9, and 4.5 Hz, 1H), 2.65−2.54 (m, 1H), 2.48 (dd, J = 15.9 and 9.7 Hz, 1H), 2.38 (dddd, J = 18.3, 7.6, 3.1 and 3.1 Hz, 1H), 0.88 (s, 9H), 0.07 (s, 6H). ^{13}C NMR: δ 198.6, 146.9, 130.0, 67.4, 47.8, 35.3, 25.5, 17.7, −5.0, −5.1. IR (neat) 2954, 2929, 2856, 1684, 1253, 1103, 837, 777. Anal. Calcd for $C_{12}H_{22}O_2Si$: C, 63.67; H, 9.79. Found: C, 63.69; H, 9.78. Similarly, the commercially available (*S*)-**3** yielded (*R*)-**1**: $[\alpha]^{25}_D$ = − 9.88 (*c* 0.664, $CHCl_3$).

(*S*)-Ethyl 3-Hydroxy-5-hexenoate [(*S*)-9]. To an ice-cooled solution of (*S*)-**4** (2.72 g, 10 mmol) in acetonitrile (40 mL) was slowly added HF (55% solution, 0.4 mL, 26 mmol). The resulting mixture was allowed to stand at r.t. for 90 min before quenching with saturated $NaHCO_3$. Extraction with AcOEt, drying ($MgSO_4$), and concentration in vacuo gave a residue purified by flash chromatography (SiO_2; hexanes−Et_2O gradient) to yield (*S*)-**9** (1.42 g, 90%) as a pale yellow oil. ^{1}H NMR: δ 5.81 (ddt, J = 17.7, 9.6 and 7.2 Hz, 1H), 5.16−5.07 (m, 2H), 4.16 (q, J = 7.2 Hz, 2H), 4.11−4.02 (m, 1H), 2.97 (br s, 1H), 2.51 (dd, J = 16.5 and 3.9 Hz, 1H), 2.41 (dd, J = 16.5 and 8.7 Hz, 1H), 2.30−2.23 (m, 2H), 1.26 (t, J = 7.2 Hz, 3H). ^{13}C NMR: δ 172.9, 134.0, 118.2, 67.3, 60.6, 40.8, 40.5. 14.0. IR (neat): 3448, 3078, 2981, 2933, 1734, 1641, 1373, 1302, 1265, 1176, 1117, 1030, 918, 850 cm^{-1}. Anal. Calcd for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 60.46; H, 9.07.

(2*S*,3*S*)-Ethyl 2-Methyl-3-hydroxy-5-hexenoate (10a). To a THF (27 mL) solution of *i*-Pr_2NH (3.75 mL, 27 mmol) cooled to −78 °C was added BuLi (1.58 M in *n*-hexane, 17.1 mL, 27 mmol). The cooling bath was removed and the mixture was allowed to stir at r.t. for 30 min. The resulting clear solution was cooled to −60 °C, and a THF solution (5 mL) of (*S*)-**9** (1.42 g, 9 mmol) was added dropwise via syringe. The mixture was stirred for 30 min from −60 to −25 °C and a mixture of MeI (1.40 mL, 22.5 mmol) and DMPU (4.23 mL; 35.1 mmol) was slowly added. The mixture was allowed to stir for 30 min from −25 to 0 °C before quenching with water. Extraction with AcOEt, drying ($MgSO_4$), and evaporation of the solvent gave an oil which was purified by flash chromatography (SiO_2; hexanes−Et_2O) to yield **10a** (1.32 g, 85%) as a pale yellow oil in a diastereomeric ratio = 9:1. *Major diastereoisomer:* ^{1}H NMR: δ 5.86 (dddd, J = 17.4, 9.6, 7.8 and 6.6 Hz, 1H), 5.18−5.09 (m, 2H), 4.17 (qd, J = 7.2 and 0.6 Hz, 2H), 3.74 (ddd, J = 7.8, 6.6 and 4.5 Hz, 1H), 2.55 (dq, J = 7.2 and 7.2 Hz, 1H), 2.40−2.30 (m, 1H), 2.27−2.15 (m, 1H), 1.28 (t, J = 7.2 Hz, 3H), 1.20 (d, J = 7.2 Hz, 3H). ^{13}C NMR: δ 176.0, 134.3, 118.1, 72.5, 60.6, 44.4, 39.0, 14.05, 14.0. IR (neat): 3462, 3076, 2979, 2939, 1734, 1641, 1462, 1375, 1257, 1184, 1095, 1043, 916, 864 cm^{-1}. Anal. Calcd for $C_9H_{16}O_3$: C, 62.77; H, 9.36. Found: C, 62.81; H, 9.60. *Minor diastereoisomer:* ^{1}H NMR: δ 3.96 (ddd, 7.5, 5.4 and 3.9 Hz, 1H).

(2*S*,3*S*)-Ethyl 2-Benzyl-3-hydroxy-5-hexenoate (10b). The proton and carbon NMR analysis of the crude mixture showed only one diastereoisomer. ^{1}H NMR: δ 7.32−7.15 (m, 5H), 5.88−5.73 (m, 1H), 5.15−5.06 (m, 2H), 4.07 (q, J = 7.2 Hz, 2H), 3.72 (dt, J = 6.3 and 4.5 Hz, 1H), 3.00 (d, J = 8.7 Hz, 1H), 2.99 (d, J = 6.9 Hz, 1H), 2.76 (ddd, J = 8.7, 6.9 and 4.5 Hz, 1H), 2.30 (br t, J = 6.7 Hz, 2H), 1.16 (t, J = 7.3 Hz, 3H). ^{13}C NMR: δ 175.0, 138.7, 134.2, 129.1, 128.5, 126.6, 118.2, 70.9, 60.5, 51.7, 40.3, 35.5, 13.9. IR (neat) 3448, 2933, 1729, 1184, 1030, 916, 700. Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.24; H, 8.17.

(2*S*,3*S*)-Ethyl 2-Methyl-3-(*tert*-butyldimethylsiloxy)-5-hexenoate (11a). To an ice-cooled solution of **10a** (1.2 g, 7.0 mmol) and imidazole (953 mg, 14 mmol) in dry DMF (14 mL) was added TBSCl (1.58 g, 10.5 mmol) in several portions; the mixture was stirred for 12 h at r.t. and quenched with water. Extraction with Et_2O, drying ($MgSO_4$), and concentration in vacuo gave a residue which was purified by flash chromatography (SiO_2; hexanes−Et_2O gradient) to yield **11a** (1.98 g, 99%) as a colorless oil (diastereomeric ratio = 9:1). *Major diastereoisomer:* ^{1}H NMR: δ 5.92−5.77 (m, 1H), 5.11−5.02 (m, 2H), 4.11 (qd, J = 7.2 and 0.8 Hz, 2H), 3.97 (dt, J = 6.9 and 4.8 Hz, 1H), 2.60 (dq, J = 7.2 and 7.2 Hz, 1H), 2.30−2.21 (m, 2H), 1.26 (t, J = 7.2 Hz, 3H), 1.08 (d, J = 7.2 Hz, 3H), 0.87 (s, 9H), 0.07 (s, 3H), 0.04 (s, 3H). ^{13}C NMR: δ 175.0, 134.3, 117.4, 73.2, 60.1, 45.2, 38.0, 25.6, 17.9, 14.0, 12.3, −4.49, −5.16. IR (neat): 2929, 2858, 1738, 1464, 1375,

(36) *N*,*N*′-(Dimethylpropylene)urea (DMPU) was employed as a substitute for the highly toxic HMPA commonly used for this reaction, see: *The Encyclopedia of Reagents in Organic Synthesis*; Paquette, L., Ed., J. Wiley and Sons: New York, 1995; pp 2123−2127 and references therein.

(37) Alexakis, A.; Cahiez, G.; Normant, J. F. *Synthesis* **1979**, 826−830.

1331, 1255, 1178, 1084, 1003, 937, 912, 837, 812, 775, 721, 665 cm^{-1}. Anal. Calcd for $C_{15}H_{30}O_3Si$: C, 62.89; H, 10.55. Found: C, 62.58; H, 10.50. *Minor diastereoisomer:* ^1H NMR: δ 1.12 (d, 7.5 Hz, 3H).

(2*S*,3*S*)-Ethyl 2-Benzyl-3-(*tert*-butyldimethylsiloxy)-5-hexenoate (11b). ^1H NMR: δ 7.28−7.11 (m, 5H), 5.99−5.82 (m, 1H), 5.18−5.08 (m, 2H), 4.10−3.88 (m, 3H), 2.90−2.77 (m, 3H), 2.48−2.24 (m, 2H), 1.02 (t, J = 7.5 Hz, 3H), 0.87 (s, 9H), 0.07 (s, 3H), 0.04 (s, 3H). ^{13}C NMR: δ 173.7, 139.6, 134.1, 129.0, 128.3, 126.2, 117.8, 72.6, 60.0, 53.6, 38.6, 33.7, 25.6, 17.9, 13.9, −4.4, −5.1. IR (neat): 2929, 2856, 1733, 912. Anal. Calcd for $C_{21}H_{34}O_3Si$: C, 69.56; H, 9.45 cm^{-1}. Found: C, 69.64; H, 9.57.

(1*RS*,2*S*,3*S*)-1-Hydroxy-2-methyl-3-(*tert*-butyldimethylsiloxy)-bicyclo[3.1.0]hexane (12a). Obtained as a complex mixture of diastereoisomers, the characterization of which was difficult. Following are some characteristic signals: ^1H NMR: δ 4.03 (ddd, J = 6.0, 6.0 and 1.5 Hz, 1H), 3.86 (m, 1H), 2.38 (dqd, J = 6.9, 6.9 and 2.4 Hz, 1H), ..., 1.52 (d, J = 13.8 Hz, 1H), ..., 1.04 (d, J = 6.9 Hz, 3H), ..., 0.86 (s, 9H), ..., 0.71−0.64 (m, 1H), 0.58−0.53 (m, 1H). ^{13}C NMR: δ 73.2, 67.8, 45.4, 37.2, 31.5, 25.7, 23.3, 22.6, 17.9, 16.4, 14.0, 9.6, −4.8, −5.3. IR (neat): 3309, 2956, 2929, 2858, 1471, 1361, 1255, 1049, 1020, 837, 775 cm^{-1}. Anal. Calcd for $C_{13}H_{26}O_2Si$: C, 64.41; H, 10.81. Found: C, 64.49; H, 10.92.

(1*RS*,2*S*,3*S*)-1-Hydroxy-2-benzyl-3-(*tert*-butyldimethylsiloxy)-bicyclo[3.1.0]hexane (12b). Obtained as a 7:3 mixture of diastereoisomers. ^1H NMR: δ 7.40−7.15 (m, 5H), 4.20 (ddd, J = 6.0, 6.0 and 1.2 Hz, 1H), 4.02−3.88 (m, 1H), 3.23 (dd, J = 14.4 and 4.0 Hz, 1H), 2.97−2.81 (m, 2H), 2.81−2.68 (m, 2H), 2.22 (ddd, J = 13.5, 5.0 and 5.0 Hz, 1H), 1.90−1.63 (m, 2H), 1.58 (d, J = 13.5 Hz, 1H), 1.46−1.38 (m, 1H), 1.36−1.25 (m, 2H), 1.19 (dd, J = 4.8 and 4.8 Hz, 1H), 0.92 (s, 9H), 0.89 (s, 9H), 0.81−0.74 (m, 1H), 0.57 (dd, J = 5.5 and 4.5 Hz, 1H), 0.06−0.15 (m, 12H). IR (neat): 3359, 2954, 2929, 2856, 1716, 1471, 1255, 1103, 1057, 837, 775, 734, 698 cm^{-1}. Anal. Calcd for $C_{19}H_{30}O_2Si$: C, 71.64; H, 9.49. Found: C, 71.80; H, 9.61.

(5*S*,6*S*)-5-(*tert*-Butyldimethylsiloxy)-6-methyl-2-cyclohexenone (2a). Obtained as a 9:1 mixture of diastereoisomers: $[\alpha]^{23}_D$ = − 28.98 (*c* 0.25, $CHCl_3$). *Major diastereoisomer:* ^1H NMR: δ 6.75 (dddd, J = 10.2, 3.9, 3.9 and 0.6 Hz, 1H), 6.01 (ddd, J = 10.2, 2.1 and 2.1 Hz, 1H), 4.21 (ddd, J = 6.0, 4.2 and 0.9 Hz, 1H), 2.60−2.37 (m, 3H), 1.13 (d, J = 6.9 Hz, 3H), 0.84 (s, 9H), 0.07 (s, 6H). ^{13}C NMR: δ 201.8, 145.1, 129.3, 71.0, 48.3, 33.5, 25.5, 17.8, 10.5, −4.9, −5.0. IR (neat) 2929, 1682, 1462, 1390, 1255, 1207, 1109, 1063, 1020, 883, 837, 775, 665. Anal. Calcd for $C_{13}H_{24}O_2Si$: C, 64.95; H, 10.06. Found: C, 64.93; H, 9.99. *Minor diastereoisomer:* ^1H NMR: δ 6.85−6.78 (m, 1H), 3.77 (ddd, J = 9.9, 8.4 and 4.8 Hz, 1H), 1.16 (d, J = 6.9 Hz, 3H). ^{13}C NMR: δ 145.8, 129.6, 72.6, 51.1, 35.4, 11.2.

(5*S*,6*S*)-5-(*tert*-Butyldimethylsiloxy)-6-benzyl-2-cyclohexenone (2b). Obtained as a single diastereoisomer. $[\alpha]^{23}_D$ = + 69.5 (*c* 1.11 $CHCl_3$). ^1H NMR: δ 7.35−7.15 (m, 5H), 6.71 (dddd, J = 9.9, 3.9, 3.9 and 1.2 Hz, 1H), 6.07 (ddd, J = 9.9, 1.8 and 1.8 Hz, 1H), 4.27−4.21 (m, 1H), 3.25 (dd, J = 14.1 and 5.1 Hz, 1H), 2.84−2.75 (m, 1H), 2.70 (ddd, J = 8.1, 5.4 and 2.7 Hz, 1H), 2.50 (ddd, J = 3.9, 3.9 and 2.1 Hz 2H), 0.87 (s, 9H), 0.06 (s, 3H), 0.02 (s, 3H). ^{13}C NMR: δ 199.7, 144.0, 140.3, 129.7, 129.2, 128.4, 126.1, 69.2, 55.9, 34.5, 30.6, 25.6, 17.9, −4.6, −4.9. IR (neat) 2927, 1681, 1454, 1390, 1259, 1095, 835, 777, 698. Anal. Calcd for $C_{19}H_{28}O_2Si$: C, 72.10; H, 8.92. Found: C, 72.28; H, 8.79.

Reactions of Higher-Order Cyanocuprates onto 1. (3*S*,5*S*)-3-(*tert*-Butyldimethylsiloxy)-5-butylcyclohexanone. Typical procedure for the reaction of higher-order cyanocuprates on enones **1** and **2** (Table 1, entry 2): Into a flame-dried Schlenck tube flushed with argon were introduced CuCN (107 mg, 1.2 mmol) and distilled THF (20 mL). The mixture was cooled to −78 °C under magnetic agitation, and BuLi (1.51 mL, 1.59 M in *n*-hexane, 2.4 mmol) was slowly added. The resulting mixture was stirred for 30 min at −78 °C, and the enone **1** (226 mg, 1 mmol) in a solution in THF (1 mL) was added dropwise at −78 °C (addition time: about 5 min). Stirring was continued for 30 min before quenching with saturated NH_4OH. Extraction with Et_2O, drying ($MgSO_4$) and evaporation of the solvent gave a colorless oil, *cis*:*trans* = <2:>98 by GC measurement; purification by flash chromatography (SiO_2, hexane:Et_2O = 9:1) yielded the title product as a colorless oil (261 mg, 0.92 mmol, 92%). ^1H NMR: δ 4.43−4.37 (m, 1H), 2.49−2.32 (m, 3H), 2.32−2.15 (m, 1H), 2.00−1.85 (m, 2H), 1.90 (br d, J = 13.5 Hz, 1H), 1.47 (ddd, J = 13.5, 11.4 and 2.1 Hz, 1H), 1.37−1.24 (m, 6H), 0.90 (t, J = 7.2 Hz, 3H), 0.86 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H). ^{13}C NMR: δ 210.4, 68.9, 49.5, 47.9, 38.9, 36.0, 32.2, 28.7, 25.5, 22.5, 17.8, 13.9, −5.1. IR (neat): 2929, 1718, 1464, 1253, 1101, 1045, 891, 837, 777 cm^{-1}. Anal. Calcd for $C_{16}H_{32}O_2Si$: C, 67.55; H, 11.34. Found: C, 67.81; H, 11.38.

(3*S*,5*S*)-3-(*tert*-Butyldimethylsiloxy)-5-methylcyclohexanone (Table 1, Entry 1). ^1H NMR: δ 4.43−4.37 (m, 1H), 2.46−2.31 (m, 4H), 2.00−1.80 (m, 2H), 1.48 (ddd, J = 13.5, 11.4 and 2.1 Hz, 1H), 1.02 (d, J = 6.6 Hz, 3H), 0.85 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H). ^{13}C NMR: δ 210.4, 69.0, 49.7, 49.1, 40.9, 27.6, 25.6, 21.8, 17.8, −5.1. IR (neat): 2954, 2929, 2856, 1718, 1251, 1116, 1088, 1043, 887, 837, 777 cm^{-1}. Anal. Calcd for $C_{13}H_{26}O_2Si$: C, 64.41; H, 10.81. Found: C, 64.51; H, 10.35.

(3*S*,5*S*)-3-(*tert*-Butyldimethylsiloxy)-5-{1-[(3*S*)-3,7-dimethyl-6-octenyl]}cyclohexanone (Table 1, Entry 3). To a freshly prepared THF solution of (2-thienyl)cyanocuprate[19] was added at −78 °C a THF (1 mL) solution of (*S*)-**1**, and the resulting mixture was stirred for 1 h at −78 °C. The reaction was quenched and the product extracted and purified (60%, not optimized) in the usual way. ^1H NMR: δ 5.08 (br t, J = 7.2 Hz, 1H), 4.41−4.35 (m, 1H), 2.47−2.30 (m, 3H), 2.27−2.10 (m, 1H), 2.06−1.83 (m, 4H), 1.67 (s, 3H), 1.58 (s, 3H), 1.45 (br t, J = 13.5 Hz, 1H), 1.44−1.20 (m, 5H), 1.20−1.03 (m, 2H), 0.90−0.78 (m, 12H), 0.03 (s, 3H), 0.02 (s, 3H). ^{13}C NMR: δ 210.4, 131.2, 124.9, 68.9, 49.5, 48.1, 38.8, 36.9, 33.7, 33.6, 32.6, 32.3, 25.6, 25.55, 25.4, 19.3, 17.8, 17.5, −5.1. IR (neat): 2927, 1718, 1459, 1373, 1253, 1091, 1035, 892, 837, 804, 777, 692 cm^{-1}. Anal. Calcd for $C_{22}H_{42}O_2Si$: C, 72.07; H, 11.55. Found: C, 71.94; H, 11.55.

(3*S*,5*S*)-3-(*tert*-Butyldimethylsiloxy)-5-(2-butyl)cyclohexanone (Table 1, Entry 4). Mixture of two diastereoisomers at *CH*-CH_3. ^1H NMR: δ 4.48−4.39 (m, 2H), 2.44−2.20 (m, 8H), 2.16−1.94 (m, 2H), 1.84−1.72 (m, 2H), 1.62−1.08 (m, 8H), 0.91−0.81 (m, 30H), 0.02 (s, 6H), 0.01 (s, 6H). ^{13}C NMR: δ 211.0, 68.9, 49.4, 49.3, 46.0, 44.1, 38.5, 38.4, 36.5, 36.0, 34.2, 26.5, 26.2, 25.6, 17.8, 15.2, 15.1, 11.5, 11.4, −5.1, −5.1. IR (neat): 2958, 2858, 1718, 1461, 1251, 1103, 1076, 1047, 893, 837, 775 cm^{-1}. Anal. Calcd for $C_{16}H_{32}O_2Si$: C, 67.55; H, 11.34. Found: C, 67.56; H, 11.23.

(3*S*,5*S*)-3-(*tert*-Butyldimethylsiloxy)-5-*tert*-butylcyclohexanone (Table 1, Entry 5). Mp = 46−47 °C. ^1H NMR: δ 4.49−4.43 (m, 1H), 2.49−2.40 (br d, J = 10.5 Hz, 1H), 2.40−2.34 (m, 2H), 2.12−1.88 (m, 3H), 1.46 (ddd, J = 13.5, 12.0 and 1.8 Hz 1H), 0.89 (s, 9H), 0.85 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H). ^{13}C NMR: δ 211.6, 68.8, 49.1, 43.4, 41.8, 33.5, 32.0, 27.1, 25.5, 17.8, −5.1, −5.2. IR (neat): 2954, 2856, 1701, 1471, 1365, 1253, 1095, 1034, 893, 837, 777 cm^{-1}. Anal. Calcd for $C_{16}H_{32}O_2Si$: C, 67.55; H, 11.34. Found: C, 67.45; H, 11.15.

(3*S*,5*S*)-3-(*tert*-Butyldimethylsiloxy)-5-phenylcyclohexanone (Table 1, Entry 6). ^1H NMR: δ 7.39−7.30 (m, 2H), 7.29−7.14 (m, 3H), 4.55−4.48 (m, 1H), 3.55 (dddd, J = 12.6, 12.6, 4.5 and 4.5 Hz, 1H), 2.67−2.43 (m, 4H), 2.14−1.93 (m, 2H), 0.89 (s, 9H), 0,07 (s, 3H), 0.06 (s, 3H). ^{13}C NMR: δ 209.5, 144.2, 128.8, 126.8, 126.7, 68.8, 49.0, 48.7, 40.1, 38.0, 25.6, 17.9, −5.10, −5.13. IR (neat): 2954, 2856, 1718, 1251, 1095, 1037, 837, 777, 698 cm^{-1}. Anal. Calcd for $C_{18}H_{28}O_2Si$: C, 71.00; H, 9.27. Found: C, 70.95; H, 8.94.

(3*S*,5*S*)-3-(*tert*-Butyldimethylsiloxy)-5-ethenylcyclohexanone (Table 1, Entry 7). ^1H NMR: δ 5.81 (ddd, J = 16.8, 10.5 and 6.5 Hz, 1H), 5.07−4.98 (m, 2H), 4.45−4.39 (m. 1H), 3.03−2.88 (m, 1H), 2.51−2.38 (m, 3H), 2.15 (ddd, J = 14.0, 11.5 and 0.9 Hz, 1H), 1.98−1.88 (m, 1H), 1.65 (ddd, J = 13.5, 11.5 and 2.1 Hz, 1H), 0.86 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H). ^{13}C NMR: δ 209.4, 141.4, 113.7, 68.6, 49.3, 46.5, 38.5, 36.0, 25.6, 17.8, −5.10, −5.13. IR (neat): 2929, 2856, 1718, 1641, 1471, 1417, 1361, 1253, 1086, 1041, 891, 837, 777 cm^{-1}. Anal. Calcd for $C_{14}H_{26}O_2Si$: C, 66.09; H, 10.30. Found: C, 66.14; H, 10.80.

Reactions of Lower−Order Cyanocuprates onto 1. (3*S*,5*R*)-3-(*tert*-Butyldimethylsiloxy)-5-butylcyclohexanone. Typical procedure for the reaction of lower-order cyanocuprates on enones **1** and **2** (Table 2, entry 3): Into a flame-dried Schlenck tube flushed with argon were introduced CuCN (107 mg, 1.2 mmol) and dry Et_2O (20 mL). The suspension was cooled to −78 °C under magnetic agitation, and BuLi (0.75 mL, 1.59 M in *n*-hexane, 1.2 mmol) was slowly added. The resulting mixture was stirred for 30 min at −78 °C (until complete

dissolution of the copper salt; the mixture can be warmed to 0 °C if needed), and **1** (113 mg, 0.5 mmol), in dry Et_2O (1 mL), was added dropwise at −78 °C (addition time: about 5 min). Stirring was continued for a further hour before quenching with saturated NH_4OH. Extraction with Et_2O, drying ($MgSO_4$), and evaporation of the solvent gave a colorless oil, *cis*:*trans* = >99.5:<0.5 by GC measurement; purification by flash chromatography (SiO_2, hexane:Et_2O = 9:1) yielded the title product as a colorless oil (130 mg, 0.455 mmol, 91%). ^{1}H NMR: δ 3.83 (dddd, 10.6, 10.6, 4.8 and 4.8 Hz, 1H), 2.59 (dddd, J = 13.8, 5.1, 2.4 and 2.4 Hz, 1H), 2.38−2.26 (m, 2H), 2.11−2.00 (m, 1H), 1.91 (dd, J = 13.2 and 13.2 Hz, 1H), 1.65−1.47 (m, 1H), 1.44−1.18 (m, 7H), 0.93−0.78 (m, 12H), 0.04 (s, 3H), 0.03 (s, 3H). ^{13}C NMR: δ 209.6, 69.6, 51.5, 46.9, 41.5, 36.1, 32.7, 28.6, 25.6, 22.5, 17.8, 13.8, −4.96, −4.98. IR (neat): 2929, 2857, 1716, 1685, 1471, 1376, 1255, 1105, 835, 777 cm^{-1}. Anal. Calcd for $C_{16}H_{32}O_2Si$: C, 67.55; H, 11.34. Found: C, 67.56; H, 11.23.

(3*S,5*R**)-3-(*tert*-Butyldimethylsiloxy)-5-methylcyclohexanone (Table 2, Entry 1).** ^{1}H NMR: δ 3.83 (dddd, J = 10.8, 10.8, 4.6 and 4.6 Hz, 1H), 2.56 (dddd, J = 13.5, 4.8, 2.1 and 2.1 Hz, 1H), 2.35−2.22 (m, 2H), 2.06−1.97 (m, 1H), 1.91 (ddd, J = 13.0, 13.0 and 1.2 Hz, 1H), 1.77−1.60 (m, 1H), 1.38 (ddd, J = 12.6, 12.6 and 10.8 Hz 1H), 1.03 (d, J = 6.3 Hz, 3H), 0.85 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H). ^{13}C NMR: δ 209.6, 69.6, 51.1, 48.8, 43.5, 28.0, 25.6, 21.8, 17.9, −4.93, −4.96. IR (neat): 2958, 2856, 1683, 1471, 1390, 1367, 1255, 877, 835, 771 cm^{-1}. Anal. Calcd for $C_{13}H_{26}O_2Si$: C, 64.41; H, 10.81. Found: C, 64.90; H, 10.45.

(3*S,5*R**)-3-(*tert*-Butyldimethylsiloxy)-5-{1-[(3*S*)-3,7-dimethyl-6-octenyl]}cyclohexanone (Table 2, Entry 6).** ^{1}H NMR: δ 5.08 (br t, J = 7.0 Hz, 1H), 3.83 (dddd, J = 10.5, 10.5, 4.8 and 4.8 Hz, 1H), 2.59 (dddd, J = 13.5, 5.1, 2.1 and 2.1 Hz, 1H), 2.38−2.28 (m, 2H), 2.11−2.01 (m, 1H), 2.01−1.86 (m, 3H), 1.67 (s, 3H), 1.59 (s, 3H), 1.60−1.45 (m, 1H), 1.45−1.22 (m, 7H), 1.20−1.02 (m, 1H), 0.95−0.85 (m, 12H), 0.04 (s, 3H), 0.03 (s, 3H). ^{13}C NMR: δ 209.8, 131.2, 124.8, 69.7, 51.6, 47.12, 46.95, 41.73, 41.55, 36.9, 33.9, 33.7, 33.1, 32.3, 25.6, 25.4, 19.4, 17.9, 17.5, −4.88, −4.91. IR (neat): 2954, 2927, 2856, 1716, 1461, 1376, 1255, 1105, 1072, 837, 777 cm^{-1}. Anal. Calcd for $C_{22}H_{42}O_2Si$: C, 72.07; H, 11.55. Found: C, 72.15; H, 11.44.

(3*S,5*R**)-3-(*tert*-Butyldimethylsiloxy)-5-(2-butyl)cyclohexanone (Table 2, Entry 8).** Mixture of two diastereoisomers at *CH*-CH_3. ^{1}H NMR: δ 3.88−3.75 (m, 2H), 2.58 (dddd, J = 13.5, 4.8, 2.1 and 2.1 Hz, 2H), 2.30 (ddd, J = 13.5, 10.8 and 0.9 Hz, 2H), 2.25−2.15 (m, 2H), 2.06 (ddd, J = 13.5, 13.5 and 0.9 Hz, 2H), 2.04−1.88 (m, 2H), 1.64−1.27 (m, 8H), 1.25−1.05 (m, 2H), 0.94−0.78 (m, 30H), 0.05 (s, 6H), 0.03 (s, 6H). ^{13}C NMR: δ 210.2, 210.1, 70.0, 69.9, 51.6, 44.7, 42.5, 39.3, 38.6, 38.4, 37.2, 36.9, 36.7, 26.5, 26.2, 25.6, 17.9, 15.2, 14.8, 11.63, 11.57, −4.9. IR (neat): 2958, 1716, 1464, 1379, 1253, 1097, 1072, 856, 835, 777 cm^{-1}. Anal. Calcd for $C_{16}H_{32}O_2Si$: C, 67.55; H, 11.34. Found: C, 67.36; H, 11.28.

(3*S,5*R**)-3-(*tert*-Butyldimethylsiloxy)-5-*tert*-butylcyclohexanone (Table 2, Entry 9).** ^{1}H NMR: δ 3.80 (dddd, J = 10.2, 10.2, 4.2 and 4.2 Hz, 1H), 2.60 (dddd, J = 13.5, 4.8, 2.1 and 2.1 Hz, 1H), 2.41−2.26 (m, 2H), 2.13−2.05 (m, 1H), 2.00 (dd, J = 13.2 and 13.2 Hz, 1H), 1.47−1.23 (m, 2H), 0.95−0.85 (m, 18H), 0.05 (s, 3H), 0.03 (s, 3H). ^{13}C NMR: δ 210.6, 70.1, 51.4, 42.6, 42.4, 36.5, 32.3, 27.1, 25.7, 17.9, −4.88, −4.90. IR (neat): 2956, 2858, 1716, 1369, 1255, 1103, 835, 777 cm^{-1}. Anal. Calcd for $C_{16}H_{32}O_2Si$: C, 67.55; H, 11.34. Found: C, 67.29; H, 11.27.

(3*S,5*R**)-3-(*tert*-Butyldimethylsiloxy)-5-phenylcyclohexanone (Table 2, Entry 10):** ^{1}H NMR: δ 7.39−7.30 (m, 2H), 7.29−7.20 (m, 3H), 4.00 (dddd, J = 10.6, 10.6, 4.8 and 4.8 Hz, 1H), 2.83 (dddd, J = 12.9, 12.9, 4.2 and 3.6 Hz, 1H), 2,71 (dddd, J = 13.5, 5.1, 2.1 and 2.1 Hz, 1H), 2.57−2.38 (m, 3H), 2.31−2.21 (m, 1H), 1.95 (ddd, J = 12.9, 12.9 and 10.5 Hz, 1H), 0.88 (s, 9H), 0,072 (s, 3H), 0.067 (s, 3H). ^{13}C NMR: δ 208.8, 143.5, 128.9, 127.0, 126.7, 69.7, 51.4, 48.3, 42.4, 38.6, 25.6, 17.9, −4.90, −4.93. IR (neat): 2959, 2858, 1716, 1251, 1099, 835, 698 cm^{-1}. Anal. Calcd for $C_{18}H_{28}O_2Si$: C, 71.00; H, 9.27. Found: C, 70.98; H, 9.25.

Elimination Reactions. Typical Procedure for the Elimination of *trans*-13 into 14 (Table 1, Entry 1). To a CH_2Cl_2 solution (3 mL) of *trans*-3-(*tert*-butyldimethylsiloxy)-5-methylcyclohexanone (201 mg, 0.83 mmol) was added at r.t. DBU (0.37 mL, 2.5 mmol). The reaction was allowed to stand for 5 h at r.t., the solvent was evaporated in vacuo and the brown residue purified by flash chromatography (SiO_2; hexane:Et_2O = 9:1), yielding the 5-methyl-2-cyclohexenone (84 mg, 92%) as a colorless oil which was Kugelrohr-distilled before measurement of the optical rotation.

Typical Procedure for the Elimination of *cis*-13 into 14 in Basic Conditions (Table 2, Entry 1). To a dry DMF (2 mL) solution of *cis*-3-(*tert*-butyldimethylsiloxy)-5-methylcyclohexanone (93 mg, 0.39 mmol) was added DBU (0.17 mL, 1.16 mmol) at r.t., and the mixture was heated between 90 and 100 °C for 1 h. The reaction was allowed to cool to r.t., taken up in 20 mL of Et_2O, and washed with H_2O (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, the solvent was evaporated, and the yield was measured by proton NMR.

Procedure for the Elimination of *cis*-13 into 14 in Acidic Conditions (Table 2, Entry 8). To a solution of *cis*-3-(*tert*-butyldimethylsiloxy)-5-(2-butyl)cyclohexanone (119 mg, 0.42 mmol) in dry CH_2Cl_2 (2 mL) was added *p*-TSA·H_2O (56 mg, 5 mol %) (*p*-TSA = *p*-toluenesulfonic acid) at r.t.; the mixture was stirred at r.t. for 3 h and quenched with saturated $NaHCO_3$. The product was extracted with CH_2Cl_2 and dried ($MgSO_4$), the solvent was evaporated, and the yield was measured by proton NMR (75%). Mixture of diastereoisomers at *CH*-CH_3: ^{1}H NMR: δ 6.99 (ddd, J = 10.0, 6.0 and 2.1 Hz, 1H), 5.98 (br d, J = 10.0 Hz, 1H), 2.42 (br d, J = 15.5 Hz, 1H), 2.38−2.25 (m, 1H), 2.25−1.95 (m, 3H), 1.50−1.07 (m, 3H), 0.94−0.78 (m, 6H). ^{13}C NMR: δ 200.9, 150.7, 150.6, 129.6, 42.4, 40.7, 39.53, 39.45, 38.33, 38.28, 30.0, 28.4, 26.1, 15.3, 11.4, 11.35.

Synthesis of Optically Active 2,5- 3,5-, and 2,3,5-Cyclohexenones. (2*S*,3*S*,5*S*)-2-Methyl-3-(*tert*-butyldimethylsiloxy)-5-(2-propyl)cyclohexanone (20aa). *Major diastereoisomer*: ^{1}H NMR: δ 4.25−4.20 (m, 1H), 2.45−2.35 (m, 2H), 2.14−1.89 (m, 3H), 1.59−1.47 (m, 2H), 1.01 (d, J = 6.6 Hz, 3H), 0.89 (d, J = 6.6 Hz, 6H), 0.84 (s, 9H), 0.03 (s, 6H). ^{13}C NMR: δ 212.0, 74.4, 49.9, 45.3, 39.1, 36.5, 32.2, 25.6, 19.5, 19.3, 17.9, 11.3, −4.7, −5.2. IR (neat): 2958, 1718, 1464, 1289, 1254, 1055, 1014, 837, 775 cm^{-1}. Anal. Calcd for $C_{16}H_{32}O_2Si$: C, 67.55; H, 11.34. Found: C, 67.77; H, 11.27.

(2*S*,3*S*,5*S*)-2-Methyl-3-(*tert*-butyldimethylsiloxy)-5-(2-propenyl)-cyclohexanone (20ab). *Major diastereoisomer:* ^{1}H NMR: δ 4.77 (s, 1H), 4.71 (s, 1H), 4.29−4.21 (m, 1H), 2.85 (dddd, J = 12.6, 12.6, 3.6 and 3.6 Hz, 1H), 2.48−2.38 (m, 2H), 2.22 (dd, J = 13.5 and 13.5 Hz, 1H), 2.03−1.94 (m, 1H), 1.80−1.68 (m, 1H), 1.72 (s, 3H), 1.01 (d, J = 6.6 Hz, 3H), 0.84 (s, 9H), 0.02 (s, 6H). ^{13}C NMR: δ 210.9, 147.6, 109.7, 74.13, 49.8, 46.3, 39.8, 38.6, 25.6, 20.5, 17.9, 11.2, −4.7, −5.2. IR (neat): 2931, 1858, 1718 1462, 1377, 1255, 1119, 1070, 1033, 876, 837, 775 cm^{-1}. Anal. Calcd for $C_{16}H_{30}O_2Si$: C, 68.03; H, 10.70. Found: C, 67.60; H, 10.84.

(2*S*,3*S*,5*S*)-2-Methyl-3-(*tert*-butyldimethylsiloxy)-5-butylcyclohexanone (20ac). *Major diastereoisomer:* ^{1}H NMR: δ 4.22−4.16 (m, 1H), 2.46−2.34 (m, 2H), 2.30−2.12 (m, 1H), 2.00−1.80 (m, 2H), 1.48 (ddd, J = 13.5, 11.7, 1.8 Hz, 1H), 1.38−1.17 (m, 6H), 1.00 (d, J = 6.6 Hz, 3H), 0.85 (t, J = 5.7 Hz, 3H), 0.83 (s, 9H), 0.01 (s, 6H). ^{13}C NMR: δ 211.5, 74.4, 50.0, 48.1, 39.9, 36.3, 33.1, 28.7, 25.6, 22.5, 17.9, 13.9, 11.3, −4.7, −5.2. IR (neat): 2956, 2858, 1716, 1464, 1387, 1255, 1097, 1055, 1014, 837, 775 cm^{-1}. Anal. Calcd for $C_{17}H_{34}O_2Si$: C, 68.40; H, 11.48. Found: C, 68.48; H, 11.20.

(2*S*,3*S*,5*S*)-2-Benzyl-3-(*tert*-butyldimethylsiloxy)-5-butylcyclohexanone (20b). ^{1}H NMR: δ 7.32−7.17 (m, 5H), 4.31−4.25 (m, 1H), 3.24 (dd, J = 13.8 and 5.1 Hz, 1H), 2.70−2.61 (m, 1H), 2.57 (dd, J = 13.8 and 7.5 Hz, 1H), 2.47 (ddd, J = 13.2, 4.2 and 2.1 Hz, 1H), 2.35−2.15 (m, 1H), 2.05−1.91 (m, 2H), 1.46 (ddd, J = 12.0, 12.0 and 1.5 Hz, 1H), 1.40−1.22 (m, 6H), 1.00−0.82 (m, 12H), 0.05 (s, 3H), 0.03 (s, 3H). ^{13}C NMR: δ 209.9, 140.9, 129.1, 128.3, 125.9, 72.6, 57.7, 48.4, 39.8, 36.3, 33.4, 31.4, 28.7, 25.7, 22.6, 18.0, 13.8, −4.1, −5.2. IR (neat): 2927, 1718, 1457, 1255, 1060, 837, 775, 698 cm^{-1}. Anal. Calcd for $C_{23}H_{38}O_2Si$: C, 73.74; H, 10.22. Found: C, 73.74; H, 9.89.

(5*S*)-2-Methyl-5-(2-propyl)-2-cyclohexenone (19aa). $[\alpha]^{23}_D$ = + 64.52 (*c* 0.31, $CHCl_3$), 97.9% ee, retention time = 5.2 min, determined by chiral GC carrier = 2.0 kg/cm^2 at 110 °C. ^{1}H NMR: δ 6.74 (br d, J = 6.3 Hz, 1H), 2.52 (br dd, J = 15.9 and 3.6 Hz, 1H), 2.35 (ddd, J = 18.9, 5.1, 5.1 Hz, 1H), 2.10 (dd, J = 15.9 and 13.5 Hz, 1H), 2.14−2.00 (m, 1H), 1.90−1.79 (m, 1H), 1.76 (br s, 3H), 1.56 (d hept., J = 6.6 and 6.6 Hz, 1H), 0.90 (d, J = 6.6 Hz, 6H). ^{13}C NMR: δ 200.9,

145.4, 135.4, 42.0, 41.9, 31.9, 29.8, 19.43, 19.38, 15.6. IR (neat): 2960, 2875, 1676, 1466, 1367, 1250, 1146, 1109, 1076, 1049, 901 cm^{-1}. Anal. Calcd for $C_{10}H_{16}O$: C, 78.90; H, 10.59. Found: C, 78.80; H, 10.79.

(*S*)-Carvone [(*S*)-19ab]. To a solution of **20ab** (106 mg, 0.375 mmol) in CH_2Cl_2 (5 mL) was added DBU (0.17 mL, 1.13 mmol) at r.t. The mixture was allowed to stand at r.t. for 24 h before usual workup, yielding after purification by flash chromatography (SiO_2; hexanes−Et_2O) (*S*)-**19ab** (40 mg, 71%), whose NMR data were identical to those of the natural product. $[\alpha]^{23}_D = +51.43$ (*c* 0.25, $CHCl_3$),[38] 93.0% ee (determined by chiral HPLC: flow = 0.6 mL·min^{-1} (hexane:*i*-PrOH = 20:1): retention time = 15.5 min).

(*S*)-2-Methyl-5-butyl-2-cyclohexenone (19ac). $[\alpha]^{23}_D = +45.59$ (*c* 0.68, $CHCl_3$). ^{1}H NMR: δ 6.70 (br d, *J* = 5.4 Hz, 1H), 2.53 (dd, *J* = 12.3 and 1.8 Hz, 1H), 2.48−2.31 (m, 1H), 2.14−1.92 (m, 3H), 1.75 (br s, 3H), 1.39−1.20 (m, 6H), 0.88 (t, *J* = 6.6 Hz, 3H). ^{13}C NMR: δ 200.6, 145.1, 135.5, 44.6, 35.6, 35.4, 32.5, 28.6, 22.6, 15.6, 13.9. IR (neat): 2956, 2924, 2858, 1716, 1452, 1363, 1252, 1119, 902 cm^{-1}. Anal. Calcd for $C_{11}H_{18}O$: C, 79.47; H, 10.91. Found: C, 79.56; H, 10.86.

(*S*)-2-Benzyl-5-butyl-2-cyclohexenone (19b). $[\alpha]^{23}_D = +33.0$ (*c* 0.48, $CHCl_3$).^{1}H NMR: δ 7.33−7.24 (m, 2H), 7.24−7.14 (m, 3H), 6.53 (br d, *J* = 5.0 Hz, 1H), 3.51 (br s, 2H), 2.56 (br d, *J* = 13.2 Hz, 1H), 2.46−2.34 (m, 1H), 2.18−1.94 (m, 3H), 1.40−1.20 (m, 6H), 0.89 (t, *J* = 6.6 Hz, 3H). ^{13}C NMR: δ 199.6, 145.9, 139.7, 139.4, 129.2, 128.4, 126.1, 44.8, 35.4, 35.3, 35.1, 32.5, 28.5, 22.5, 13.9. IR (neat): 2925, 1673, 1454, 1378, 698 cm^{-1}. Anal. Calcd for $C_{17}H_{22}O$: C, 84.25; H, 9.15. Found: C, 84.30; H, 9.26.

(1*RS*,5*S*)-1-Hydroxy-1-methyl-5-butyl-2-cyclohexene (21). To a solution of **14** (76 mg, 0.5 mmol) in THF (1 mL) was added at −78 °C MeLi (1.40 M in Et_2O, 0.43 mL, 0.6 mmol). The agitation was continued for 1 h, and the reaction was quenched with water. Extraction with Et_2O, drying ($MgSO_4$), and concentration in vacuo gave a residue purified by flash chromatography (SiO_2; hexanes−Et_2O gradient) to yield **21** (80 mg, 95%) as a colorless oil: diastereomeric ratio = 1:1. ^{1}H NMR: δ 5.77 (ddd, *J* = 9.9, 5.4 and 2.1 Hz, 1H), 5.68−5.60 (m, 2H), 5.59−5.53 (m, 1H), 1.85 (br dd, *J* = 15.0 and 15.0 Hz, 2H), 1.92−1.78 (m, 2H), 1.78−1.44 (m, 6H), 1.34−1.22 (m, 18H), 0.93−0.83 (m, 6H). ^{13}C NMR: δ 134.6, 133.2, 129.5, 127.0, 70.8, 68.3, 45.6, 44.3, 36.3, 36.2, 33.1, 32.0, 30.0, 29.7, 28.9, 28.6, 22.8, 22.7, 14.0. IR (neat): 3367, 2924, 1718, 1653, 1458, 1375, 1259, 1156, 1134, 1078, 995, 906, 800, 731 cm^{-1}. Anal. Calcd for $C_{11}H_{20}O$: C, 78.51; H, 11.98. Found: C, 78.30; H, 11.98.

(*R*)-3-Methyl-5-butyl-2-cyclohexenone (22). To PCC (pyridinium chlorochromate) (205 mg, 0.95 mmol) in CH_2Cl_2 (2 mL) was added dropwise **21** (80 mg, 0.48 mmol) in solution in CH_2Cl_2 (0.2 mL). The resulting dark brown mixture was stirred at r.t. for 2 h, quenched with water, and extracted with Et_2O. Drying ($MgSO_4$), and concentration in vacuo gave an oil which was purified by flash chromatography (SiO_2; hexanes−Et_2O) to yield **22** (66 mg, 83%) as a colorless oil. $[\alpha]^{23}_D = -51.43$ (*c* 0.49, $CHCl_3$), 97.9% ee (determined by chiral GC:carrier = 1.4 at 115 °C: retention time = 14.7 min). ^{1}H NMR: δ 5.85 (br s, 1H), 2.44 (br d, *J* = 12.0 Hz, 1H), 2.30 (br d, *J* = 15.3 Hz, 1H), 2.08−1.94 (m, 3H), 1.94 (br s, 3H), 1.44−1.22 (m, 6H), 0.88 (t, *J* = 6.6 Hz, 3H). ^{13}C NMR: δ 200.3, 162.2, 126.5, 43.4, 37.6, 35.3, 34.8, 28.6, 24.3, 22.6, 13.9. IR (neat): 2925, 2858, 1670, 1635, 1457, 1436, 1379, 1298, 1273, 1248, 1144, 1030, 887, 849, 814, 733 cm^{-1}. Anal. Calcd for $C_{11}H_{18}O$: C, 79.47; H, 10.91. Found: C, 79.41; H, 10.88.

(1*RS*,5*S*)-1-Hydroxy-1,2-dimethyl-5-(2-propyl)-2-cyclohexene(23aa). Obtained as a 6:1 mixture of diastereomers. *Major diastereoisomer:* ^{1}H NMR: δ 5.30 (br d, *J* = 4.8 Hz, 1H), 1.98−1.85 (m, 2H), 1.81 (dd, *J* = 9.6 and 1.5 Hz, 1H), 1.66 (br s, 3H), 1.72−1.54 (m, 1H), 1.48−1.27 (m, 3H), 1.24 (br s, 3H), 0.90−0.70 (m, 6H). ^{13}C NMR: δ 138.7, 123.1, 72.6, 43.6, 39.2, 32.1, 29.2, 26.5, 19.7, 19.5, 16.6. IR (neat): 3369, 2958, 1639, 1450, 1367, 1269, 1119, 1070, 972, 924, 806 cm^{-1}. Anal. Calcd for $C_{11}H_{20}O$: C, 78.51; H, 11.98. Found: C, 78.28; H, 11.86.

(38) $[\alpha]^{20}_D = -62.6$ for (*R*)-carvone and + 61.2 for (*S*)-carvone: *Merck Index*, 12th ed.; Merck and Co., Inc.: Whitehouse Station, NJ, 1996. $[\alpha]_D = -61$ and + 54, respectively: *Aldrich Catalog Handbook of Fine Chemicals*; Sigma-Aldrich Co.: Milwaukee, WI, 1998−1999.

(1*RS*,5*S*)-1-Hydroxy-1,2-dimethyl-5-butyl-2-cyclohexene (23ac). Obtained as a 2:1 mixture of diastereoisomers. ^{1}H NMR: δ 5.51−5.41 (m, 1H), 5.40−5.34 (m, 1H), 2.16−2.01 (m, 1H), 1.90−1.78 (m, 1H), 1.74 (br s, 1H), 1.70−1.46 (m, 3H), 1.35−1.16 (m, 9H), 0.93−0.85 (m, 3H). IR (neat): 3406, 2926, 1734, 1458, 1377, 1259, 1018, 896 cm^{-1}. Anal. Calcd for $C_{12}H_{22}O$: C, 79.06; H, 12.16. Found: C, 78.89; H, 12.27.

(*S*)-2,3-Dimethyl-5-(2-propyl)-2-cyclohexenone [24aa]: $[\alpha]^{23}_D = -114.5$ (*c* 2.61, $CHCl_3$). ^{1}H NMR: δ 2.48 (ddd, *J* = 15.9, 3.6 and 1.5 Hz, 1H), 2.28 (br dd, *J* = 18.0 and 4.5 Hz, 1H), 2.16 (br d, *J* = 10.8 Hz, 1H), 2.04 (dd, *J* = 15.6 and 13.5 Hz, 1H), 1.92 (br s, 3H), 1.83−1.68 (m, 1H), 1.74 (br s, 3H), 1.53 (d hept, *J* = 6.6 and 6.6 Hz, 1H), 0.91 (br d, *J* = 6.6 Hz, 3H), 0.88 (br d, *J* = 6.6 Hz, 3H). ^{13}C NMR: δ 200.1, 154.9, 130.7, 41.2, 40.5, 36.7, 31.9, 21.5, 19.4, 19.3, 10.6. IR (neat): 2960, 1664, 1466, 1431, 1381, 1340, 1313, 1144, 1124, 1086, 704, 663 cm^{-1}. Calcd for $C_{11}H_{18}O$: C, 79.47; H, 10.91. Found: C, 79.56; H, 10.86.

(*S*)-2,3-Dimethyl-5-butyl-2-cyclohexenone (24ac). $[\alpha]^{23}_D = -83.33$ (*c* 0.55, $CHCl_3$). ^{1}H NMR: δ 2.49 (br d, *J* = 12.0 Hz, 1H), 2.33 (br d, *J* = 16.5 Hz, 1H), 2.14−1.93 (m, 3H), 1.91 (br s, 3H), 1.74 (br s, 3H), 1.39−1.19 (m, 6H), 0.88 (t, *J* = 6.6 Hz, 3H). ^{13}C NMR: δ 199.8, 154.6, 130.8, 43.9, 39.4, 35.5, 34.2, 28.6, 22.6, 21.4, 13.9, 10.6. IR (neat): 2956, 2924, 2858, 1666, 1537, 1448, 1379, 1319, 1132, 1084, 733 cm^{-1}. Anal. Calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.18. Found: C, 80.39; H, 11.36.

Synthesis of Penienone and Penihydrone. Hept-3-en-1-yne (27). Bp_{760} = 91 °C. ^{1}H NMR: δ 6.24 (dt, *J* = 16.5 and 7.5 Hz, 1H), 5.42 (dtd, *J* = 16.5, 1.8 and 1.8 Hz, 1H), 2.75 (d, *J* = 1.8 Hz, 1H), 2.08 (dtd, *J* = 7.2, 7.2 and 1.8 Hz, 2H), 1.41 (tq, *J* = 7.5 and 7.5 Hz, 2H), 0.90 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR: δ 146.8, 108.6, 82.6, 75.5, 34.9, 21.6, 13.4.[32]

(+)-(2*R*,3*R*,5*R*)-2-Hydroxymethyl-3-(1,3-heptadienyl)-5-(*tert*-butyldimethylsiloxy)cyclohexanone (28). Into a flame-dried Schlenck tube flushed with argon and shielded into aluminum foil were introduced $Cp_2Zr(H)Cl$ (516 mg, 2 mmol) and freshly distilled THF (2 mL). To the slurry was added a THF (1 mL) solution of hept-3-ene-1-yne[32] (132 mg, 1.4 mmol), and the mixture was stirred at r.t. until a deep-orange coloration appeared (about 15−20 min). Then, the reaction flask was cooled to −78 °C, MeLi (3.0 mL, 1.40M in Et_2O, 4.2 mmol) was added via syringe over a period of 5 min, and the resulting bright orange mixture was stirred for 10 min at −78 °C. Separately, anhydrous LiCl (118 mg, 2.8 mmol) and CuCN (126 mg, 1.4 mmol) were introduced into a dry round-bottom flask purged with argon and dry THF (2 mL) was added; the resulting suspension was energetically stirred at room temperature until complete dissolution of the salts (5 min); the mixture was then cooled to −78 °C and slowly transferred via cannula into the Schlenck tube containing the vinylic zirconocene species. The resulting brown-orange mixture was stirred energetically for 5 min at −78 °C, and (*R*)-**1** (114 mg, 0.5 mmol) in solution in THF (1 mL) was added via syringe over a period of 10 min. The mixture was stirred for 40 min at −78 °C, and an ethereal solution of formaldehyde[39] (large excess) was slowly added. After 1 h at −78 °C, the cooling bath was removed, saturated NH_4OH (5 mL) then water (10 mL) were added, and the product was extracted with Et_2O (3 × 20 mL). The combined organic layers were dried ($MgSO_4$) and filtered through a pad of Celite (3 × 5 cm) and again through a pad of silica (3 × 5 cm) which was finally washed with Et_2O (100 mL). Evaporation of the solvent gave a colorless oil which upon analysis by proton NMR showed the presence of a single diastereoisomer of the desired product. Purification by flash chromatography (SiO_2, hexanes−Et_2O) yielded the title compound (120 mg, 0.34 mmol, 68%) as white crystals: mp = 54−55 °C. $[\alpha]^{23}_D = +13.3$ (*c* 0.1125 $CHCl_3$). ^{1}H NMR: δ 6.07 (dd, *J* = 14.5 and 10.5 Hz, 1H), 5.95 (ddt, *J* = 14.5, 10.5 and 1.2 Hz, 1H), 5.65 (dt, *J* = 14.5 and 6.9 Hz, 1H), 5.41 (dd, *J* = 14.5 and 9.0 Hz, 1H), 4.45−4.39 (m, 1H), 3.78−3.64 (m, 2H), 2.80 (dddd, *J* = 11.9, 11.9, 9.0 and 4.2 Hz, 1H), 2.75−2.65 (br s, 1H), 2.52 (dd, *J* = 13.8 and 3 Hz, 1H), 2.42 (ddd, *J* = 13.8, 3.3 and 2.4 Hz, 1H), 2.25 (ddd, *J* = 11.0, 6.2 and 3.9 Hz, 1H), 2.04 (dt, *J* = 7.2 and 7.2 Hz, 2H), 1.89 (dm, *J* = 13.5 Hz, 1H), 1.76 (ddd, *J* = 12.9, 12.0 and 1.8 Hz, 1H), 1.40 (tq, *J* = 7.5 and 7.5 Hz,

(39) Stork, G.; d'Angelo, J. *J. Am. Chem. Soc.* **1974**, *96*, 7114−7116.

2H), 0.9 (t, $J = 7.2$ Hz, 3H), 0.85 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H). ^{13}C NMR: δ 212.4, 134.6, 132.5, 131.9, 129.7, 69.0, 60.5, 56.2, 49.7, 39.6, 38.6, 34.6, 25.5, 22.3, 17.8, 13.6, −5.11, −5.14. IR (KBr) 3567, 3307, 2927, 1706, 1459, 1344, 1251, 1091, 1053, 987, 912, 838, 777. Anal. Calcd for $C_{20}H_{36}O_3Si$: C, 68.13; H, 10.29. Found: C, 67.90; H, 10.21.

Penienone (25). To a solution of **28** (60 mg, 0.17 mmol) in dry CH_2Cl_2 (2 mL) was added DBU (0.08 mL, 0.51 mmol) at r.t., and the resulting mixture allowed to stand for 12 h at r.t. Evaporation of the solvent and purification of the brown residue by flash chromatography (SiO_2, hexanes−Et_2O) gave **25** (28 mg, 0.126 mmol, 74%) as white crystalline plates. $[\alpha]^{23}_D = -47.5$ (*c* 0.3, EtOH). ^{1}H NMR: δ 6.97 (ddd, $J = 10.0$, 5.7 and 2.4 Hz, 1H), 6.15−5.93 (m, 3H), 5.65 (dt, $J =$ 14.1 and 7.2 Hz, 1H), 5.43 (dd, $J = 14.7$ and 9.0 Hz, 1H), 3.94−3.83 (m, 1H), 3.76−3.65 (m, 1H), 2.95 (br dd, $J = 8.3$ and 5.0 Hz, 1H), 2.74−2.59 (m, 1H), 2.44 (ddd, $J = 19.5$, 5.4 and 5.4 Hz, 1H), 2.38−2.25 (m, 2H), 2.03 (dt, $J = 7.4$ and 7.4 Hz, 2H), 1.39 (tq, $J = 7.4$ and 7.4 Hz, 2H), 0.89 (t, $J = 7.4$ Hz, 3H).^{13}C NMR: δ 202.5, 150.1, 135.1, 132.7, 131.4, 129.6, 129.5, 60.8, 52.7, 40.8, 34.6, 32.9, 22.2, 13.6. IR (KBr) 2929, 1670, 1392, 1097, 1045, 995, 725. Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: C, 76.24; H, 9.31.

Penihydrone (26). Into a dry plastic vessel purged with argon were introduced **18** (60 mg, 0.17 mmol), dry acetonitrile (10 mL), and pyridine (0.5 mL). The mixture was cooled to 0 °C, and HF·pyridine (0.5 mL) was added. The resulting mixture was allowed to stand for 12 h at r.t. The reaction was quenched with saturated $NaHCO_3$, the product was extracted with CH_2Cl_2 and dried ($MgSO_4$), and concentration in vacuo gave a pale brown oil which was purified by flash chromatography (SiO_2, hexanes−Et_2O) to yield **26** (25 mg, 0.105 mmol, 62%) as white needles (recrystallization: CH_2Cl_2-hexane). $[\alpha]^{23}_D = +4.5$ (*c* 0.3, MeOH). ^{1}H NMR: δ 6.08 (dd,$J = 14.1$ and 10.5 Hz, 1H), 5.97 (ddt, $J = 14.7$, 10.5 and 1.2 Hz, 1H), 5.63 (dt, $J = 14.4$ and 7.2 Hz, 1H), 5.39 (dd, $J = 14.7$ and 9.0 Hz, 1H), 4.52−4.45 (m, 1H), 3.81−3.65 (m, 2H), 2.91−2.76 (m, 1H), 2.77−2.66 (br s, 1H), 2.60 (dd, $J = 14.4$ and 3.3 Hz, 1H), 2.52 (ddd, $J = 14.4$, 2.4 and 2.4 Hz, 1H), 2.44−2.24 (br s, 1H), 2.35−2.25 (m, 1H), 2.09−1.80 (m, 3H), 1.82 (ddd, $J = 13.4$, 12.3 and 2.1 Hz, 1H), 1.39 (tq, $J = 7.2$ and 7.2 Hz, 2H), 0.85 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR: δ: 212.6, 134.8, 132.3, 131.9, 129.6, 68.5, 60.1, 56.3, 49.1, 38.60, 38.55, 34.6, 22.3, 13.6. IR (KBr) 3394, 2956, 2927, 1701, 1373, 1072, 983, 962. Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.56; H, 9.30. Found: C, 70.27; H, 9.13.

Synthesis of (*R*)-Carvone. (1*S*,2*R*,3*RS*,5*R*)-1-(*tert*-Butyldimethylsiloxy)-2-methyl-3-hydroxy-5-(2-propenyl)cyclohexane (reduced-20ab). To an ice-cooled solution of **20ab** (265 mg, 0.94 mmol) in MeOH (5 mL) was added $NaBH_4$ (18 mg, 0.47 mmol) in several portions. The ice bath was then removed and the mixture allowed to stir for 1 h at r.t. After dilution with water (5 mL), the product was extracted with AcOEt and the combined organic layers were washed with brine and dried ($MgSO_4$); evaporation of the solvent gave an oil which was purified by flash chromatography (SiO_2; hexanes−Et_2O) to yield the reduced-**20ab** (238 mg, 89%) as a colorless oil. ^{1}H NMR: δ 4.73 (br s, 1H), 4.71 (br s, 1H), 4.01 (br s, 1H), 3.83 (br s, 2H), 2.67 (dddd, $J = 12.6$, 12.6, 2.7 and 2.7 Hz, 1H), 2.10−2.00 (m, 1H) 1.96−1.86 (m, 1H), 1.73 (s, 3H), 1.57−1.45 (m, 1H), 1.45−1.30 (m, 2H), 1.13 (d, $J = 7.2$ Hz, 3H), 0.91 (s, 9H), 0.09 (s, 6H). ^{13}C NMR: δ 149.6, 108.9, 74.2, 72.3, 39.1, 38.9, 38.2, 31.8, 25.6, 21.0, 17.8, 15.6, −4.9, −5.3. Anal. Calcd for $C_{16}H_{32}O_2Si$: C, 67.54; H, 11.34. Found: C, 67.36; H, 11.28.

(2*R*,3*RS*,5*R*)-2-Methyl-3-(benzyloxy)-5-(2-propenyl)cyclohexanone (30). To an ice-cooled solution of **29** (238 mg, 0.84 mmol) in THF (2 mL) was added NaH (55% dispersion in oil, 55 mg, 1.26 mmol) in one portion. The resulting mixture was stirred for 30 min at 0 °C, and benzyl bromide (0.15 mL, 1.26 mmol) was added followed by NaI (14 mg, 0.09 mmol) and dry DMF (0.1 mL); the agitation was carried on for 12 h at r.t. Hydrolysis at 0 °C, extraction with Et_2O, drying ($MgSO_4$), and evaporation of the volatiles gave the crude benzyl ether which was dissolved in MeOH (10 mL) and treated at 0 °C with a methanolic hydrochloric acid solution (0.5 M, 1.68 mL, 0.84 mmol). The mixture was allowed to stir for 4.5 h at r.t. before quenching at 0 °C with saturated $NaHCO_3$. The mixture was taken up in CH_2Cl_2, extracted (CH_2Cl_2), and dried ($MgSO_4$). Evaporation in vacuo gave a residue which was passed through a pad of silica (elution hexane: Et_2O = 1:9) to give the (benzyloxy)cyclohexanol, pure enough to be used in the next step.

To the crude cyclohexanol (197 mg, 0.76 mmol) in dry CH_2Cl_2 (4 mL) and Et_3N (0.32 mL, 2.27 mmol) was slowly added at −10 °C a DMSO (2 mL) solution of SO_3·Pyr (361 mg, 2.27 mmol); the mixture was allowed to stir at r.t. for 10 h. Dilution with water, extraction with Et_2O, drying ($MgSO_4$), and concentration in vacuo gave an oil which was purified by flash chromatography (SiO_2; hexane−Et_2O) to give **30** (154 mg, 71% overall) as a colorless oil. ^{1}H NMR: δ 7.38−7.23 (m, 5H), 4.79 (s, 1H), 4.76 (s, 1H), 4.61 (d, $J = 12.0$ Hz, 1H), 4.40 (d, $J = 12.0$ Hz, 1H), 3.99−3.94 (m, 1H), 2.80 (dddd, $J = 12.6$, 12.6, 3.6 and 3.6 Hz, 1H), 2.56−2.45 (m, 2H), 2.34−2.19 (m, 2H), 1.74 (s, 3H), 1.65 (dd, $J = 13.2$ and 13.2 Hz, 1H), 1.13 (d, $J = 6.9$ Hz, 3H). ^{13}C NMR: δ 210.5, 147.4, 138.5, 128.4, 127.6, 127.5, 109.9, 79.8, 70.7, 49.2, 46.3, 39.6, 33.3, 20.5, 10.8.

(*R*)-Carvone [(*R*)-19ab]: *p*-TSA·H_2O (133 mg, 0.70 mmol) was added in one portion at r.t to a solution of **30** (154 mg, 0.60 mmol) in benzene (5 mL). The mixture was allowed to stand for 6 h at r.t. before quenching with saturated $NaHCO_3$ (5 mL); the product was extracted with Et_2O, dried ($MgSO_4$), and purified by flash chromatography (SiO_2; hexane−Et_2O) to give (*S*)-**19ab** (50 mg, 78%) as a colorless oil. 96.2% ee (determined by chiral HPLC, flow = 0.6 mL/min (hexane:*i*-PrOH = 20:1) retention time = 13.7 min).

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of compounds **1**, **2a,b**, **7**, and **12a,b**, 1,4-addition products reported in Table 1 and Table 2, products reported in Scheme 7 and Scheme 8, and products **25**, **26**, and **28** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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