π-Facial Diastereoselection in the 1,2-Addition of Allylmetal Reagents to 2-Methoxycyclohexanone and Tetrahydrofuranspiro-(2-cyclohexanone)

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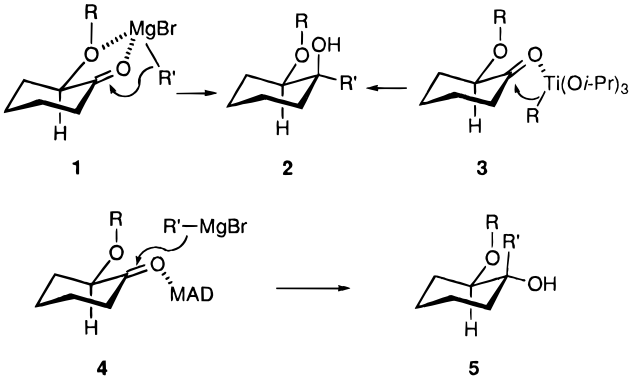
Abstract: The stereochemical course of the 1,2-addition of several allylmetal reagents and of the Normant Grignard [$ClMgO(CH_2)_3MgCl$] to 2-methoxycyclohexanone and tetrahydrofuranspiro-(2-cyclohexanone) has been determined. In four of the six substrates examined, a 4-*tert*-butyl group is present to serve as a conformational anchor. The neighboring methoxyl substituent is shown to be capable of engaging effectively in chelation, although special circumstances can dictate otherwise. Experiments involving the allylindium reagent as the nucleophile in aqueous solution reveal that the presence of water does not inhibit the operation of chelation control, which often exceeds that attainable with the corresponding magnesium, cerium, and chromium reagents in anhydrous media by significant margins. The extent to which cooperation between the α-oxygen atom and control of π-facial nucleophilic attack reaches a maximum (>97:3) is when the system is conformationally rigid and the 2-methoxy and 4-*tert*-butyl groups are both oriented equatorially. As the steric bulk about the oxygen is increased, the ability of indium to anchor onto the heteroatom is significantly lessened. The results of competition experiments are detailed. The prospects for useful synthetic applications of indium catalysis in water or water/THF mixtures appear to be very promising.

The capture by conformationally rigid cyclohexanones of sterically unhindered nucleophiles preferentially from the axial direction has been extensively documented.[1] The central importance of this phenomenon to our understanding of π-facial selectivity has resulted in the proposal of several mechanistic models. Dauben's early explanation in terms of product development control[2] and Felkin's original suggestion of torsional strain[3] have more recently been joined by theoretically-based treatments. Klein's analysis in terms of the unsymmetrical distribution of π orbitals,[4] Cieplak's concept of "transition-state stabilization by electron donation into the vacant $\sigma^{*\ddagger}$ orbital associated with the incipient bond,"[5] and the frontier orbital analyses offered by Houk and Paddon-Row,[6] Reetz,[7] Dannenberg,[8] Coxon,[9] and Boyd[10] attest to the challenging nature of the problem. Ab initio calculations have also appeared.[11]

The impact of a neighboring polar substituent on the control of diastereofacial stereoselection has commanded considerable attention.[12a] With α-alkoxy cyclohexanones, Grignard reagents add with chelation-controlled selectivity (see **1**) to give **2** predominantly.[12b] $TiCl_4$-promoted additions proceed via equatorial attack under conditions where the intervention of a chelate complex has been established.[13a] Although $RTi(O\textit{i}\text{-}Pr)_3$ reagents are incapable of chelation, the R group is again delivered preferably to the face opposite to that occupied by the alkoxy group (see **3**).[13b] In fact, bonding from the axial surface can be reliably achieved only by prior formation of a complex between the ketone and the bulky methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide) (MAD) reagent.[14] Under these circumstances, MAD so sterically encumbers the less congested side of the carbonyl carbon (see **4**) that nucleophilic attack proceeds as shown to provide **5**.



Although an α-chloro substituent can be expected to exhibit diminished chelating ability relative to alkoxy, stereoselectivity

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(1) (a) Li, H.; le Noble, W. J. *Recl. Trav. Chim. Pays-Bas* **1992**, *111*, 199. (b) Houk, K. N.; Wu, Y.-D. In *Stereochemistry of Organic and Bioorganic Transformations*; Bartmann, W.; Sharpless, K. B., Eds., VCH: Weinheim, Germany, 1987; pp 247−260. (c) Boone, J. R.; Ashby, E. C. *Top. Stereochem.* **1979**, *11*, 53.

(2) Dauben, W. G.; Fonken, G. J.; Noyce, D. S. *J. Am. Chem. Soc.* **1956**, *78*, 2579.

(3) (a) Chérest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199. (b) Chérest, M.; Felkin, H. *Tetrahedron Lett.* **1968**, 2205.

(4) Klein, J. *Tetrahedron Lett.* **1973**, 4307.

(5) (a) Cieplak, A. S. *J. Am. Chem. Soc.* **1981**, *103*, 4540. (b) Cieplak, A. S.; Tait, B. D.; Johnson, C. R. *J. Am. Chem. Soc.* **1989**, *111*, 8447.

(6) (a) Paddon-Row, M. N.; Wu, Y.-D.; Houk, K. N. *J. Am. Chem. Soc.* **1992**, *114*, 10638. (b) Wu, Y.-D.; Houk, K. N.; Paddon-Row, M. N. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1019. (c) Wong, S. S.; Paddon-Row, M. N. *J. Chem. Soc., Chem. Commun.* **1991**, 327.

(7) (a) Frenking, G.; Köhler, K. F.; Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1146. (b) Frenking, G.; Köhler, K. F.; Reetz, M. T. *Tetrahedron* **1993**, *49*, 3971, 3983.

(8) (a) Huang, X. L.; Dannenberg, J. J. *J. Am. Chem. Soc.* **1993**, *115*, 6017. (b) Huang, X. L.; Dannenberg, J. J.; Duran, M.; Bertrán, J. *J. Am. Chem. Soc.* **1993**, *115*, 4024.

(9) (a) Coxon, J. M.; Houk, K. N.; Luibrand, R. T. *J. Org. Chem.* **1995**, *60*, 418. (b) Coxon, J. M.; Luibrand, R. T. *Tetrahedron Lett.* **1993**, *34*, 7093, 7097.

(10) Shi, Z.; Boyd, R. J. *J. Am. Chem. Soc.* **1993**, *115*, 9614.

(11) Mori, S.; Nakamura, M.; Nakamura, E.; Koga, N.; Morokuma, K. *J. Am. Chem. Soc.* **1995**, *117*, 5055.

(12) (a) Ashby, E. C.; Laemmle, J. T. *Chem. Rev.* **1975**, *75*, 521. (b) Maruoka, K.; Itoh, T.; Sakurai, M.; Nonoshita, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1988**, *110*, 3588.

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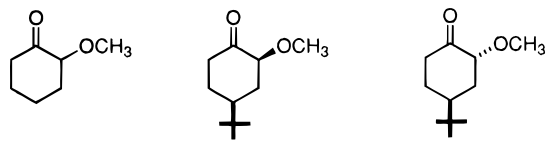
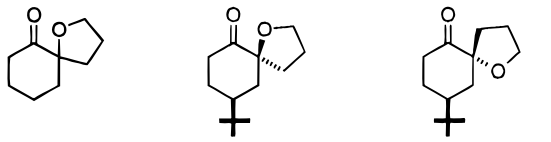
can apparently be achieved under the proper circumstances. A dramatic example has been uncovered in the tetraphenylstibonium bromide-promoted addition of tin enolates to six-ring α-chloro ketones. The resulting chlorohydrins are formed exclusively in that manner in which the Cl and OH groups are cis-disposed.[15]

As a consequence of the need to utilize organometallics or moisture-sensitive Lewis acids in the condensations discussed above, all of these many reactions have been routinely conducted in the strict absence of water. In recent years, the intriguing observation has been made that indium is capable of promoting addition reactions to carbonyl compounds in water as the reaction medium.[16,17] Given that essentially no information is available on the stereochemical response of cyclohexanones in general to metal-based reagents in aqueous environments, we set out to undertake an in-depth study in which C-alkylation and related condensations were accomplished by a variety of methods including aqueous indium protocols. The systems examined here include 2-methoxycyclohexanone (**6**), its conformationally rigidified 4-*tert*-butyl homologues **7** and **8**, and the three tetrahydrofuranspiro-substituted examples **9**−**11**.



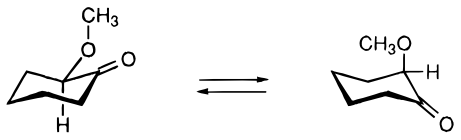
6 **7** **8**



9 **10** **11**

Results

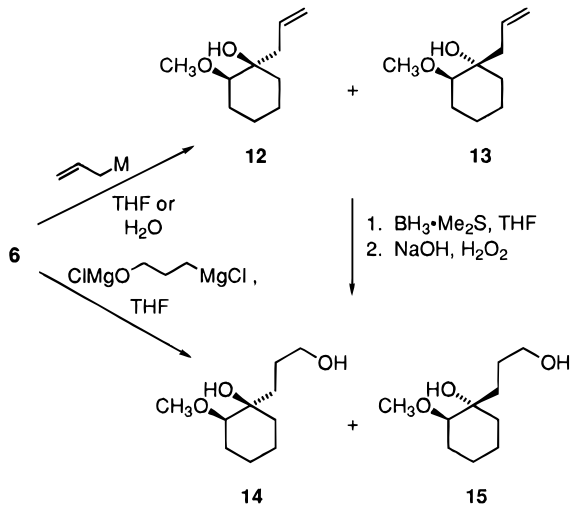
2-Methoxycyclohexanone (6). The conformational equilibrium defined by **6** was initially reported by Robinson in 1974 to be heavily dominated by the axial form regardless of solvent.[18] Subsequent refinements by ^{1}H NMR showed **6a** to



6e **6a**

be favored (63%) in CCl_4 but appreciably disfavored (20%) in a more polar solvent.[19] This widely disseminated finding,[20] believed to be in conformity with decreased hyperconjugative[21] and dipole−dipole interactions[22] as well as reduced A$^{(1,3)}$ strain,[23] has recently been further reevaluated at 500 MHz.[24] The percent of **6a** was found in this setting to range from 57 (in C_6D_{12}) to 16 (CD_3CN). The important conclusion that can be drawn from these studies is that the energy barrier between

Scheme 1



12 **13** **14** **15**

6a and **6e** is sufficiently low that the involvement of **6e** in chelation control should not be energetically impeded.

Treatment of **6** with allylmagnesium chloride in THF at 0 °C afforded **12** and **13** (Scheme 1) in a ratio of 2.3:1 (Table 1, entry 1).[25] Equatorial attack was similarly favored when recourse was made to the organocerate[26] and allylchromium reagents[27] (entries 2 and 3). The proportion of the less polar axial alcohol was greatest in the $CrCl_2$-promoted example. This distribution was closely approximated when recourse was made to the Normant reagent $ClMgO(CH_2)_3MgCl$ (entry 4).[28] The diols **14** and **15**, produced in a 1.5:1 ratio, were alternatively available by hydroboration of **12** and **13**[25] and were identified in this manner.

Coupling of **6** to allyl bromide in the presence of indium resulted in a significantly heightened increase in the level of **12** irrespective of the solvent employed (entries 5−8). The best selectivity (14.1:1) was observed in 1:1 THF−H_2O, and the yields were maximized when the reaction medium was purely water. Product composition was modestly affected when the

(13) (a) Reetz, M. T.; Kesseler, K.; Schmidtberger, S.; Wenderoth, B.; Steinbach, R. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 989. (b) Reetz, M. T.; *Organotitanium Reagents in Organic Synthesis*; Springer-Verlag: Berlin, 1986.

(14) (a) Maruoka, K.; Oishi, M.; Yamamoto, H. *Synlett* **1993**, 683. (b) Maruoka, K.; Oishi, M.; Shiohara, K.; Yamamoto, H. *Tetrahedron* **1994**, *50*, 8983.

(15) Yasuda, M.; Oh-hata, T.; Shibata, I.; Baba, A.; Matsuda, H.; Sonoda, N. *Tetrahedron Lett.* **1994**, *35*, 8627.

(16) The reactivity of allylindium reagents was first recognized in organic solvents by Butsugan. For selected references, see: (a) Araki, S.; Ito, H.; Butsugan, Y. *J. Org. Chem.* **1988**, *53*, 1831. (b) Araki, S.; Ito, H.; Katsumura, N.; Butsugan, Y. *J. Organomet. Chem.* **1989**, *369*, 291. (c) Araki, S.; Katsumura, N.; Ito, H.; Butsugan, Y. *Tetrahedron Lett.* **1989**, *30*, 1581. (d) Araki, S.; Butsugan, Y. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2395. (e) Araki, S.; Katsumura, N.; Butsugan, Y. *J. Organomet. Chem.* **1991**, *415*, 7. (f) Araki, S.; Shimizu, T.; Johar, P. S.; Jin, S.-J.; Butsugan, Y. *J. Org. Chem.* **1991**, *56*, 2538. (g) Araki, S.; Imai, A.; Shimizu, K.; Butsugan, Y. *Tetrahedron Lett.* **1992**, *33*, 2581. (h) Jin, S.-J.; Araki, S.; Butsugan, Y. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 1528. For a general review of selective reactions involving allylic metal reagents, see: Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207.

(17) For reviews which focus attention on allylation in aqueous media, consult: (a) Li, C. J. *Chem. Rev.* **1993**, *93*, 2023. (b) Chan, T. H.; Li, C. J.; Lee, M. C.; Wei, Z. Y. *Can. J. Chem.* **1994**, *72*, 1181. (c) Lubineau, A.; Augé, J.; Queneau, Y. *Synthesis* **1994**, 741.

(18) Robinson, M. J. T. *Tetrahedron* **1974**, *30*, 1971.

(19) Cantacuzene, D.; Tordeux, M. *Can. J. Chem.* **1976**, *54*, 2759.

(20) Lambert, J. B. In *The Conformational Analysis of Cyclohexenes, Cyclohexadienes, and Related Hydroaromatic Compounds*; Rabideau, P., Ed.; VCH: Weinheim, Germany, 1989; Chapter 2.

(21) Eisenstein, O.; Anh, N. T.; Jean, Y.; Devaquet, A.; Cantacuzene, J.; Salem, L. *Tetrahedron* **1974**, *30*, 1717.

(22) Corey, E. J.; Burke H. J. *J. Am. Chem. Soc.* **1955**, *77*, 5418.

(23) Johnson, F. *Chem. Rev.* **1968**, *68*, 375.

(24) Fraser, R. R.; Faibish, N. C. *Can. J. Chem.* **1995**, *73*, 88.

(25) This reaction has been previously conducted in refluxing ether. Under these circumstances, the **12**/**13** composition is 6.6:1 [Negri, J. T.; Paquette, L. A. *J. Am. Chem. Soc.* **1992**, *114*, 8835].

(26) Imamoto, T.; Takiyama, N.; Nakamura, K. *Tetrahedron Lett.* **1985**, *26*, 4763.

(27) Hiyama, T.; Okude, Y.; Kimura, K.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 561.

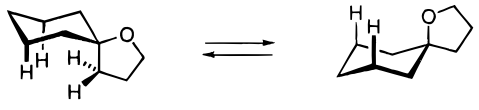
Table 1. Facial Selectivity in Nucleophilic Additions to **6** and **9**[a]

entry	reagent	solvent (T, °C)	chelate/ non-chelate ratio	yield, %
For **6**:				
1	CH_2=$CHCH_2MgCl$	THF, 0	2.3 : 1	94
2	CH_2=$CHCH_2MgCl$, $CeCl_3$	THF, 0	4.5 : 1	82
3	CH_2=$CHCH_2Br$, $CrCl_2$	THF, 0	1.2 : 1	78
4	$ClMgO(CH_2)_3MgCl$	THF, 0	1.5 : 1	85
5	CH_2=$CHCH_2Br$, In	THF, 25	9.0 : 1	84
6	CH_2=$CHCH_2Br$, In	THF-H_2O (1:1), 25	14.1 : 1	93
7	CH_2=$CHCH_2Br$, In	H_2O, 25	12.5 : 1	95
8	CH_2=$CHCH_2Br$, In	THF, 25[b]	12.2 : 1	83
For **9**:				
9	CH_2=$CHCH_2MgCl$	THF, 0	1.2 : 1	88
10	CH_2=$CHCH_2MgCl$, $CeCl_3$	THF, 0	1 : 2.4	96
11	CH_2=$CHCH_2Br$, $CrCl_2$	THF, 0	1 : 2.6	90
12	$ClMgO(CH_2)_3MgCl$	THF, 0	1 : 8.8	76
13	CH_2=$CHCH_2Br$, In	THF, 25	5.6 : 1	82
14	CH_2=$CHCH_2Br$, In	THF-H_2O (1:1), 25	3.9 : 1	95
15	CH_2=$CHCH_2Br$, In	H_2O, 25	2.7 : 1	81
16	CH_2=$CHCH_2Br$, In	THF, 25[b]	3.4 : 1	72

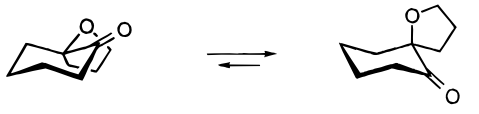
[a] All experiments were conducted minimally in duplicate, and the reported data represent the average of these experiments. [b] The allyl bromide and indium powder were refluxed in THF for 1 h and cooled to 25 °C before the ketone was added.

allylindium reagent was preformed in refluxing THF (entry 8) prior to addition of the ketone (compare entry 5).

1-Oxaspiro[4.5]decan-6-one (9). A change in the nature of the polar substituent to a spirocyclic tetrahydrofuran ring introduces several conformationally counterbalancing influences. The geminal disubstitution requires that the oxygen atom and a methylene carbon be concomitantly projected axially and equatorially. For **16**, the O-axial isomer has been shown to predominate (ca. 68%) in CS_2 solution at 35 °C.[29] This ΔG°_{308} of 0.46 kcal/mol favoring **16a** has been attributed to the reduction in syn-axial compression that materializes when the oxygen atom is projected axially. Although the conformational properties of **9**[30] have not been comparably scrutinized, it would appear logical to assume that the extent to which **9a** is populated



16e **16a**



9e **9a**

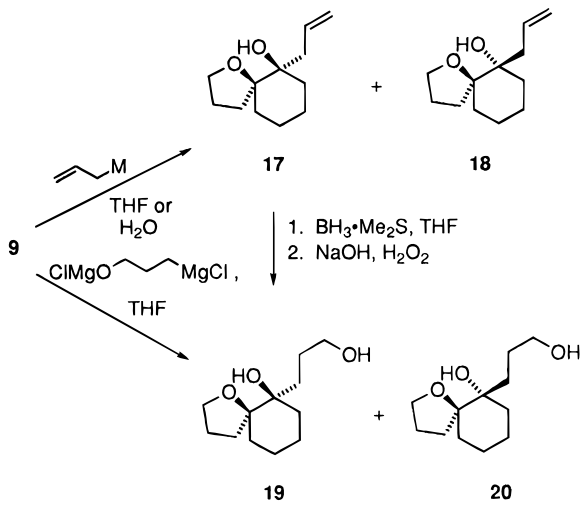
is significantly greater than that of **6a**. In light of the fact that the *A* values for ethyl and methoxyl are 1.8 and 0.6 kcal/mol, respectively, simple additivity does not appear to be applicable. This may be because other structural deformations are also operative. In any event, it should prove more difficult to entice

(28) Cahiez, G.; Alexakis, A.; Normant, J. F. *Tetrahedron Lett.* **1978**, 3013.

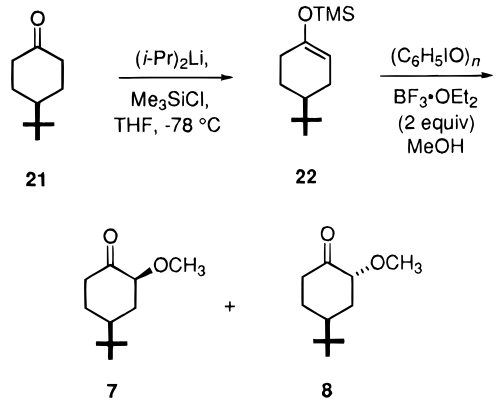
(29) (a) Picard, P.; Moulines, J. *Tetrahedron* **1978**, *34*, 671. (b) Picard, P.; Moulines, J. *Tetrahedron Lett.* **1970**, 5133.

(30) Paquette, L. A.; Negri, J. T.; Rogers, R. D. *J. Org. Chem.* **1992**,*57*, 3947.

Scheme 2



Scheme 3



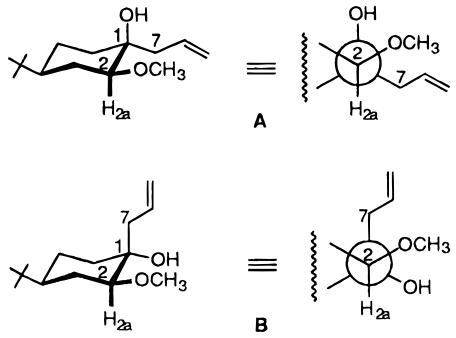
9 to adopt the O-equatorial conformation relative to **6**, thereby diminishing the attractiveness of metal chelation.

The experimental results appear to support this hypothesis. Thus, when the same battery of experiments was applied to **9** (Scheme 2), the level of diastereoselection in favor of the cis isomers (**17** and **19**) was noticeably more normalized (entries 9−16). Although the indium-promoted couplings generally exhibited heightened chelate/non-chelate behavior as before, the more favorable distribution was now encountered in THF (entry 13) and not in aqueous THF (entry 14). Quite unexpected was the discovery that the Normant reagent was notably effective in eliciting a very respectable (8.8:1) non-chelate-controlled response from **9** (entry 12). Due to the conformational flexibility of products **17**−**20**, unambiguous assignment of relative stereochemistry was accomplished by hydroborative interconversion. Diol **19** has previously been transformed into the C_s symmetric dispiro heterocycle by dehydrative cyclization.[30]

Conformationally Disparate 2-Methoxy-4-*tert*-butylcyclohexanones 7 and 8. Significant reduction in the conformational mobility of both **6** and **9** was viewed as an invaluable tool for gaining insight into the stereochemical course of the reactions described above. The classical tactic of incorporating a 4-*tert*-butyl substituent onto the cyclohexanone ring was adopted. The preparation of **7** and **8** began by conversion of **21** into the silyl enol ether **22** (Scheme 3). Subsequent oxidation of this intermediate with iodosobenzene in cold (−70 °C) methanol containing 2 equiv of boron trifluoride etherate led directly to **7** and **8** in 60% yield.[31,32] The more dominant equatorial isomer **7** (3:1), which was readily separated from **8** by chromatography

on silica gel, provided the highest face selectivity observed in this study (entries 17−24, Table 2). In all experiments, **23** or **25** proved to be so dominant in the reaction mixtures (>97:3) that the products of axial attack were not observed upon ^{1}H NMR analysis (Scheme 4). Only in the $CeCl_3$-promoted coupling was **24** formed to a detectable level that permitted its characterization (Table 2).

DEPT experiments[33] were particularly useful in defining the stereochemical features of **23** and **24**. This technique takes advantage of heteronuclear three-bond coupling, with the degree of signal enhancement achieved by pulsing a selected hydrogen frequency and observing a ^{13}C nucleus being maximized when the dihedral angle relationships are at 0° or 180°. As for carbinol **23**, models show the dihedral angle between H-2a and C-7 to be approximately 60° (see **A**) and the same angle for **24** to be significantly widened to about 180° (see **B**). Only in the



latter instance was C-7 measurably coupled to H-2a. The methoxyl carbon was seen to exhibit an enhanced signal in both products, the result of heteronuclear coupling through the oxygen atom.

Addition of the Normant reagent to **7** proved to be a highly stereocontrolled process as well, giving rise to **25** in 96% yield (entry 20). Since hydroboration−oxidation of **23** also led to **25**, its stereochemical assignment was considered secure. Cyclization of **25** by initial regioselective tosylation of its primary hydroxyl followed by intramolecular S_N2 displacement[25] provided the spirotetrahydrofuran **27**.

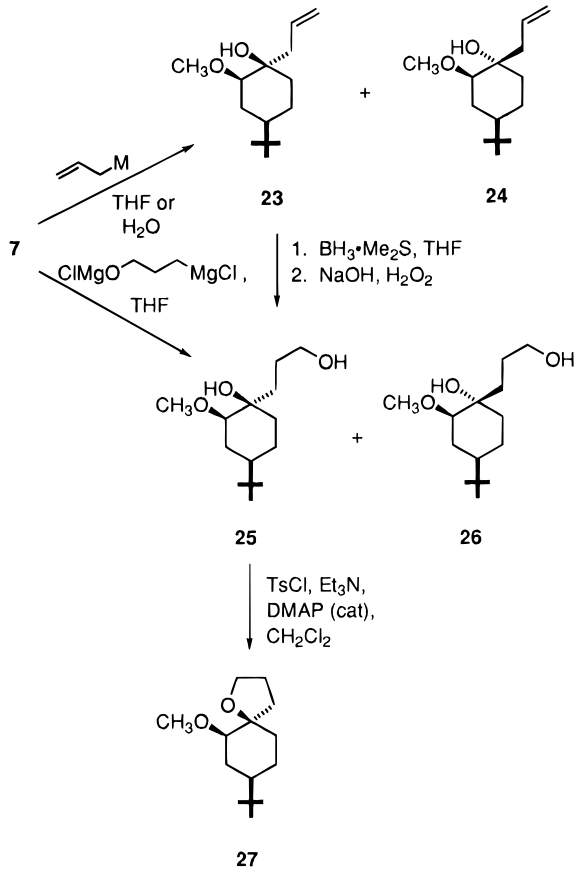
The conformational inflexibility of **7** virtually guarantees that the methoxyl oxygen is projected equatorially. This advantageous situation so orients the nonbonded electron pairs that a cooperatively matched arrangement exists. The stereoisomeric nature of **8** positions the methoxyl substituent axially when in the chair form (**8ch**), thereby discounting the possibility of chelation control. However, whereas **7** is certain to be conformationally rigid, **8** is likely to be only conformationally biased toward **8ch**.[34] Thus, its methoxyl group need not be confined to an axial disposition by virtue of equilibration with the twist conformer **8tw**. In this geometry, the ethereal oxygen is projected pseudoequatorially and now resides in close proximity to the carbonyl group. In simple cyclohexanes, the twist form

Table 2. Facial Selectivity in Nucleophilic Additions to **7** and **8**[a]

entry	reagent	solvent (T, °C)	chelate/ non-chelate ratio	yield, %
For **7**:				
17	CH_2=$CHCH_2MgCl$	THF, 0	>97 : 3	77
18	CH_2=$CHCH_2MgCl$, $CeCl_3$	THF, 0	>97 : 3	78
19	CH_2=$CHCH_2Br$, $CrCl_2$	THF, 0	9 : 1	72
20	$ClMgO(CH_2)_3MgCl$	THF, 0	>97 : 3	96
21	CH_2=$CHCH_2Br$, In	THF, 25	>97 : 3	76
22	CH_2=$CHCH_2Br$, In	THF-H_2O (1:1), 25	>97 : 3	82
23	CH_2=$CHCH_2Br$, In	H_2O, 25	>97 : 3	80
24	CH_2=$CHCH_2Br$, In	THF, 25[b]	>97 : 3	60
For **8**:				
25	CH_2=$CHCH_2MgCl$	THF, 0	1 : 1.9	81
26	CH_2=$CHCH_2MgCl$, $CeCl_3$	THF, 0	1 : 1	90
27	CH_2=$CHCH_2Br$, $CrCl_2$	THF, 0	13.2 : 1	55
28	$ClMgO(CH_2)_3MgCl$	THF, 0	1.3 : 1	90
29	CH_2=$CHCH_2Br$, In	THF, 25	13.1 : 1	88
30	CH_2=$CHCH_2Br$, In	THF-H_2O (1:1), 25	9.5 : 1	74
31	CH_2=$CHCH_2Br$, In	H_2O, 25	6.3 : 1	83
32	CH_2=$CHCH_2Br$, In	THF, 25[b]	9.4 : 1	84

[a] All experiments were conducted minimally in duplicate, and the reported data represent the average of these experiments. [b] The allyl bromide and indium powder were refluxed in THF for 1 h and cooled to 25 °C before the ketone was added.

Scheme 4



is somewhat more than 5 kcal/mol less stable than the chair. For the parent cyclohexanone, the twist form is only 2.7 kcal/mol above the chair,[35] a value considerably lower because the ring happens to be flattened at the carbonyl carbon and the

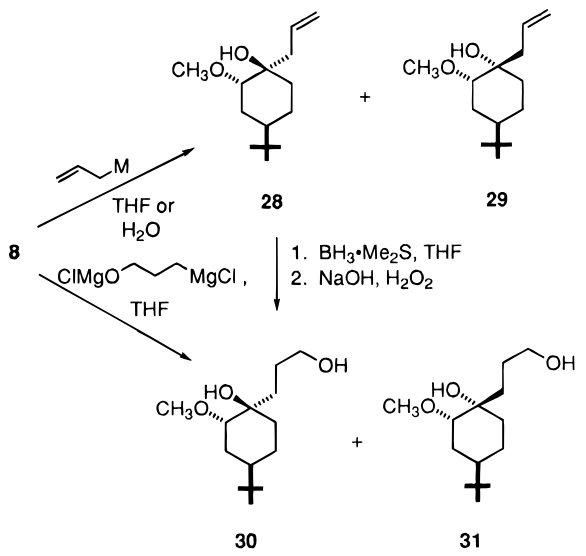
(31) Haight, A. R. Ph.D. Thesis, University of Wisconsin−Madison, 1990. We thank Prof. E. Vedejs for making the relevant part of this thesis available to us.

(32) (a) Moriarty, R. M.; Prakash, O.; Duncan, M. P.; Vaid, R. K.; Musallam, H. A. *J. Org. Chem.* **1987**, *52*, 150. (b) House, H. O.; Czuba, L. J.; Gall, M.; Olmstead, H. D. *J. Org. Chem.* **1969**, *34*, 2324. (c) Cousins, R. P. C.; Simpkins, N. S. *Tetrahedron Lett.* **1989**, *30*, 7241. (d) Cain, C. M.; Cousins, R. P. C.; Coumbarides, G.; Simpkins N. S. *Tetrahedron* **1990**, *46*, 523.

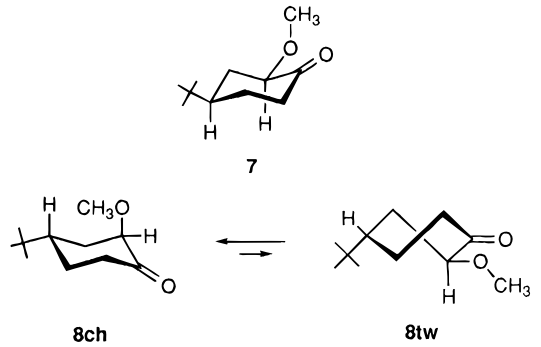
(33) (a) Bax, A. *J. Magn. Reson.* **1983**, *52*, 330; **1983**, *53*, 517. (b) Rutar, V. *J. Am. Chem. Soc.* **1983**, *105*, 4095. (c) Rutar, V. *J. Magn. Reson.* **1984**, *56*, 87. (d) Wimperis, S.; Freeman, R. *J. Magn. Reson.* **1984**, *58*, 348. (e) Lin, L.-J.; Cordell, G. A. *J. Chem. Soc., Chem. Commun.* **1986**, 377.

(34) Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Carbon Compounds*; John Wiley and Sons, Inc.: New York, 1994; Chapter 11.

Scheme 5

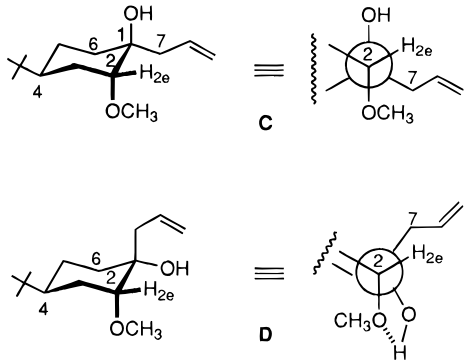


opposite end.[36,37] The difference in $\Delta G°$ between **8ch** and **8tw** is very likely of even lesser magnitude because the steric interaction of the axial methoxyl in **8ch** is relieved when proceeding to the twist geometry.



With the exception of the allylmagnesium chloride and allylcerium examples (entries 25 and 26), the ability of **8** to engage in chelate-controlled metal-mediated allylation reactions is very respectable (entries 27−32). The stereoselectivity of the 1,2-addition process when indium is involved proved to be consistently very good. The change in solvent from THF to H_2O modestly erodes the proportion of **28** formed (Scheme 5). This phenomenon has previously been observed with **9**. The emergence of the allylchromium addition as a highly stereocontrolled process merits comment. When α-alkoxy aldehydes are involved,[38] crotylchromium reagents have been shown to attack with a high level of anti selectivity. Thus, the chelation-controlled response of **7** and **8** is not entirely unexpected, although the phenomenon is not observed in all of the examples studied in this investigation.

We had originally hoped to apply to **28** and **29** the same DEPT analysis that proved so successful earlier. The Karplus angle between H-2e and C-7 in **28** can reasonably be expected to be close to 60° (see **C**), while that in **29** should be significantly smaller because of unfavorable 1,3-diaxial interactions involving the allyl substituent and likely hydrogen bonding of the hydroxyl to the methoxyl oxygen (see **D**).



However, in neither case was heteronuclear coupling observed between H-2e and C-7. This may simply be a reflection of the fact that equatorial/equatorial and axial/equatorial couplings are significantly smaller than those of the axial/axial type, with the result that the associated signals are of much lower intensity.

Alternatively, $^1H/^1H$ COSY 90 experiments performed on **29** in C_6D_6 solution confirmed H-6a to reside at δ 1.69, its downfield location stemming from deshielding contributions arising from the nearby methoxyl oxygen. Irradiation of H-6a[39] under DEPT conditions caused C-7 to exhibit a strong signal in the carbon subspectrum. Further confirmation of the axial orientation of the allyl group was derived from an NOE study in which 10% integral enhancements were seen for H-3a and H-5a when H-7/H-7′ were irradiated. In **29**, the H-7 protons appear at δ 2.28 as a narrowly split ($\Delta\mu = 15.8$, $J_{AB} = 14.3$ Hz) component of an ABX pattern. In contrast, H-7 and H-7′ in **28** are much more widely spaced (δ 2.40 and 2.16) since the magnetic environment of one of them is significantly pertured by the proximal methoxy group.

Reaction of **8** with the Normant reagent provided a 1.3:1 mixture of **30** and **31** in 90% yield (entry 28). The structural features of these 1,4-diols were established as before by the hydroboration−oxidation of **28**. The resulting **30** proved identical in all respects to the major constituent obtained earlier.

Evaluation of the Haptophilic Properties of the Tetrahydrofuran Ring in 10 and 11. When chelation operates, nucleophilic attack by the organometallic reagent is skewed toward addition from the equatorial surface of the carbonyl as a consequence of the haptophilic influence of the neighboring ether oxygen. An interesting relevant question inquires whether the coordinating capability of methoxyl oxygen is superior to or less than that of the tetrahydrofuran ring oxygen. Also, is the trend comparable for different metals? A quick glance at the experimental data for **6** and **9** (Table 1) might lead one to conclude in favor of methoxyl. However, the differing conformational dynamics of this pair of α-oxygenated cyclohexanones, as pointed out earlier, could bias the experimental observations. For this reason, the selectivities observed for the **7**/**10** and **8**/**11** pairs could prove informative. Although subtle differences in the conformational predisposition of these systems are evident, an analysis of the extent of haptophilic control was considered to be necessary and worthwhile.

(35) Anet, F. A. L.; Chmurny, G. N.; Krane, J. *J. Am. Chem. Soc.* **1973**,*95*, 4423.

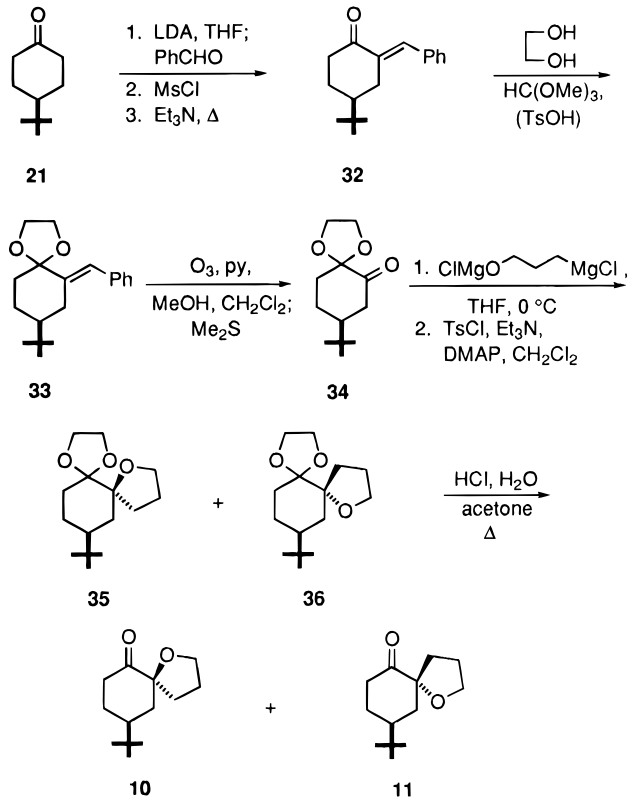
(36) Lambert, J. B.; Carhart, R. E.; Corfield, P. W. R. *J. Am. Chem. Soc.* **1969**, *91*, 3567.

(37) 2-*tert*-Butylcyclohexanone is reported to reside predominantly in the twist conformation: ref 34, p 733.

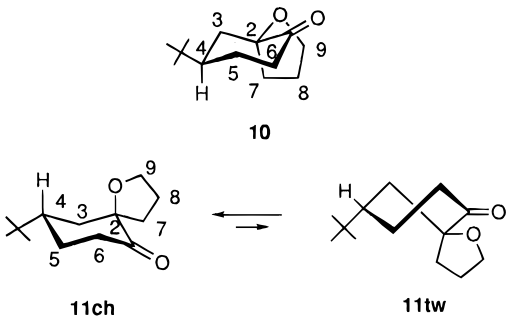
(38) (a) Martin, S. F.; Li, W. *J. Org. Chem.* **1989**, *54*, 6129. (b) Mulzer, J.; de Lasalle, P.; Freissler, A. *Liebigs Ann. Chem.* **1986**, 1152. (c) Hiyama, T.; Okude, Y.; Kimura, K.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 561. (d) Lewis, M. D.; Kishi, Y. *Tetrahedron Lett.* **1982**, *23*, 2343. (e) Nagaoka, H.; Kishi, Y. *Tetrahedron* **1981**, *37*, 3873. (f) Hiyama, T.; Kimura, K.; Nozaki, H. *Tetrahedron Lett.* **1981**, *22*, 1037. (g) Buse, C. T.; Heathcock, C. H. *Tetrahedron Lett.* **1978**, 1685. (h) Okude, Y.; Hirano, S.; Hiyama, T.; Nozaki, H. *J. Am. Chem. Soc.* **1977**, *99*, 3179.

(39) In actuality, the signal for H-6a is overlapped by those for H-3e and H-6e. However, these protons cannot exert an effect on C-7 resulting from heteronuclear coupling.

Scheme 6



The route selected for the preparation of **10** and **11** is outlined in Scheme 6. The conversion of **21** to **32** was quickly



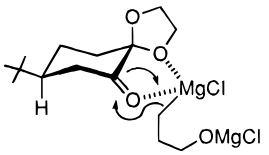
determined to be problematic because of competitive formation of the dibenzylidene derivative under conventional aldol condensation conditions.[40a] In order to curtail the formation of this product, the aldol reaction mixture was treated with methanesulfonyl chloride 5 s after introduction of the benzaldehyde.[40b] The subsequent addition of triethylamine was followed either by a reflux period of 1 h or overnight stirring at room temperature. Product purification was most easily achieved after ketalization. Once this step had been performed, **33** was obtained in 50% overall yield by direct crystallization from 95% ethanol. Ozonolysis of **33** resulted in oxidative cleavage of the double bond to give **34** (91%). Implementation of Normant technology at this stage gave rise in 84% yield to a 4.5:1 mixture of diols. The fact that axial attack had predominated was made clear following monotosylation of the two diols and intramolecular S_N2 cyclization of these functionalized intermediates to furnish **35** and **36**. For convenience, separation of the diastereomers was deferred until after deketalization with concentrated HCl in hot aqueous acetone.

(40) (a) Sanghvi, Y. S.; Rao, A. S. *Ind. J. Chem.* **1987**, *263*, 671. (b) Heathcock, C. H.; Buse, C. T.; Kleschick, W. A.; Pirrung, M. C.; Sohn, J. E.; Lampe, J. J. *J. Org. Chem.* **1980**, *45*, 1066.

With pure samples of cyclohexanones **10** and **11** in hand, it was initially assumed that they might be distinguished on the basis of standard NOE measurements. Analysis was highlighted by the fact that the major diastereomer displayed four protons between δ 4.2 and 1.8, while the minor constituent exhibited five protons between δ 3.8 and 2.1 at 300 MHz. For added corroboration, ^{1}H/^{1}H COSY 90 studies were carried out on both compounds. As seen in Figure 1, H-9 and H-9′ in **10** appear at appreciably lower field than the remaining protons, with H-9 residing well into the deshielding cone of the ketone carbonyl. This identification allowed H-8 and H-8′, and subsequently H-7 and H-7′, to be uncovered. Three of these protons appear as multiplets in the heavily overlapped δ 1.63−1.43 region, while H-8′ is centered at δ 1.38. As expected, H-6e is characterized by one large geminal and two small vicinal couplings. The proximity of H-6e and H-6a to H-5e and H-5a provided key information relative to their location in the spectrum. Clearly indicated was the fact that the signal for H-5e was overlapped with those of H-7/H-7′ and H-8. Also, H-5a is sufficiently shielded that it constitutes the ring proton to highest field. The methine proton H-4 could not be traced from H-5a or H-5e. However, because H-5e shows strong W-plan coupling to H-3e and the latter is demonstrably coupled to H-4 and H-3a, the remaining protons were easily located. The principal adoption of a chairlike conformation is supported by the existence of a diagnostic W-coupling between H-3e and H-5e.

Full assignment to **11** could be made in an entirely analogous way (Figure 2). Additionally, the significant deshielding experienced by H-4 and H-6a as a consequence of their 1,3-diaxial relationship to the tetrahydrofuranyl oxygen is striking. As seen with **10**, the normal sequencing in rigid six-membered rings is for equatorial protons to appear downfield of their axial counterparts. This phenomenon is also reflected in the chemical shifts of H-5e/H-5a and H-3e/H-3a in **11**.

With the stereochemistry of **10** and **11** established, the Normant reagent deployed in their synthesis was seen to exhibit a kinetic preference for equatorial attack. A logical rationalization of this finding would be to involve intramolecular delivery from the equatorial oxygen of the acetal as in **E**. The preferred intervention of **E** is believed to reflect the usual steric advantages associated with chelation to the less encumbered oxygen atom.



E

The two diastereomeric allylation products of **10** proved to be conveniently amenable to chromatographic separation. The less polar diastereomer (R_f 0.35), when subjected to ^{1}H/^{1}H COSY 90 and NOE experiments, was confirmed to be **37** (see **F**). Comparable analysis of the more polar homoallylic alcohol (R_f 0.18) was consistent with its formulation as **38** (see **G**). With the unequivocal identification of H-6a, semiselective long-range DEPT studies established its trans relationship to C-10 (^3J).

The polarity distinction defined above is very pervasive and, in our view, can serve as a very reliable indicator of stereochemistry in this series. We have noted that those cyclohexanols which preferentially adopt an axial hydroxyl are invariably less polar than their equatorial counterparts (Table 3). This is believed to be a reflection of the inability of the sterically more crowded axial OH to bind as tightly to the adsorbent. Interestingly, a polarity reversal has been noted once the same oxygen becomes incorporated into a tetrahydrofuran ring and a second

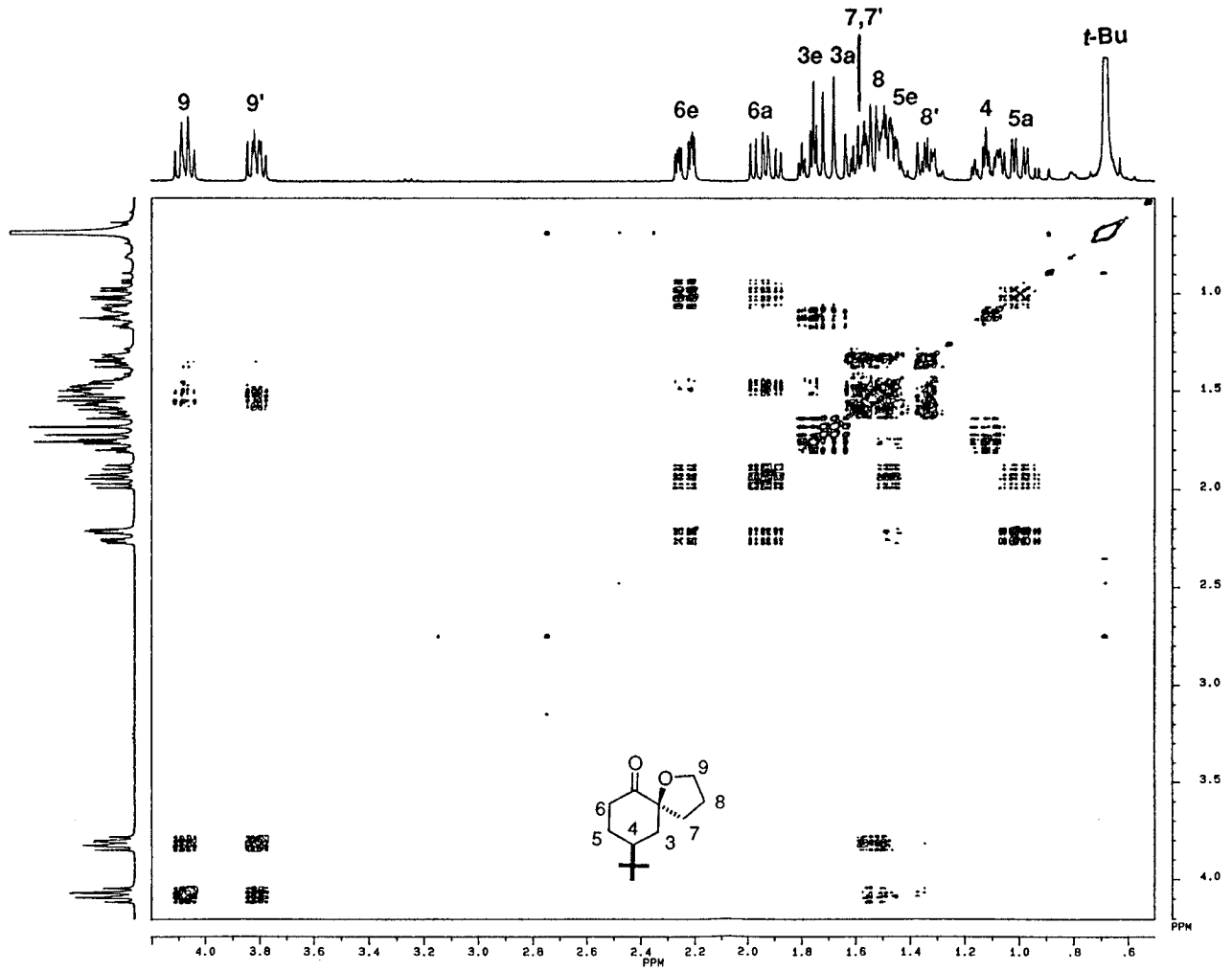
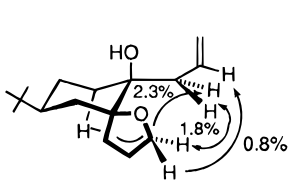
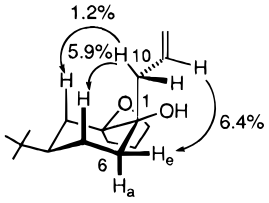


Figure 1. 300 MHz $^1H/^1H$ COSY 90 spectrum of **10** in $CDCl_3$ solution.



F



G

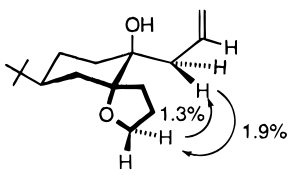
ether functionality resides on an adjacent carbon. We speculate that this effect may originate from the greater dipole moments present in those molecules that feature at least one axial C−O bond. Beyond that, the stereochemical projection of the second ether oxygen appears to be inconsequential.

As shown in Table 4, the substitution of an equatorial methoxyl by a spirotetrahydrofuran ring has extensive consequences on π-facial stereoselectivity (Scheme 7). While the allyl Grignard reagent attacks from both possible directions with approximately equal facility (entry 33), the cerate and chromium reagents exhibit an almost 2-fold preference for axial attack (entries 34 and 35). The Normant reagent gives rise predominantly to **40**, and by a very large margin (14.2:1, entry 36). We are not aware of reports in which an axial preference of this magnitude has been observed previously.

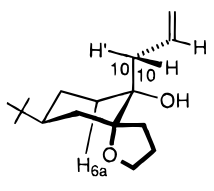
The stereoselectivity of the last reaction may be fostered by projection of the methylene of the heterocyclic ring in the axial direction resulting in steric impedance to bonding from the adjacent equatorial surface of the carbonyl. If this is the case, then the experiments defined in entries 33−35 (Table 4) could reflect some overriding of this steric effect by modest chelation to oxygen. The result is the formation of "reduced" amounts of **38**, although this diastereomer continues to predominate.

The behavior detailed above clearly does not extend to the allylations promoted by indium (entries 37−40). In all four condensations studied, the equatorial homoallylic alcohol **37** proved to be the major product. Thus, **10** reacts with the allylindium reagent with much greater chelation control than the other organometallic reagents, irrespective of whether the reaction is conducted in THF or water.

The studies involving diastereomer **11** were equally revealing. The structural distinction between **41** and **42** was made by means paralleling those developed earlier for **37** and **38**. For example, the axial alcohol **41** was less polar than **42** (Table 3) and exhibited the confirmatory NOE effects given in **H**. Also, whereas W-coupling between H-6a and H-10 was not evident in **41**, it was clearly apparent in the spectrum of **42** (see **I**). Semiselective long-range DEPT experiments again confirmed the trans-diaxial relationship of H-6a and C-10.



H



I

Although **43** and **44** proved difficult to separate chromato-

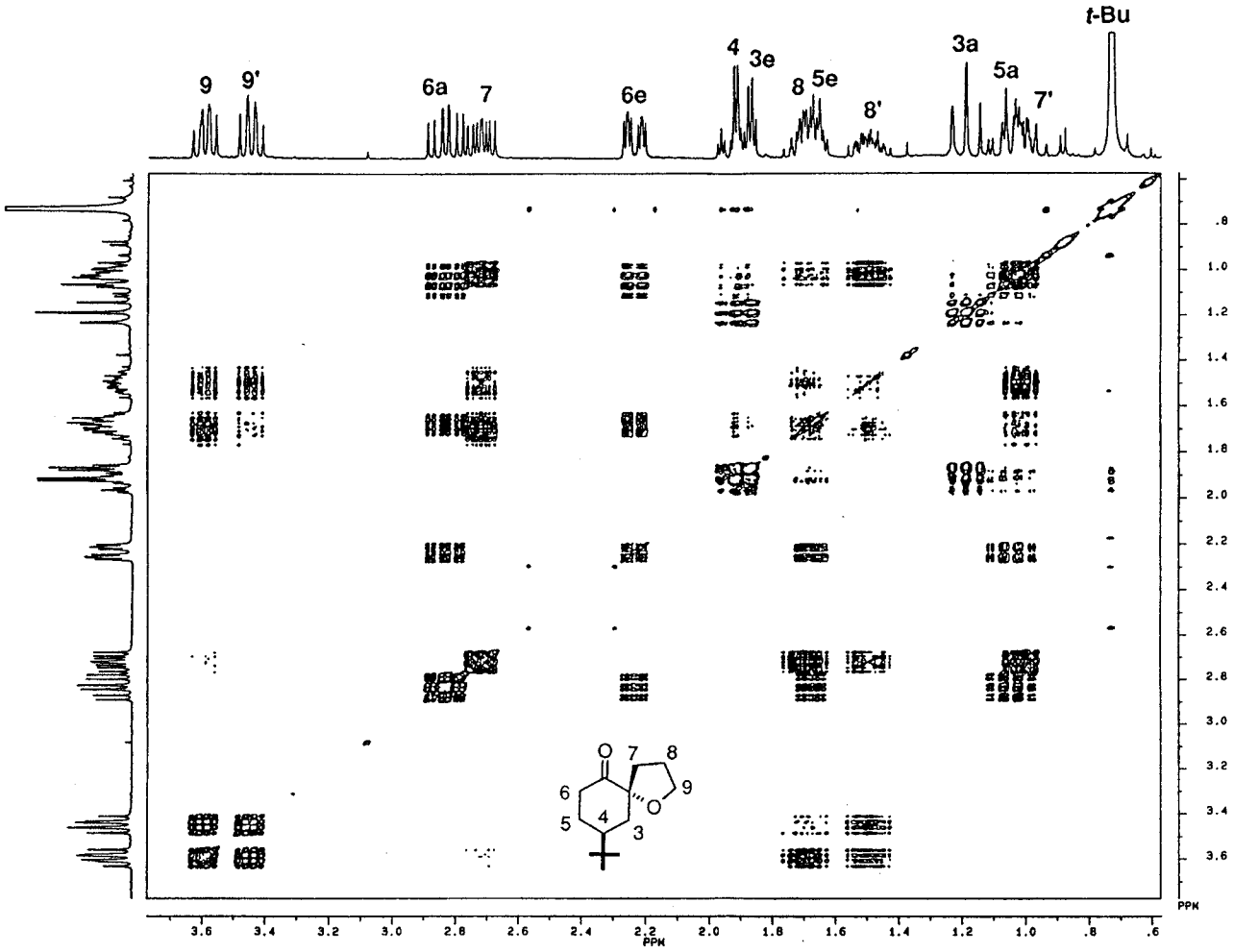


Figure 2. 300 MHz $^1H/^1H$ COSY 90 spectrum of **11** in $CDCl_3$ solution.

graphically, they could be independently prepared by hydroboration of **41** and of **42**. Structural proof, realized in this manner, also permitted configurational assignment to be made with confidence to the dispiro ethers **45** and **46** (Scheme 8).

Despite the axial disposition of the ether oxygen in **11**, the Grignard and cerium reagents add with a modest preference from the diaxial direction (entries **41** and **42**). All of the other organometallics, and particularly the indium reagents, exhibit a respectable kinetic preference for the bonding to the equatorial face of the carbonyl group (entries 43−48). Proper understanding of these facts is dependent on a reasonable knowledge of the extent to which conformations **11ch** and **11tw** become involved in the rate-determining transition states. We have earlier discussed how small the free energy difference between these conformers might be. If chelation to **11tw** operates to a significant degree, heightened levels of equatorial attack should be operational as is seen.

Competition Experiments. Eliel, Frye, and co-workers[41] have recently called attention to the fact that in the absence of kinetic studies it becomes impossible to distinguish between chelation as a product-determining event or an unproductive reversible process.[42] In their words, "if chelation is the cause of the high stereoselectivity observed in additions to alkoxy ketones, it must also be true that the chelated transition state provides a lower energy pathway to products than the less stereoselective pathway not involving chelation which is available to all ketones". In order to probe this important issue in the present context, we have conducted a series of competition experiments designed to elucidate whether those examples exhibiting increased stereoselectivity are indeed mediated by more reactive indium chelates. In the interpretation of these findings, we have assumed that chelation/non-chelation is the only kinetic consideration at issue. Possible contributions stemming from differing field/inductive effects, orbital overlap factors, electronegativity effects, and steric contributions are assumed to play a lesser role, but strictly speaking,[43] this need not be the case. However, since the order of reactivity does follow the observed stereoselection order and since the ketones carry only a single α-oxygen atom, it can be argued that the correlation is reasonable.

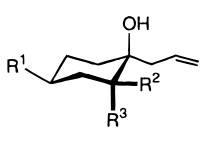
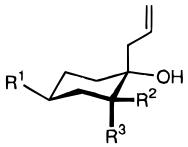
Several revealing pieces of information have emerged from this aspect of the study. Thus, direct competition between **6** and **7** has revealed these two ketones to be almost equally reactive toward the allylindium reagent (entry 49, Table 5). Since both of these substrates project their α-methoxyl substituent equatorially for possible complexation to the incoming organometallic reagent and comparable levels of chelation are anticipated, it would be necessary that quite similar rates of addition be observed if complexation to methoxyl oxygen is kinetically relevant. The sensitivity of the allylindium reagent to steric screening is made evident in the direct competition between ketones **7** and **10** (entry 51). Although both of these ketones project their ether oxygens equatorially, only **7** reacts with the

(41) (a) Chen, X.; Hortelano, E. R.; Eliel, E. L.; Frye, S. V. *J. Am. Chem. Soc.* **1990**, *112*, 6130. (b) Frye, S. V.; Eliel, E. L.; Cloux, R. *J. Am. Chem. Soc.* **1987**, *109*, 1862.

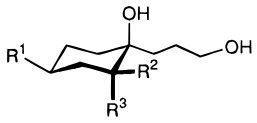
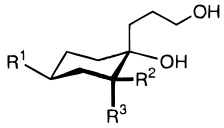
(42) Laemmle, J.; Ashby, E. C.; Neumann, H. M. *J. Am. Chem. Soc.* **1971**, *93*, 5120.

(43) Das, G.; Thornton, E. R. *J. Am. Chem. Soc.* **1993**, *115*, 1302.

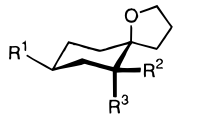
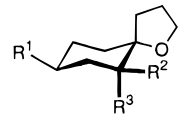
Table 3. Polarities of Selected Cyclohexanols and Spirotetrahydrofuran Derivatives (R_f Values)

			solvent system
$R^1 = R^3 = H, R^2 = CH_3$	0.13	0.10	10% ether in pet. ether
$R^1 = R^3 = H, R^2 = C_6H_5$	0.18	0.13	20% ether in pet. ether
$R^1 = R^3 = H, R^2 = OCH_3$	0.35	0.21	10% ether in pet. ether
$R^1 = t$-Bu, $R^2 = OCH_3$, $R^3 = H$	0.51	0.46	15% EtOAc in hexanes
$R^1 = t$-Bu, $R^2 = H$, $R^3 = OCH_3$	0.56	0.47	10% EtOAc in hexanes
$R^1 = H$, $R^2/R^3 = O(CH_2)_3$[a]	0.40	0.31	15% ether in pet. ether
$R^1 = t$-Bu, $R^2/R^3 = O(CH_2)_3$[a]	0.35	0.18	15% EtOAc in hexanes
$R^1 = t$-Bu, $R^2/R^3 = (CH_2)_3O$[a]	0.25	0.15	8% EtOAc in hexanes

$R^1 = t$-Bu, $R^2 = OCH_3$, $R^3 = H$	0.23	0.11	50% EtOAc in hexanes
$R^1 = t$-Bu, $R^2 = H$, $R^3 = OCH_3$	0.25	0.16	40% EtOAc in hexanes
$R^1 = t$-Bu, $R^2/R^3 = O(CH_2)_3$[a]	0.15	0.09	25% EtOAc in hexanes

$R^1 = R^3 = H, R^2 = CH_3$	0.25	0.13	15% ether in pet. ether
$R^1 = R^3 = H, R^2 = C_6H_5$	0.20	0.13	15% ether in pet. ether
$R^1 = R^3 = H, R^2 = OCH_3$	0.10	0.18	15% ether in pet. ether
$R^1 = H$, $R^2/R^3 = O(CH_2)_3$[a]	0.14	0.29	20% ether in pet. ether
$R^1 = t$-Bu, $R^2/R^3 = O(CH_2)_3$[a]	0.22	0.48	15% EtOAc in hexanes
$R^1 = t$-Bu, $R^2/R^3 = (CH_2)_3O$[a]	0.61	0.76	75% EtOAc in hexanes

[a] The symbolism $O(CH_2)_3$ is meant to indicate that the oxygen atom resides at R^2 (=equatorial), while $(CH_2)_3O$ denotes axial attachment at R^3.

organometallic reagent to the point where it is completely consumed. Evidently, therefore, the incorporation of the α-oxygen atom into a tetrahydrofuran ring does not allow for the generation of a kinetically relevant chelate structure as rapidly as that associated with **7**. This does not mean that **10** is unable to engage in chelation. However, it does so much less effectively than **7**.

Entries 50 and 52 point out the differences in relative rate associated with axial and equatorial projection of the flanking ether oxygen. Since chelation to **10** is sterically impeded, it is not surprising to find that **10** reacts only 2.5 times faster than **11**. The extent to which the latter ketone may adopt a twist-boat conformation in order to engage in chelation is not known. However, the latter option appears rather unlikely when viewed in the context of the less than maximal complexing capacity of **10**. More revealing in this context is the data associated with entry 50. In this instance, the two possible epimers are substituted by methoxyl and are not sterically disadvantaged. The exclusivity with which **7** reacts in the presence of **8** denotes the substantive kinetic advantage associated with equatorial projection of the methoxyl substituent. The corresponding highly stereoselective behavior of **7**, which gives only the product predicted by Cram's chelate rule, is in complete accord with the proposal that allylation proceeds via the chelated transition state. A provocative aspect of this finding is that the parallelism between reactivity and stereoselectivity unequivocally operates in water as the reaction medium.

Conclusions

Allylation reactions performed with indium under aqueous conditions have generally been shown to be more stereoselective toward α-alkoxy cyclohexanones than related reactions involving other organometallics under anhydrous conditions. In fact, this new reagent system ranks as the most highly selective allylating agent yet reported *for aqueous systems*, as long as steric effects do not gain heightened importance. In the companion paper,[44] neighboring unprotected hydroxyl substituents are shown to be capable of still greater directing effects. Consequently, this chemistry clearly constitutes a synthetically useful operation well suited for application to more complex problems in organic syntheses.

The fortuitous situation that the rate effects arising from chelation are kinetically dominant has allowed us to probe the orientational consequences of flanking C−O bond geometry on stereoselective attack at a cyclohexanone carbonyl. It turns out that good agreement with a chelate transition state model is seen, from which heuristic value may be derived. Studies are

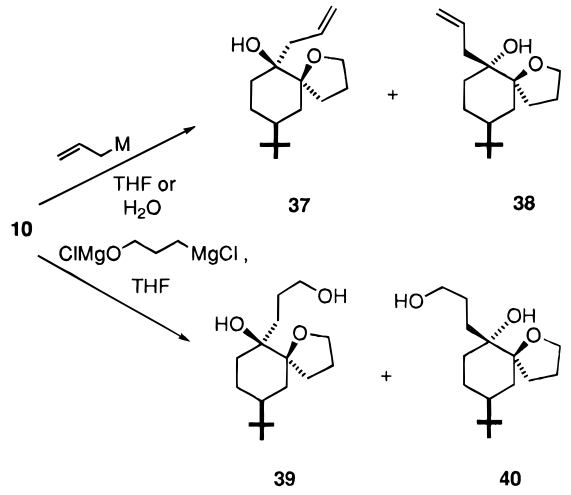
(44) Paquette, L. A.; Mitzel, T. M. *J. Am. Chem. Soc.* **1996**, *118*, 1931.

Table 4. Facial Selectivity in Nucleophilic Additions to **10** and **11**[a]

entry	reagent	solvent (T, °C)	chelate/ non-chelate ratio	yield, %
For **10**:				
33	CH_2=$CHCH_2MgCl$	THF, 0	1 : 1.1	81
34	CH_2=$CHCH_2MgCl$, $CeCl_3$	THF, 0	1 : 1.8	87
35	CH_2=$CHCH_2Br$, $CrCl_2$	THF, 0	1 : 1.7	95
36	$ClMgO(CH_2)_3MgCl$	THF, 0	1 : 14.2	90
37	CH_2=$CHCH_2Br$, In	THF, 25	11.8 : 1	85
38	CH_2=$CHCH_2Br$, In	THF-H_2O (1:1), 25	6.7 : 1	91
39	CH_2=$CHCH_2Br$, In	H_2O, 25	6.7 : 1	84
40	CH_2=$CHCH_2Br$, In	THF, 25[b]	10.6 : 1	91
For **11**:				
41	CH_2=$CHCH_2MgCl$	THF, 0	1 : 2.4	80
42	CH_2=$CHCH_2MgCl$, $CeCl_3$	THF, 0	1 : 2.0	75
43	CH_2=$CHCH_2Br$, $CrCl_2$	THF, 0	4.2 : 1	72
44	$ClMgO(CH_2)_3MgCl$	THF, 0	7.6 : 1	88
45	CH_2=$CHCH_2Br$, In	THF, 25	14.0 : 1	68
46	CH_2=$CHCH_2Br$, In	THF-H_2O (1:1), 25	6.5 : 1	87
47	CH_2=$CHCH_2Br$, In	H_2O, 25	6.8 : 1	70[c]
48	CH_2=$CHCH_2Br$, In	THF, 25[b]	11.0 : 1	77

[a] All experiments were conducted minimally in duplicate, and the reported data represent the average of these experiments. [b] The allyl bromide and indium powder were refluxed in THF for 1 h and cooled to 25 °C before the ketone was added. [c] Based on recovered starting material.

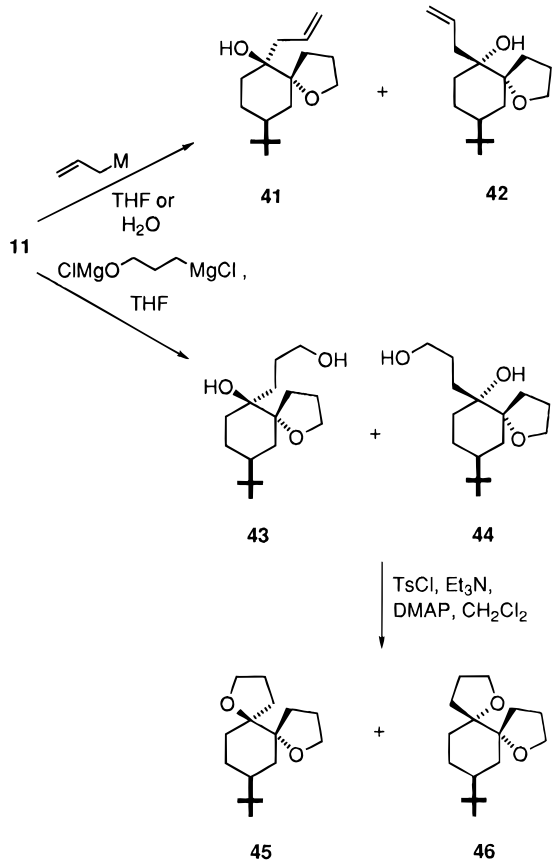
Scheme 7



underway which should ascertain the extent to which other types of effects can possibly contribute to rate enhancement *and* stereoselection.

The present work establishes for the first time that ketones are indeed reactive in indium-promoted allylations conducted in aqueous media. Further, relative reactivities are unquestionably governed by chelation effects, which in turn are especially sensitive to nonbonded steric congestion. The same correlation is exhibited by aldehydes[44] as well as ketones. In effect, an unencumbered α-oxygen which is not deactivated by acylation or silylation is capable of controlling π-facial diastereoselection in water. The potential synthetic utility of this stereocontrol is made clear by direct comparison with the diastereoselectivities of other allylations performed by different metals in anhydrous organic solvents.

Scheme 8



Experimental Section

Melting points were determined in open capillaries and are uncorrected. Mass spectra were recorded at The Ohio State University Chemical Instrumentation Center. Elemental analyses were performed by the Scandinavian Microanalytical Laboratory, Herlev, Denmark, and Atlantic Microlab, Inc., Norcross, GA. All organic solvents were predried by standard methods. Unless otherwise indicated, all separations were carried out under flash chromatography conditions on silica gel 60 (230−400 mesh, 60 Å) using the indicated solvents. The organic extracts were dried over anhydrous magnesium or sodium sulfate. The purity of all compounds was shown to be ≥95% by high-field ^{1}H NMR analysis.

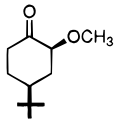
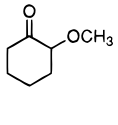
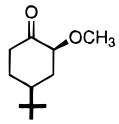
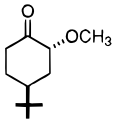
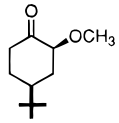
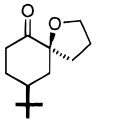
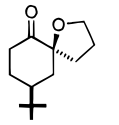
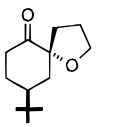
Additions Involving Allylmagnesium Chloride. A. 2-Methoxycyclohexanone. Magnesium turnings were washed with 10% HCl, rinsed several times with water, slurried in acetone, and dried under vacuum before use. A 446 mg (18.3 mmol) sample of magnesium turnings was flushed with dry nitrogen, covered with dry THF (15 mL), warmed gently, and treated slowly with allyl chloride (0.872 mL, 10.7 mmol) at a rate sufficient to maintain reflux. After 1 h, the Grignard solution was cooled to 0 °C. The reaction mixture was stirred at this temperature for 1.5 h, quenched with saturated NH_4Cl solution, and extracted with ether. The combined organic layers were washed with brine, dried, and evaporated, and the product alcohols were separated by chromatography on silica gel (elution with 10% ether in petroleum ether). The spectral properties of **12** and **13** are identical to those previously reported.[25]

B. 1-Oxaspiro[4.5]decan-6-one. Ketone **9** reacted with equal facility to give **17** and **18**, the high-field ^{1}H and ^{13}C spectra of which are identical to those previously reported.[30]

C. *cis*-2-Methoxy-4-*tert*-butylcyclohexanone. Submission of **7** to the same reaction conditions afforded alcohols **23** and **24**, which were separated by MPLC on silica gel (elution with 10% ethyl acetate in hexanes).

23: colorless oil; IR (neat, cm^{-1}) 3472, 1639; ^{1}H NMR (300 MHz, C_6D_6) δ 5.98−5.84 (m, 1 H), 5.10−5.02 (m, 2 H), 3.08 (s, 3 H), 2.75 (dd, J = 11.2, 4.6 Hz, 1 H), 2.45 (ddt, J = 13.5, 6.5, 1.3 Hz, 1 H), 2.25 (dd, J = 13.6, 8.3 Hz, 1 H), 1.98 (d, J = 2.3 Hz, 1 H), 1.87−1.80

Table 5. Competitive Indium-Promoted Allylations in Water at 25 °C

entry	first ketone	second ketone	reaction time, h	relative rate ratio[a]
49	 **7**	 **6**	10	1.1 : 1[b]
50	 **7**	 **8**	5	>99 : 1[b,c]
51	 **7**	 **10**	12	>99 : 1[c]
52	 **10**	 **11**	48	2.5 : 1[c]

[a] All experiments were conducted minimally in duplicate, and the reported data represent the average of these experiments. [b] The relative rate ratio was ascertained by quantitative analysis of the alcohol products formed. [c] The relative rate ratio was determined by quantitative assessment of the levels of unreacted ketones remaining.

(m, 2 H), 1.53 (dq, J = 12.7, 3.6 Hz, 1 H), 1.40−1.32 (m, 2 H), 1.06 (tq, J = 13.6, 2.2 Hz, 1 H), 0.85 (s, 9 H), 0.79 (tt, J = 12.4, 3.1 Hz, 1 H); ^{13}C NMR (75 MHz, C_6D_6) δ 135.3, 117.3, 83.0, 72.5, 56.2, 46.5, 45.3, 34.4, 32.4, 27.7, 26.9, 22.1; MS *m/z* ($M^+ - C_3H_5$) calcd 185.1542, obsd 185.1546. Anal. Calcd for $C_{14}H_{26}O_2$: C, 74.29; H, 11.58. Found: C, 74.48; H, 11.60.

24: colorless crystals, mp 47−48 °C; IR (film, cm^{-1}) 3484, 1639, 1467, 1393, 1366, 1328, 1245, 1186; ^{1}H NMR (300 MHz, C_6D_6) δ 5.99−5.85 (m, 1 H), 5.09−5.03 (m, 2H), 3.07 (s, 3 H), 2.68 (dd, J = 11.2, 4.9 Hz, 1 H), 2.45 (dd, J = 13.6, 6.4 Hz, 1 H), 2.26 (dd, J = 13.6, 8.4 Hz, 1 H), 1.97 (s, 1 H), 1.90 (dt, J = 13.5, 3.1 Hz, 1 H), 1.86−1.48 (m, 4 H), 0.93 (br t, J = 12.9 Hz, 1 H), 0.83 (s, 9 H), 0.87−0.65 (m, 1 H); ^{13}C NMR (75 MHz, C_6D_6) δ 135.3, 117.3, 82.3, 73.3, 56.1, 45.8, 41.7, 35.9, 32.0, 27.6, 25.9, 25.3; MS *m/z* ($M^+ - C_3H_5$) calcd 185.1541, obsd 185.1548. Anal. Calcd for $C_{14}H_{26}O_2$: C, 74.29; H, 11.58. Found: C, 74.06; H, 11.56.

D. *trans*-2-Methoxy-4-*tert*-butylcyclohexanone. Comparable treatment of **8** provided **28** and **29**, which were separated by chromatography on silica gel (elution with 10% ethyl acetate in hexanes).

28: colorless oil; IR (neat, cm^{-1}) 3475, 1365, 1100; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.74−5.44 (m, 1 H), 5.18−5.09 (m, 2 H), 3.74 (s, 3 H), 3.04 (br t, J = 1.6 Hz, 1 H), 2.40 (dd, J = 13.6, 7.3 Hz, 1 H), 2.16 (dd, J = 13.6, 7.9 Hz, 1 H), 1.93−1.87 (m, 1 H), 1.64−1.25 (m, 6 H), 0.86 (s, 9 H); ^{13}H NMR (75 MHz, $CDCl_3$) ppm 133.8, 119.1, 81.3, 71.6, 56.1, 43.8, 40.3, 33.6, 32.0, 27.4, 24.2, 21.9; MS *m/z* (M^+) calcd 226.1933, obsd 226.1924. Anal. Calcd for $C_{14}H_{26}O_2$: C, 74.29; H, 11.58. Found: C, 73.68; H, 11.55.

29: colorless oil; IR (neat, cm^{-1}) 3566, 1391, 1366, 1094; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.02−5.84 (m, 1 H), 5.12−5.03 (m, 2 H), 3.35 (s, 3 H), 3.19 (br t, J = 1.8 Hz, 1 H), 2.82 (br s, 1 H), 2.28 (ABq of ABX, $\Delta\mu$ = 15.8 Hz, J_{AB} = 14.3 Hz, J_{AX} = 6.9 Hz, J_{BX} = 7.4 Hz, 2 H), 2.00 (br dq, J = 14.1, 3.1 Hz, 1 H), 1.69−1.51 (m, 3 H), 1.31 (br tt, J = 12.6, 3.1 Hz, 1 H), 1.18−0.97 (m, 2 H), 0.87 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 133.7, 117.4, 82.2, 72.4, 56.4, 39.9 (2 C), 34.2, 31.8, 27.5, 25.3, 23.8; MS *m/z* (M^+) calcd 226.1933, obsd 226.1959. Anal. Calcd for $C_{14}H_{26}O_2$: C, 74.29; H, 11.58. Found: C, 74.22; H, 11.59.

E. (5*R,9*R**)-9-*tert*-Butyl-1-oxaspiro[4.5]decan-6-one (10).** Analogous addition of allylmagnesium chloride to **10** gave rise to **37** and **38**, separation of which by chromatography on silica gel (elution with 19:1 → 6:1 hexanes/ethyl acetate) provided the pure diastereomers.

37: colorless oil; IR (neat, cm^{-1}) 3478, 1065; ^{1}H NMR (300 MHz, C_6D_6) δ 6.22−6.08 (m, 1 H), 5.14−5.08 (m, 2 H), 3.60−3.53 (m, 2 H), 2.37 (ddt, J = 13.8, 5.4, 1.6 Hz, 1 H), 2.27 (br s, 1 H), 2.02−1.87 (m, 3 H), 1.63 (td, J = 12.8, 3.8 Hz, 1 H), 1.57−1.29 (m, 6 H), 1.06−0.74 (m, 2 H), 0.85 (s, 9 H); ^{13}C NMR (75 MHz, C_6D_6) δ 135.9, 116.7, 88.4, 74.3, 67.6, 46.2, 41.4, 36.0, 33.7, 32.6, 32.3, 27.7, 27.4, 21.9; MS *m/z* (M^+) calcd 252.2089, obsd 252.2085. Anal. Calcd for $C_{16}H_{28}O_2$: C, 76.14; H, 11.18. Found: C, 76.34; H, 11.21.

38: colorless oil; IR (neat, cm^{-1}) 3476, 1365, 1068; ^{1}H NMR (300 MHz, C_6D_6) δ 6.12−5.98 (m, 1 H), 5.13−5.06 (m, 2 H), 3.76−3.69 (m, 1 H), 3.62 (dd, J = 14.5, 7.8 Hz, 1 H), 2.76 (ddd, J = 14.6, 6.1, 1.4 Hz, 1 H), 2.50 (dd, J = 14.6, 8.5 Hz, 1 H), 2.31 (ddd, J = 12.1, 8.7, 5.4 Hz, 1 H), 1.86−1.80 (m, 1 H), 1.74−1.53 (m, 3 H), 1.51−1.21 (m, 6 H), 1.05−0.98 (m, 1 H), 0.78 (s, 9 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 135.5, 117.6, 88.6, 75.5, 67.7, 45.8, 38.4, 36.4, 33.8, 32.1, 31.9, 27.7, 27.3, 23.3; MS *m/z* (M^+) calcd 252.2089, obsd 252.2079. Anal. Calcd for $C_{16}H_{28}O_2$: C, 76.14; H, 11.18. Found: C, 75.97; H, 11.23.

F. (5*R,9*S**)-9-*tert*-Butyl-1-oxaspiro[4.5]decan-6-one (11).** Comparable treatment of **11** produced a mixture of **41** and **42**, which were separated chromatographically on silica gel (elution with 10:1 hexanes/ethyl acetate).

41: colorless solid, mp 46−47 °C; IR (film, cm^{-1}) 3498, 1467, 1437, 1064; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.96−5.82 (m, 1 H), 5.17−5.07 (m, 1 H), 3.88−3.73 (m, 2 H), 2.32 (dd, J = 13.6, 7.1 Hz, 1 H), 2.26−2.16 (m, 2 H), 1.95−1.72 (series of m, 2 H), 1.65−1.18 (series of m, 10 H), 0.84 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.3, 118.8, 86.3, 73.7, 68.0, 42.5, 40.3, 35.1, 33.9, 33.2, 31.9, 27.4, 26.3, 21.5; MS *m/z* (M^+) calcd 252.2089, obsd 252.2083. Anal. Calcd for $C_{16}H_{28}O_2$: C, 76.14; H, 11.18. Found: C, 76.24; H, 11.17.

42: colorless oil; IR (neat, cm^{-1}) 3563, 1365, 1055; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.01−5.87 (m, 1 H), 5.12−5.05 (m, 2 H), 3.92−3.79 (m, 2 H), 2.31 (dd, J = 14.2, 8.4 Hz, 1 H), 2.24−2.12 (m, 2 H), 1.95−1.81 (m, 3 H), 1.72 (dt, J = 13.7, 3.0 Hz, 1 H), 1.64−1.34 (series of m, 5 H), 1.12 (t, J = 13.2 Hz, 1 H), 1.04 (dq, J = 12.9, 3.6 Hz, 1 H), 0.84 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.1, 117.2, 87.8, 74.0, 67.7, 42.1, 37.9, 34.1, 34.0, 31.8, 31.2, 27.5, 25.6, 23.6; MS *m/z* (M^+) calcd 252.2089, obsd 252.2088. Anal. Calcd for $C_{16}H_{28}O_2$: 76.14; H, 11.18. Found: C, 75.79; H, 11.13.

Prototypical $CeCl_3$-Mediated Coupling. A 364 mg (0.98 mmol) sample of cerium trichloride heptahydrate was dried according to standard protocol.[45] The cooled salt was slurried with anhydrous THF (3.6 mL) for 3 h under N_2 at room temperature (rt). A solution of allylmagnesium chloride (1.1 mL of 1 M in THF, 1.1 mmol), prepared in the predescribed manner, was added via syringe into this slurry, and the reaction mixture was stirred at 0 °C for 20 min. The ketone (0.15 mmol) dissolved in dry THF (1.0 mL) was next introduced slowly at 0 °C. Upon completion of the addition (monitored by TLC, most commonly 45 min), aqueous NH_4Cl solution was added and the usual workup was applied.

Prototypical $CrCl_2$-Promoted Coupling. Freshly distilled thionyl chloride (45 mL) was added dropwise during 10 min to finely divided chromium trichloride hexahydrate (17.5 g, 65.7 mmol). The magnetically stirred mixture was slowly warmed to reflux, maintained at this temperature for 2.5 h, and freed of the excess thionyl chloride under reduced pressure to leave a purple-rose powder. This solid was stored overnight in a desiccator charged with KOH pellets and free of oxygen.[46]

A slurry of anhydrous chromium trichloride (4.32 g, 23.7 mmol) in cold (0 °C), dry THF (54 mL) was cautiously treated in five portions with lithium aluminum hydride (517 mg, 13.6 mmol), stirred for 15

(45) (a) Imamoto, T.; Takiyama, N.; Nakumura, K. *Tetrahedron Lett.* **1985**, *26*, 4763. (b) *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; **1995**; Volume 2, pp 1031−1034.

(46) Pray, A. R. *Inorg. Synth.* **1954**, *5*, 153.

min at this temperature, and allowed to warm to 20 °C during another 20 min, at which point the reaction mixture became characteristic dark brown in color. The mixture was recooled to 0 °C, the ketone (3.90 mmol) was introduced via syringe, and stirring was maintained for 15 min before allyl bromide (1.42 g, 11.7 mmol) was added dropwise. After 3 h at 0 °C and 30 min at rt, the reaction mixture was quenched with saturated $NaHCO_3$ solution and diluted with ether. The aqueous phase was extracted with CH_2Cl_2 (3×), and the combined organic extracts were washed with brine (2×), dried, and concentrated.

Prototypical Indium-Promoted Couplings. A. In Dry THF. To a magnetically stirred suspension of indium powder (168 mg, 1.46 mmol) in dry THF (5 mL) was introduced allyl bromide (0.126 mL, 1.46 mmol) via syringe, and the mixture was agitated for 5 min prior to introduction of neat ketone (0.97 mmol). Reaction was allowed to proceed for 3 h at room temperature, 10% hydrochloric acid was then added, and the usual workup conditions were applied.

B. In 50% Aqueous THF. To a reaction vessel containing allyl bromide (26 mg, 0.21 mmol), indium powder (37 mg, 0.32 mmol), and the ketone (0.19 mmol) were added THF (2.0 mL) and water (2.0 mL). The reaction mixture was stirred at rt until ketone consumption was complete (TLC analysis), quenched with 10% HCl, and extracted with ether. The combined organic phases were washed once with brine, dried, and concentrated to leave an oily residue that was purified chromatographically.

C. In Water. A mixture of allyl bromide (30 mg, 0.25 mmol), indium powder (29 mg, 0.25 mmol), ketone (0.15 mmol), and water (2.0 mL) was stirred at rt until ketone consumption was complete (TLC analysis). A workup identical to that in **B** was employed.

D. In THF with Prior Formation of the Allylindium Reagent. A magnetically stirred mixture of allyl bromide (31 mg, 0.26 mmol), indium powder (28 mg, 0.25 mmol), and THF (0.71 mL) was gently refluxed for 1 h, cooled to rt, and treated with the ketone (0.181 mmol) dissolved in 0.71 mL of THF. The reaction mixture was stirred for 1 h, filtered through a small pad of silica gel (elution with ethyl acetate), and concentrated. Diastereomer separation was accomplished by chromatography on silica gel.

Prototypical Normant Alkylations. A cold (0 °C), magnetically stirred solution of 3-chloro-1-propanol (3.78 g, 40 mmol) in dry THF (40 mL) was treated dropwise with a solution of isopropylmagnesium chloride in ether (20 mL of 2.0 M, 40 mmol) during 20 min and subsequently warmed to room temperature. Flame-dried magnesium turnings (1.46 g, 60 mmol) were quickly added, and the mixture was refluxed for 1 h and left to stand overnight without stirring in order to allow the excess magnesium to settle. The concentration of active Grignard reagent was established by titration of a small portion of the supernatant with menthol and 1,10-phenanthroline according to established procedure.[47]

To a cold (0 °C), magnetically stirred solution of the ketone (1.93 mmol) in dry THF (7.5 mL) was added dropwise the Normant reagent (5.88 mL of 0.365 M, 2.15 mmol). The reaction mixture was stirred at 0 °C for 1 h, quenched with 10% HCl, and diluted with ether. The organic phase was washed with brine (2×), dried, and concentrated.

The spectral properties for **14** and **15**[25] and of **19** and **20**[30] are identical to those previously reported.

(1*R,2*R**,4*R**)-1-(3-Hydroxypropyl)-2-methoxy-4-*tert*-butylcyclohexanol (25):** colorless solid, mp 86 °C; IR (film, cm^{-1}) 3734, 1644, 1422, 1265; ^1H NMR (300 MHz, C_6D_6) δ 3.51−3.42 (m, 2 H), 3.08 (s, 3 H), 2.67 (dd, J = 11.2, 4.6 Hz, 1 H), 1.93 (dt, J = 13.8, 3.3 Hz, 1 H), 1.87−1.26 (series of m, 10 H), 0.90 (dd, J = 13.6, 4.3 Hz, 1 H), 0.86 (s, 9 H), 0.84−0.74 (m, 1 H); ^{13}C NMR (75 MHz, C_6D_6) δ 84.3, 72.2, 63.5, 56.5, 46.4, 37.2, 34.0, 32.4, 27.7, 27.4, 27.1, 22.1; MS *m/z* (M^+) calcd 244.2038, obsd 244.2038. Anal. Calcd for $C_{14}H_{28}O_3$: C, 68.81; H, 11.55. Found: C, 68.96; H, 11.50.

(1*S,2*R**,4*R**)-1-(3-Hydroxypropyl)-2-methoxy-4-*tert*-butylcyclohexanol (26):** colorless solid, mp 104 °C; IR (film, cm^{-1}) 3943, 3430, 1630; ^1H NMR (300 MHz, C_6D_6) δ 3.47−3.42 (m, 2 H), 3.07 (s, 3 H), 2.59 (dd, J = 11.2, 4.8 Hz, 1 H), 1.98 (dt, J = 13.4, 3.1 Hz, 1 H), 1.81−1.31 (series of m, 10 H), 0.85 (s, 9 H), 0.86−0.64 (m, 2 H); ^{13}C NMR (75 MHz, C_6D_6) δ 82.4, 72.1, 62.5, 55.3, 40.7, 36.6, 34.4, 31.0, 26.7, 26.3, 25.0, 24.2; MS *m/z* (M^+) calcd 244.2038, obsd 244.2034. Anal. Calcd for $C_{14}H_{28}O_3$: C, 68.81; H, 11.55. Found: C, 68.98; H, 11.38.

(1*R,2*S**,4*R**)-1-(3-Hydroxypropyl)-2-methoxy-4-*tert*-butylcyclohexanol (30):** colorless solid, mp 114−115 °C; IR (CCl_4, cm^{-1}) 3334, 1549, 1252, 1218, 1098, 1005; ^1H NMR (300 MHz, $CDCl_3$) δ 3.73−3.60 (m, 2 H), 3.24 (s, 3 H), 3.19 (s, 1 H), 2.40 (br s, 2 H), 1.92 (br d, J = 13.5 Hz, 1 H), 1.77−1.25 (series of m, 10 H), 0.86 (s, 9 H); ^{13}C (75 MHz, $CDCl_3$) δ 80.9, 71.8, 63.5, 56.1, 40.3, 36.4, 33.8, 32.0, 27.4, 25.7, 24.0, 21.4; MS *m/z* (M^+) calcd 244.2038, obsd 244.2041. Anal. Calcd for $C_{14}H_{28}O_3$: C, 68.81; H, 11.55. Found: C, 68.98; H, 11.40.

(1*S,2*S**,4*R**)-1-(3-Hydroxypropyl)-2-methoxy-4-*tert*-butylcyclohexanol (31):** colorless oil; IR (neat, cm^{-1}) 3388, 1460, 1393, 1365, 1097; ^1H NMR (300 MHz, $CDCl_3$) δ 3.67−3.63 (m, 2 H), 3.35 (s, 3 H), 3.21 (br d, J = 1.7 Hz, 1 H), 2.68 (br s, 2 H), 2.02 (dq, J = 14.0, 3.1 Hz, 1 H), 1.74−1.51 (series of m, 5 H), 1.31 (tt, J = 12.6, 3.1 Hz, 1 H), 1.20 (t, J = 6.9 Hz, 1 H), 1.18−0.87 (series of m, 3 H), 0.85 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 82.5, 72.6, 63.3, 56.4, 40.1, 33.7, 32.1, 31.8, 27.5, 26.1, 25.5, 23.9; MS *m/z* (M^+) calcd 244.2038, obsd 244.2033. Anal. Calcd for $C_{14}H_{28}O_3$: C, 68.81; H, 11.55. Found: C, 68.40; H, 11.42.

(5*R,6*R**,9*R**)-9-*tert*-Butyl-6-hydroxy-1-oxaspiro[4.5]decane-6-propanol (39):** colorless solid, mp 98.9−99.5 °C; IR (film, cm^{-1}) 3428, 1468, 1365, 1065; ^1H NMR (300 MHz, C_6D_6) δ 3.66−3.46 (m, 4 H), 2.05−1.73 (m, 4 H), 1.68−1.19 (series of m, 10 H), 0.93−0.76 (m, 2 H), 0.86 (s, 9 H); ^{13}C NMR (75 MHz, C_6D_6) δ 88.7, 74.4, 67.3, 63.6, 46.0, 36.0, 33.1, 32.8, 32.7, 32.3, 27.7, 27.5, 27.1, 21.9; MS *m/z* (M^+) calcd 270.2195; obsd 270.2197. Anal. Calcd for $C_{16}H_{30}O_3$: C, 71.07; H, 11.18. Found: C, 70.98; H, 11.10.

(5*R,6*S**,9*R**)-9-*tert*-Butyl-6-hydroxy-1-oxaspiro[4.5]decane-6-propanol (40):** colorless solid, mp 106−107 °C; IR (film, cm^{-1}) 3404, 1459, 1365, 1067, 1027, 1002; ^1H NMR (300 MHz, C_6D_6) δ 3.77 (td, J = 7.6, 5.0 Hz, 1H), 3.65 (td, J = 7.8, 6.7 Hz, 1 H), 3.56−3.44 (m, 2 H), 2.38−2.29 (m, 1 H), 2.06 (br s, 2 H), 1.94−1.25 (series of m, 12 H), 1.03−0.93 (m, 2 H), 0.80 (s, 9 H); ^{13}C NMR (75 MHz, C_6D_6) δ 89.2, 75.5, 67.6, 63.4, 45.8, 36.4, 33.2, 32.1, 31.9, 29.9, 27.7, 27.3, 26.6, 23.5; MS *m/z* (M^+) calcd 270.2195, obsd 270.2192. Anal. Calcd for $C_{16}H_{30}O_3$: C, 71.07; H, 11.18. Found: C, 71.11; H, 11.12.

(5*R,6*S**,9*S**)-9-*tert*-Butyl-6-hydroxy-1-oxaspiro[4.5]decane-6-propanol (43):** colorless solid, mp 109 °C; IR (KBr, cm^{-1}) 3384, 1415, 1364, 1197, 1059, 1003, 972; ^1H NMR (300 MHz, C_6D_6) δ 3.73−3.59 (m, 2 H), 3.50−3.43 (m, 1 H), 3.38−3.31 (m, 1 H), 2.18 (qd, J = 8.9, 5.9 Hz, 1 H), 2.04 (br s, 1 H), 1.79−1.28 (series of m, 15 H), 0.92 (s, 9 H); ^{13}C NMR (75 MHz, C_6D_6) δ 86.9, 73.7, 68.0, 63.5, 42.8, 35.3, 33.4, 33.2, 32.6, 32.1, 27.7, 26.7, 26.3, 22.1; MS *m/z* (M^+) calcd 270.2195, obsd 270.2196. Anal. Calcd for $C_{16}H_{30}O_3$: C, 71.07; H, 11.18. Found: C, 71.51; H, 10.97.

(5*R,6*R**,9*S**)-9-*tert*-Butyl-6-hydroxy-1-oxaspiro[4.5]decane-6-propanol (44):** colorless solid, mp 99.8−100.2 °C; IR (film, cm^{-1}) 3417, 1366, 1055; ^1H NMR (300 MHz, C_6D_6) δ 3.70−3.54 (m, 3 H), 3.48 (dd, J = 15.4, 7.6 Hz, 1 H), 2.7−2.2 (br, 2 H), 2.07 (ddd, J = 12.0, 9.3, 9.3 Hz, 1 H), 1.97 (dt, J = 13.0, 3.3 Hz, 1 H), 1.90−1.79 (m, 1 H), 1.71−1.35 (series of m, 9 H), 1.16−1.09 (m, 1 H), 1.03−0.89 (m, 2 H), 0.80 (s, 9 H); ^{13}C NMR (75 MHz, C_6D_6) δ 88.1, 74.3, 67.6, 63.3, 42.6, 34.4, 33.7, 31.8, 31.3, 30.1, 27.7, 26.8, 25.8, 24.3; MS *m/z* (M^+) calcd 270.2195, obsd 270.2189. Anal. Calcd for $C_{16}H_{30}O_3$: C, 71.07; H, 11.18. Found: C, 70.88; H, 11.13.

(2*S,4*S**)-2-Methoxy-4-*tert*-butylcyclohexanone (7) and (2*R**,4*S**)-2-Methoxy-4-*tert*-butylcyclohexanone (8).** A nitrogen-blanketed, magnetically stirred suspension of iodosobenzene[48] (20.5 g, 0.094 mmol) in dry methanol (500 mL) was treated with boron trifluoride etherate (20.39 mL, 0.169 mol) via syringe to give a clear solution which was subsequently cooled to −78 °C. A solution of **22**[32] (20.0 g, 0.088 mol) in dry methanol (200 mL) was cooled to −78 °C and introduced slowly dropwise via cannula. The reaction mixture was stirred for 3 h at −78 °C, allowed to stir at rt for 2 h, and freed of methanol under reduced pressure. The residue was diluted with CH_2Cl_2 and washed three times with saturated $NaHCO_3$ solution and once with

(47) (a) Furniss, B. S.; Hannaford, A. J.; Smith, P. W. G.; Tatchell, A. R. In *Vogel's Textbook of Practical Organic Chemistry*, 5th ed.; Longman: Essex, U.K., 1989; pp 443−444. (b) Watson, S. C.; Eastham, J. F. *J. Organomet. Chem.* **1967**, *9*, 165.

(48) Saltzman, H.; Sharefkin, J. S. *Organic Synthesis*; Wiley: New York,1973; Collect. Vol. V, p 658.

brine prior to drying. Chromatography on silica gel, gradient elution with 15:1 → 9:1 hexanes/ethyl acetate, afforded 2.00 g (12%) of **8** and 8.15 g (50%) of **7**. The spectral properties of these ketones are identical to those previously reported.[31]

6-[(*E*)-Benzylidene]-8-*tert*-butyl-1,4-dioxaspiro[4.5]decane (33).[49] A cold (−78 °C), nitrogen-blanketed solution of diisopropylamine (43.2 mL, 0.311 mmol) in dry THF (650 mL) was treated with *n*-butyllithium (210.5 mL of 1.6 M in hexanes, 0.337 mol), allowed to warm to rt during 1 h, and returned to −78 °C before a solution of **21** (40.0 g, 0.259 mol) in dry THF (400 mL) was slowly introduced via cannula. After this mixture had stirred in the cold for 1 h, benzaldehyde (26.3 mL, 0.233 mol) was added, followed 5 s later by methanesulfonyl chloride (40.0 mL, 0.508 mol). The reaction mixture was warmed to rt during 2 h, treated with triethylamine (300 mL), and refluxed for 1 h or stirred overnight at rt prior to dilution with water (400 mL) and extraction with ether (4 × 100 mL). The combined organic layers were washed with saturated NH_4Cl solution and brine, dried, and evaporated to leave 31.5 g of a yellow oil which was used without further purification.

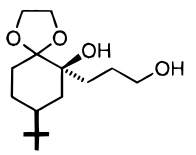
The above oil was taken up in ethylene glycol (215 mL, 5.73 mol) and trimethyl orthoformate (200 mL, 1.83 mol), treated with *p*-toluenesulfonic acid (1.24 g, 6.52 mmol), stirred overnight, quenched with one drop of triethylamine, diluted with 50% saturated $NaHCO_3$ solution, and extracted with ether. The combined organic phases were dried and evaporated to leave a thick oil which was crystallized from 95% ethanol. There was obtained 37.0 g (50%) of **33** as a fluffy cream-colored solid: mp 87.5 °C; IR (film, cm^{-1}) 1479, 1366, 1188, 1098; ^1H NMR (300 MHz, C_6D_6) δ 7.50−7.47 (m, 2 H), 7.41−7.37 (m, 3 H), 7.29−7.23 (m, 1 H), 3.96−3.83 (m, 2 H), 3.81−3.73 (m, 2 H), 3.27 (br d, 1 H), 2.35−2.24 (m, 2 H), 2.11−1.97 (m, 1 H), 1.94−1.86 (m, 2 H), 1.44−1.34 (m, 1 H), 0.99 (s, 9 H); ^{13}C NMR (75 MHz, C_6D_6) δ 141.6, 138.1, 129.3, 128.4, 126.7, 122.1, 109.0, 65.4, 63.6, 49.2, 38.1, 32.7, 28.7, 27.5, 25.1; MS *m/z* (M^+) calcd 286.1933, obsd 286.1930. Anal. Calcd $C_{19}H_{26}O_2$: C, 79.68; H, 9.15. Found: C, 79.37; H, 9.21.

8-*tert*-Butyl-1,4-dioxaspiro[4.5]decan-6-one (34). A solution of **33** (5.00 g, 17.5 mmol) in a 1:1 mixture of methanol and CH_2Cl_2 (150 mL) containing 1% pyridine was ozonolyzed at −78 °C until a faint blue color appeared. The reaction mixture was purged with oxygen, treated with dimethyl sulfide (8 mL), allowed to warm to rt for 2 h, diluted with 1% $NaHCO_3$ solution, and extracted with CH_2Cl_2. The combined organic layers were dried and concentrated, and the residue was chromatographed on silica gel (elution with 8:1 hexanes/ethyl acetate) to give 3.37 g (91%) of **34** as a faintly yellow oil: IR (neat, cm^{-1}) 1731, 1479, 1367, 1103, 1063, 1029; ^1H NMR (300 MHz, C_6D_6) δ 3.99 (dt, J = 14.1, 7.3 Hz, 1 H), 3.63 (dt, J = 13.1, 7.3 Hz, 1 H), 3.47−3.36 (m, 2 H), 2.44−2.31 (m, 2 H), 1.99 (dt, J = 13.5, 3.2 Hz, 1 H), 1.74−1.63 (m, 1 H), 1.59−1.43 (m, 2 H), 1.15−1.04 (m, 1 H), 0.63 (s, 9 H); ^{13}C NMR (75 MHz, C_6D_6) δ 205.1, 106.6, 66.1, 64.2, 48.3, 41.4, 35.7, 32.3, 27.1, 24.1; MS *m/z* (M^+) calcd 212.1412, obsd 212.1388. Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 67.52; H, 9.51.

(6*R,8*R**)-8-*tert*-Butyl-6-hydroxy-1,4-dioxaspiro[4.5]decane-6-propanol (47) and (6*R**,8*S**)-8-*tert*-Butyl-6-hydroxy-1,4-dioxaspiro-[4.5]decane-6-propanol (48).** A magnetically stirred solution of **34** (1.21 g, 5.66 mmol) in dry THF (75 mL) was cooled to 0 °C and treated dropwise via syringe with a solution of the Normant reagent[28] in THF (14.15 mL, 6.79 mmol). After completion of the addition, the reaction mixture was stirred for 15 min at 0 °C, quenched with saturated NH_4Cl solution, and extracted with ether. The combined organic phases were washed with brine, dried, and evaporated. Chromatography of the residue on silica gel (elution with 90% ethyl acetate in hexanes) afforded 1.33 g (84%) of a 4.4:1 mixture of **47** and **48**. A second chromatography under more controlled conditions afforded pure samples of the two 1,4-diols.

47: colorless crystals, mp 62−66 °C; IR (film, cm^{-1}) 3406, 1449, 1366, 1184; ^1H NMR (300 MHz, C_6D_6) δ 3.78−3.42 (series of m, 6 H), 2.89 (br s, 1 H), 2.43 (br s, 1 H), 2.09−2.03 (m, 1 H), 1.99 (dt, J = 12.8, 3.6 Hz, 1 H), 1.92−1.73 (m, 2 H), 1.69−1.57 (m, 2 H), 1.54−1.44 (m, 1 H), 1.32 (t, J = 12.3 Hz, 1 H), 1.34−1.22 (m, 1 H), 1.04 (tt, J = 12.5, 3.0 Hz, 1 H), 0.83 (s, 9 H); ^{13}C NMR (75 MHz, C_6D_6) δ 111.6, 76.1, 65.9, 65.3, 63.3, 44.2, 36.4, 32.7, 32.2, 30.3, 27.6, 26.8, 24.5; MS *m/z* (M^+) calcd 272.1987, obsd 272.2000. Anal. Calcd for $C_{15}H_{28}O_4$: C, 66.14; H, 10.36. Found: C, 66.15; H, 10.33.

48: colorless crystals, mp 107 °C; IR (film, cm^{-1}) 3398, 1365, 1189, 1151, 1088; ^1H NMR (300 MHz, C_6D_6) δ 3.56−3.42 (m, 6 H), 2.13 (td, J = 13.0, 4.0 Hz, 1 H), 2.04 (dt, J = 13.2, 3.0 Hz, 1 H), 1.80−1.53 (m, 7 H), 1.45−1.30 (m, 1 H), 1.33 (t, J = 12.8 Hz, 1 H), 0.90 (s, 9 H); ^{13}C NMR (75 MHz, C_6D_6) δ 111.5, 75.5, 65.4, 65.1, 63.6, 41.4, 34.4, 32.2, 32.1, 31.3, 27.8, 26.6, 24.3; MS *m/z* (M^+) calcd 272.1987, obsd 272.2010. Anal. Calcd for $C_{15}H_{28}O_4$: C, 66.14; H, 10.36. Found: C, 66.11; H, 10.36.



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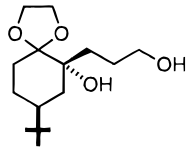

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(6*R,12*R**)-12-*tert*-Butyl-1,4,7-trioxadispiro[4.0.4.4]tetradecane (35).** To a magnetically stirred solution of **47** (2.07 g, 7.60 mmol) in dry CH_2Cl_2 (35 mL) was added trimethylamine (2.4 mL, 17.1 mmol), *p*-toluenesulfonyl chloride (1.39 g, 9.89 mmol), and DMAP (46 mg, 0.38 mmol). The reaction mixture was stirred overnight at 45 °C, cooled, diluted with ether, and washed with brine prior to drying and concentration. Purification of the residue by chromatography on silica gel (elution with 8:1 hexanes/ethyl acetate) afforded 1.54 g (79%) of **35** as a viscous, colorless oil: IR (film, cm^{-1}) 1514, 1468, 1442, 1394, 1366; ^1H NMR (300 MHz, $CDCl_3$) δ 4.21−4.12 (m, 1 H), 4.00−3.88 (m, 3 H), 3.87−3.75 (m, 2 H), 2.11−1.79 (m, 3 H), 1.72−1.45 (m, 6 H), 1.38−1.31 (m, 1 H), 1.14−1.02 (m, 1 H), 0.89 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) $\delta\delta$ 111.2, 87.2, 68.2, 65.9, 65.7, 45.7, 37.4, 34.4, 32.7, 32.1, 27.7, 26.7, 23.9; MS *m/z* (M^+) calcd 254.1882, obsd 254.1890. Anal. Calcd for $C_{15}H_{20}O_3$: C, 70.83; H, 10.30. Found: C, 70.75; H, 10.25.

(6*R,12*S**)-12-*tert*-Butyl-1,4,7-trioxadispiro[4.0.4.4]tetradecane (36).** Analogous cyclization of **48** (2.69 g, 9.87 mmol) furnished 1.73 g (69%) of **36** as a faintly yellow oil following chromatographic purification on silica gel (elution with 8:1 hexanes/ethyl acetate): IR (neat, cm^{-1}) 2951, 2871, 1478, 1435, 1366, 1186; ^1H NMR (300 MHz, C_6D_6) δ 3.98 (dd, J = 14.5, 7.6 Hz, 1 H), 3.81 (ddd, J = 15.0, 7.4, 4.8 Hz, 1 H), 3.60−3.49 (series of m, 4 H), 2.18−2.04 (m, 2 H), 1.82−1.56 (series of m, 7 H), 1.44−1.30 (m, 2 H), 0.87 (s, 9 H); ^{13}C NMR (75 MHz, C_6D_6) δ 111.6, 85.8, 68.9, 65.1, 64.5, 42.6, 38.4, 32.6, 32.0, 31.1, 27.8, 26.6, 24.4; MS *m/z* (M^+) calcd 254.1882, obsd 254.1883. Anal. Calcd for $C_{15}H_{26}O_3$: C, 70.83; H, 10.30. Found: C, 70.78; H, 10.35.

(5*R,9*R**)-9-*tert*-Butyl-1-oxaspiro[4.5]decan-6-one (10).** A magnetically stirred solution of **35** (1.54 g, 6.01 mmol) in acetone (15 mL) and water (15 mL) was treated with concentrated HCl (0.1 mL), refluxed for 12 h, quenched with a few drops of triethylamine, and extracted with ether. The combined organic phases were dried and concentrated to leave a residue that was chromatographed on silica gel (elution with 8:1 hexanes/ethyl acetate). There was isolated 1.11 g (88%) of **10** as a colorless solid: mp 65 °C; IR (film, cm^{-1}) 3014, 2694, 2870, 1718, 1216, 1074; ^1H NMR (300 MHz, C_6D_6) δ 4.08 (dd, J = 14.2, 7.1 Hz, 1 H), 3.81 (ddd, J = 13.9, 7.3, 2.2 Hz, 1 H), 2.24 (ddd, J = 14.8, 4.2, 2.6 Hz, 1 H), 1.93 (ddd, J = 14.7, 13.5, 6.1 Hz, 1 H), 1.78 (ddd, J = 12.9, 3.3, 3.3 Hz, 1 H), 1.68 (dd, J = 12.4, 12.4 Hz, 1 H), 1.63−1.42 (m, 4 H), 1.37−1.28 (m, 1 H), 1.12 (dddd, J = 12.2, 12.2, 3.4, 2.8 Hz,1 H), 1.02 (dddd, J = 12.4, 12.4, 4.3, 1.1 Hz, 1 H), 0.69 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.3, 87.7, 68.4, 45.7, 40.5, 38.8, 35.2, 32.2, 27.5, 27.4, 25.2; MS *m/z* (M^+) calcd 210.1620, obsd 210.1622. Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54. Found: C, 74.20; H, 10.53.

(5*R,9*S**)-9-*tert*-Butyl-1-oxaspiro[4.5]decan-6-one (11).** Analogous treatment of **36** (461 mg, 1.80 mmol) provided 274 mg (74%) of **11** as a clear oil following chromatographic purification: IR (neat, cm^{-1}) 1721, 1480, 1428, 1366, 1234, 1096, 1049; ^1H NMR (300 MHz, C_6D_6) δ 3.63−3.56 (m, 1 H), 3.48−3.41 (m, 1 H), 2.83 (ddd, J = 14.1, 13.3, 5.9 Hz, 1 H), 2.12 (ddd, J = 13.3, 8.5, 5.1 Hz, 1 H), 2.23 (ddd, J =

(49) We thank Mr. Anthony Lombardo for performing this experiment.

13.2, 6.7, 3.7 Hz, 1 H), 1.97−1.85 (m, 2 H), 1.74−1.63 (m, 2 H), 1.56−1.43 (m, 1 H), 1.19 (dd, J = 12.9, 12.9 Hz, 1 H), 1.13−0.97 (m, 2 H), 0.73 (s, 9 H); ^{13}C NMR (75 MHz, C_6D_6) δ 208.6, 86.4, 68.0, 43.0, 40.5, 38.0, 31.9, 30.9, 28.2, 27.6, 26.1; MS *m/z* (M^+) calcd 210.1620, obsd 210.1608. Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54. Found: C, 74.37; H, 10.64.

Hydroboration−Oxidation of 23. A cold (0 °C), nitrogen-blanketed, magnetically stirred solution of **23** (198 mg, 0.87 mmol) in dry THF (2.0 mL) was treated dropwise with the borane−dimethyl sulfide complex (0.48 mL of 2.0 M in THF, 0.963 mmol) via syringe, and the reaction was allowed to proceed at 0 °C for 2 h and at rt for 2 h. With external ice cooling, 3 M NaOH (1 mL) and 30% hydrogen peroxide (1 mL) were introduced and the product was extracted into ethyl acetate. The combined organic layers were washed with brine, dried, and concentrated to leave a residue which was chromatographically purified (silica gel, elution with 2:1 ethyl acetate/hexanes). There was isolated 101 mg (47%) of **25** as a fluffy white solid, mp 86 °C.

Hydroboration−Oxidation of 28. Analogous treatment of **28** (36 mg, 0.16 mmol) furnished 22 mg (57%) of **30** as a white solid, mp 114−115 °C.

Hydroboration−Oxidation of 37. Reaction of **37** (292 mg, 1.15 mmol) with the borane−dimethyl sulfide complex (0.634 mL of 2.0 M in THF, 1.27 mmol) at 0 °C in the predescribed manner (1 h 45 min) afforded 188 mg (60%) of **39**.

Hydroboration−Oxidation of 38. From 54 mg (0.21 mmol) of **38** and 0.234 mmol of the borane−dimethyl sulfide complex (0 → 20 °C overnight), there was isolated 41 mg (72%) of **40**.

Hydroboration−Oxidation of 41. From 114 mg (0.453 mmol) of **41** and 0.543 mmol of the borane−dimethyl sulfide complex (0 → 20 °C over 2 h), there was obtained 92 mg (75%) of **43**.

Hydroboration−Oxidation of 42. Reaction of **42** (303 mg, 1.20 mmol) in the predescribed manner (0 °C for 5 h) led to the isolation of **44** (292 mg, 90%).

(5*R,6*R**,8*R**)-8-*tert*-Butyl-6-methoxy-1-oxaspiro[4.5]decane (27).** To a nitrogen-blanketed, magnetically stirred solution of **25** (900 mg, 0.368 mmol) in dry CH_2Cl_2 (2 mL) were added 4-(dimethylamino)-pyridine (2 mg), triethylamine (0.154 mL, 1.11 mmol), and *p*-toluenesulfonyl chloride (105 mg, 0.552 mmol). After 36 h, the reaction mixture was diluted with water and 10% HCl (1.5 mL) and extracted with ether. The combined organic phases were washed with 3% NaOH solution (2 × 1.5 mL) and brine, dried, and concentrated. Chromatography of the residue on silica gel (elution with 6:1 hexanes/ethyl acetate) provided 64 mg (77%) of **27** as a colorless oil: IR (neat, cm^{-1}) 1456, 1366, 1138, 1100, 1054; ^{1}H NMR (300 MHz, C_6D_6) δ 3.98 (dd, J = 14.6,7.0 Hz, 1 H), 3.76 (ddd, J = 7.4, 7.4, 5.5 Hz, 1 H), 3.18 (s, 3 H), 2.78 (dd, J = 11.4, 4.2 Hz, 1 H), 2.11 (ddd, J = 11.7, 8.6, 6.8 Hz, 1 H), 2.00−1.90 (m, 1 H), 1.89−1.82 (m, 1 H), 1.72−1.51 (m, 4 H), 1.48−1.41 (m, 1 H), 1.32 (ddd, J = 11.7, 8.7, 5.7 Hz, 1 H), 1.17−1.07 (m, 1 H), 0.95 (ddd, J = 12.2, 12.2, 3.4 Hz, 1 H), 0.87 (s, 9 H); ^{13}C NMR (75 MHz, C_6D_6) δ 85.8, 82.9, 68.9, 56.6, 47.1, 37.8, 34.6, 32.6, 27.6, 26.8, 23.5; MS *m/z* (M^+) calcd 226.1933, obsd 226.1952. Anal. Calcd for $C_{14}H_{26}O_2$: C, 74.28; H, 11.58. Found: C, 74.12; H, 11.54.

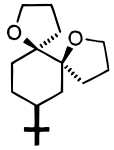
(5*R,6*S**,12*R**)-12-*tert*-Butyl-1,7-dioxadispiro[4.0.4.4]tetradecane (45) and (5*R**,6*R**,12*S**)-12-*tert*-Butyl-1,7-dioxadispiro[4.0.4.4]tetradecane (46).** Comparable cyclization of a 7.6:1 mixture of **43** and **44** (53 mg, 0.20 mmol) during 24 h followed by gradient elution chromatography on silica gel (16:1 → 5:1 hexanes/ethyl acetate) gave 34 mg (68%) of **45** and 6 mg (12%) of **46**.

45: colorless oil; IR (neat, cm^{-1}) 1469, 1392, 1365, 1058; ^{1}H NMR (300 MHz, C_6D_6) δ 3.73−3.60 (m, 4 H), 1.91−1.77 (m, 3 H), 1.71−1.36 (series of m, 12 H), 0.92 (s, 9 H); ^{13}C NMR (75 MHz, C_6D_6) δ 86.4, 85.1, 67.6 (2 C), 43.0, 35.8, 35.0, 33.7, 33.1, 32.1, 27.8, 26.5, 26.4, 23.0; MS *m/z* (M^+) calcd 252.2089, obsd 252.2095. Anal. Calcd for $C_{16}H_{28}O_2$: C, 76.14; H, 11.18. Found: C, 76.26; H, 11.22.

46: colorless solid, mp 53−54 °C; ^{1}H NMR (300 MHz, C_6D_6) δ 4.03 (ddd, J = 8.7, 7.8, 6.4 Hz, 1 H), 3.87 (td, J = 7.4, 3.7 Hz, 1 H), 3.77−3.61 (m, 2 H), 2.31 (tdd, J = 13.6, 4.1, 1.0 Hz, 1 H), 2.00−1.90 (m, 2 H), 1.84 (tt, J = 12.5, 3.6 Hz, 1 H), 1.78−1.43 (series of m, 7 H), 1.28−1.17 (m, 2 H), 1.00 (t, J = 12.9 Hz, 1 H); ^{13}C NMR (75 MHz, C_6D_6) δ 87.5, 86.7, 68.8, 67.7, 42.1, 38.7, 33.4, 32.7, 32.2, 31.9, 27.7, 26.6, 26.5, 25.1; MS *m/z* (M^+) calcd 252.2089, obsd 252.2107. Anal. Calcd for $C_{16}H_{28}O_2$: C, 76.14; H, 11.18. Found: C, 76.16; H, 11.17.

(5*R,6*R**,12*R**)-12-*tert*-Butyl-1,7-dioxadispiro[4.0.4.4]tetradecane (49).** Analogous processing of **39** (100 mg, 0.370 mmol) during 36 h afforded 75 mg (80%) of **49** as a colorless oil: IR (neat, cm^{-1}) 1440, 1365, 1060; ^{1}H NMR (300 MHz, C_6D_6) δ 4.05 (dd, J = 14.9, 7.8 Hz, 1 H), 3.89 (td, J = 7.4, 3.6 Hz, 1 H), 3.83−3.68 (m, 2 H), 2.10 (t, J = 12.5 Hz, 1 H), 2.03−1.93 (m, 1 H), 1.82−1.56 (m, 8 H), 1.50−1.14 (series of m, 4 H), 1.07 (tt, J = 12.6, 3.4 Hz, 1 H), 0.94 (s, 9 H); ^{13}C NMR (75 MHz, C_6D_6) δ 88.2, 85.7, 68.4, 67.5, 46.4, 37.2, 34.9, 33.2, 32.4, 32.0, 27.9, 26.8, 26.7, 22.6; MS *m/z* (M^+) calcd 252.2089, obsd 252.2092. Anal. Calcd for $C_{16}H_{28}O_2$: C, 76.14; H, 11.18. Found: C, 75.82; H, 11.07.

(5*R,6*S**,12*S**)-12-*tert*-Butyl-1,7-dioxadispiro[4.0.4.4]tetradecane (50).** Parallel cyclization of **40** (31 mg, 0.12 mmol) delivered 21 mg (73%) of **50** as a colorless oil: IR (neat, cm^{-1}) 1448, 1394, 1366, 1080, 1034; ^{1}H NMR (300 MHz, C_6D_6) δ 3.81−3.70 (m, 4 H), 2.45−2.34 (m, 2 H), 2.01−1.83 (m, 2 H), 1.74−1.37 (series of m, 8 H), 1.34 (t, J = 12.6 Hz, 1 H), 1.06−0.83 (m, 2 H), 0.80 (s, 9 H); ^{13}C NMR (75 MHz, C_6D_6) δ 87.9, 87.6, 68.1, 67.9, 45.9, 39.1, 37.2, 32.1, 32.0, 31.0, 27.7, 27.6, 27.4, 25.1; MS *m/z* (M^+) calcd 252.2089, obsd 252.2089. Anal. Calcd for $C_{16}H_{28}O_2$: C, 76.14; H, 11.18. Found: C, 76.07; H, 11.13.



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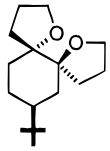

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Competition Experiments. A mixture of **10** (105 mg, 0.50 mmol), **11** (105 mg, 0.50 mmol), allyl bromide (91 mg, 0.75 mmol), indium powder (63 mg, 0.55 mmol), and water (5.5 mL) was stirred at 25 °C in a stoppered flask for 48 h. Following the addition of 10% HCl, the reaction mixture was extracted with ether, and the combined organic phases were washed with brine, dried, and evaporated. The resulting oil was subjected to chromatography on silica gel (gradient elution with 16:1 → 4:1 hexanes/ethyl acetate). There were isolated 31 mg of **10** and 77 mg of **11**, representing essentially quantitative recovery (viz. 51%) of the unreacted ketones.

In entry 49, the two starting ketones proved difficult to separate cleanly. However, the pairs of allylated epimers formed from each ketone possess distinctively different R_f values and analysis was therefore accomplished in this manner. For example, when 0.50 mmol quantities of **6** and **7** were treated with allyl bromide and indium in water as described above and the crude product mixture was subjected to silica gel chromatography, there were isolated 62 mg of **23/24** and 40 mg of **12/13**. The combined total represents an essential quantitative recovery of possible product alcohols.

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