Evaluation of Chelation Effects Operative during Diastereoselective Addition of the Allylindium Reagent to 2- and 3-Hydroxycyclohexanones in Aqueous, Organic, and Mixed Solvent Systems

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The unprotected 2- and 3-hydroxycyclohexanones **1**−**8** were prepared by methods that skirted as much as possible their proclivity for α-ketol rearrangement (where the possibility for such isomerization exists). The diastereofacial selectivity of their reaction with the allylindium reagent in water, 50% aqueous THF, and anhydrous THF is described. The neighboring α-hydroxyl substituent is construed to be capable of engaging in chelation, thereby controlling the stereochemical outcome of the coupling process. When the hydroxyl substituent is oriented in the equatorial plane, kinetic acceleration accompanies exclusive entry of the allyl group from the equatorial direction. Steric congestion in the vicinity of the binding hydroxyl and ketonic centers is well tolerated. Alternative projection of the OH group into the more crowded axial region may not curtail chelation. For coordination to occur, however, a twist-boat conformation must initially be adopted. While the evidence suggests that this may indeed occur in water, the necessity of crossing the added energy barrier precludes the attainment of rates that are competitive with those exhibited by the equatorial epimers (competition experiments). Placement of the hydroxyl group at C-3 provides no evident opportunity for chelation control. However, excellent stereoselectivity is seen upon axial orientation of the 3-OH group. This phenomenon is attributed to steric and/or electronic effects alone or in combination.

The causative factors underlying the diastereofacial selectivity of 1,2-additions to carbonyl compounds continue to be actively probed because of the central position this process holds in asymmetric organic synthesis.[1] This is particularly true for allyl organometallics of different type, which are now recognized to enter into nucleophilic attack via one or another structurally well-defined cyclic transition state.[2,3] In recent years, allylindium reagents have been developed for use in aqueous media,[4] alongside corresponding investigations aimed at elucidating the extent to which π-facial stereocontrol might be achieved in water.[5] Where α- and β-hydroxy aldehydes are concerned, the coupling reactions take place rapidly, chelated intermediates are involved, and significantly heightened levels of *syn*-1,2-diols and *anti*-1,3-diols are produced.[6−8] The allyl group continues to be introduced anti to an adjacent ether oxygen, provided that minimal substitution is involved (e.g., OCH_3, OMOM,[8a,b,9] or spirotetrahydrofuranyl[9,10]). More sterically bulky polar groups (e.g., OBn and OTBS) direct C−C bond formation via alternative Felkin−Ahn transition states.[8,11] Dimethylamino[12] and carboxyl substituents[13] that neighbor the carboxaldehyde functionality likewise exhibit a useful capacity for precoordination to In(III) under aqueous conditions.

Intramolecular chelation can also materialize within an allylindium reagent when a second polar functional group such as hydroxyl and carbomethoxy is present.[14] Although this class of reagents has shown considerable promise for accomplishing effective 1,4-asymmetric induction,[15−17] questions persist concerning the precise manner in which unprotected polar groups *resident within the organometallic species* dictate the observed π-facial discrimination.

(1) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew Chem., Int. Ed. Engl.* **1985**, *24*, 1.
(2) Roush, W. R. In *Comprehensive Organic Synthesis*; Heathcock, C., Ed.; Pergamon Press: Oxford, 1991; Vol. 2, p 1.
(3) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207.
(4) (a) Li, C. J. *Chem. Rev.* **1993**, *93*, 2023. (b) Li, C. J. *Tetrahedron* **1996**, *52*, 5643. (b) Li, C.-J.; Chan, T.-H. *Organic Reactions in Aqueous Media*; John Wiley and Sons., Inc.: New York, 1997.
(5) Paquette, L. A. In *Green Chemistry: Frontiers in Benign Chemical Synthesis and Processing*; Anastas, P., Williamson, T., Eds.; Oxford University Press: Oxford, in press.
(6) Li, C. J.; Chan, T. H. *Tetrahedron Lett.* **1991**, *32*, 7017.
(7) (a) Kim, E.; Gordon, D. M.; Schmid, W.; Whitesides, G. M. *J. Org. Chem.* **1993**, *58*, 5500. (b) Gao, J.; Härter, R.; Gordon, D. M.; Whitesides, G. M. *J. Org. Chem.* **1994**, *59*, 3714.
(8) (a) Paquette, L. A. Mitzel, T. M. *Tetrahedron Lett.* **1995**, *36*, 6863. (b) Paquette, L. A.; Mitzel, T. M. *J. Am. Chem. Soc.* **1996**, *118*, 1931. (c) Paquette, L. A.; Mitzel, T. M. *J. Org. Chem.* **1996**, *61*, 8799.
(9) Paquette, L. A.; Lobben, P. C. *J. Am. Chem. Soc.* **1996**, *118*, 1917.
(10) Paquette, L. A.; Stepanian, M.; Mallavadhani, U. V.; Cutarelli, T. D.; Lowinger, T. B.; Klemeyer, H. J. *J. Org. Chem.* **1996**, *61*, 7492.
(11) Isaac, M. B.; Paquette, L. A. *J. Org. Chem.* **1997**, *62*, 5333.
(12) Paquette, L. A.; Mitzel, T. M.; Isaac, M. B.; Crasto, C. F.; Schomer, W. W. *J. Org. Chem.* **1997**, *62*, 4293.
(13) Bernardelli, P.; Paquette, L. A. *J. Org. Chem.* **1997**, *62*, 8284.
(14) (a) Paquette, L. A.; Isaac, M. B. *Heterocycles* **1998**, *47*, 107. (b) Paquette, L. A.; Rothhaar, R. R.; Isaac, M. B.; Rogers, L. M.; Rogers, R. D. *J. Org. Chem.* **1998**, *63*, in press.
(15) (a) Maguire, R. J.; Mulzer, J.; Bats, J. W. *Tetrahedron Lett.* **1996**, *37*, 5487. (b) Maguire, R. J.; Mulzer, J.; Bats, J. W. *J. Org. Chem.* **1996**, *61*, 6936.
(16) Paquette, L. A.; Bennett, G. D.; Chhatriwalla, A.; Isaac, M. B. *J. Org. Chem.* **1997**, *62*, 3370.
(17) Paquette, L. A.; Bennett, G. D.; Isaac, M. B.; Chhatriwalla, A. *J. Org. Chem.*, **1998**, *63*, 1836.

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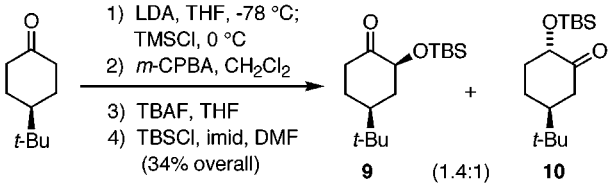
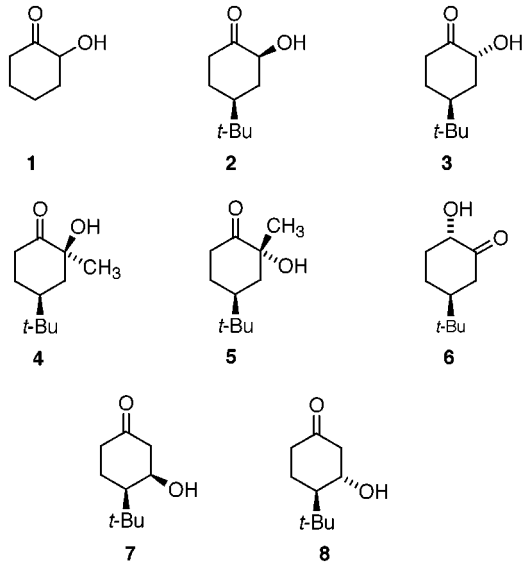
Scheme 1



The insensitivity of allylindium reagents to moisture obviously dismisses the need for protecting groups for either reactant. For this reason, it is of special importance that the mechanistic role of the "naked" polar functionality be clearly appreciated. Such studies have not heretofore been possible because of the preexisting requirement that the great majority of organometallic reactions be performed on protected substrates in anhydrous solvents. The systems selected for the present allylindation study include 2-hydroxycyclohexanone (**1**), the four conformationally restricted 4-*tert*-butyl homologues **2**−**5**, the transposed ketone **6**, and the stereoisomeric 3-hydroxy derivatives **7** and **8**. This group of

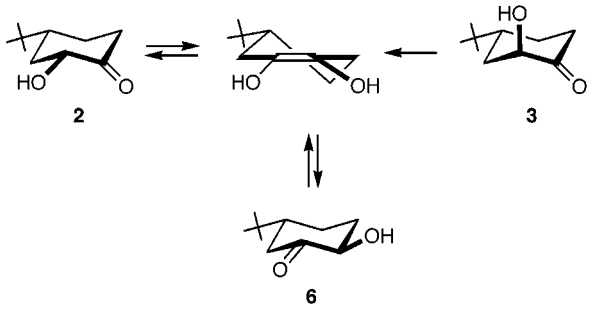


substrates fulfills certain relevant requirements: (a) positioning the potential anchoring hydroxyl both α and *β* to the carbonyl, (b) orienting the OH substituent both axially and equatorially in fixed chair conformations, and (c) modulating the level of steric crowding in the immediate vicinity of the hydroxyl (and carbonyl) as in **4** and **5** and its placement relative to the *tert*-butyl group (as in **6**). Consequently, **1**−**8** expand upon the acyclic systems and nicely complement the α-alkoxycyclohexanones probed so successfully earlier.[8,9]

Results

Preparation of the Hydroxycyclohexanones. Commercially available **1** was obtained as a dimer which equilibrates with the monomer when dissolved in water under ambient conditions. Despite existing reports detailing the synthesis of **2** and **3**,[18,19] difficulties were encountered on attempted Rubottom oxidation[20] of 4-*tert*-butylcyclohexanone (Scheme 1). When the hydroxy ketone mixture generated in this manner was found to decompose/polymerize irreversibly on standing for several hours at room temperature or on overnight storage at −10 °C, recourse was made to direct silylation. This protection maneuver led to the discovery that the spectral properties of **9** and **10** were found not to be suitably matched. Consequently, their individual structures were unambiguously determined by ^{1}H/^{1}H COSY 90 NMR experiments. Defined by these studies was the existence of a single methylene spacer between the OTBS and *t*-Bu substituents in **9**, but *two* intervening CH_2 groups in **10**. The evidence was unmistakable that the initially generated 2-hydroxy ketones **2** and **3** had undergone equilibration either during their formation or their silylation. This observation conforms with earlier claims that "**3** could not be obtained free of **2**" [19] and recent studies by Parker et al. involving 2,4-dihydroxycyclohexanone systems.[21] Attention is called to the equatorial preference of this equilibration process (Scheme 2), which contrasts with the axial preference exhibited by 2-halocyclohexanones.[22]

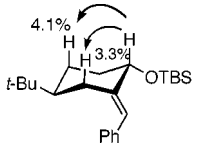
Scheme 2



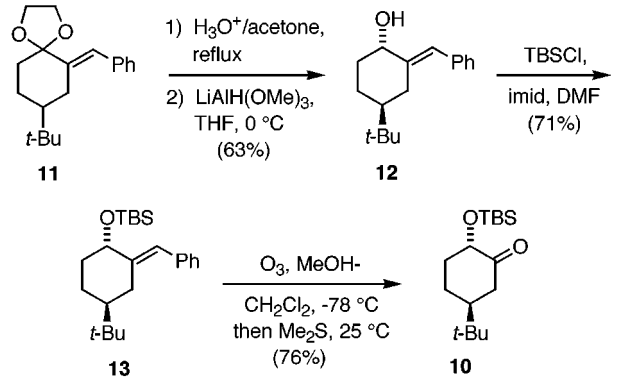
The deprotection of **9** and **10** with fluoride ion was expectedly met with modest levels of α-ketol rearrangement. The extent to which this occurred (∼10%) precluded the acquisition of useful amounts of **6** by this route. Therefore, this isomer was independently prepared from the known acetal **11**[9] by hydrolysis and stereoselective (axial attack)[23] 1,2-reduction to give **12** (Scheme 3). Following conversion to **13**, the benzylidene double bond was cleaved ozonolytically to deliver isomerically pure **10** in 76% yield. As with **9** and the other protected hydroxy ketones described here, **10** was stable to long-term storage at or below room temperature.

Access to the rather elusive *trans*-4-*tert*-butyl-2-hydroxycyclohexanone (**3**) proved to be more circuitous. The observations summarized in Scheme 4 revealed to us that a *nonhydrolytic* deprotection strategy had to be implemented. Reduction of keto acetal **14**[9] with Dibal-H in hexanes at −78 °C proceeded very efficiently to give a

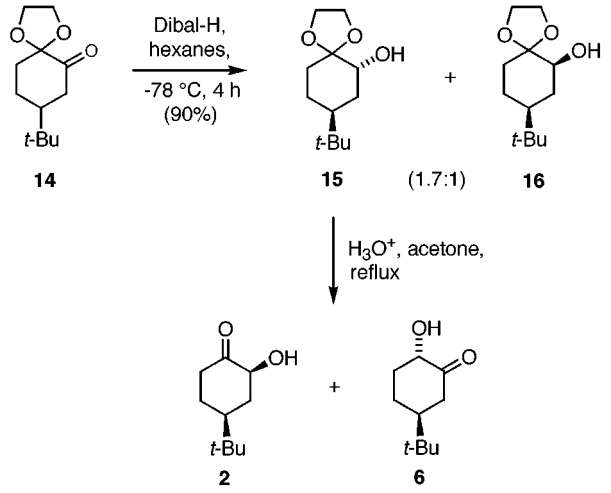
(18) Vedejs, E. Dent, W. H., III *J. Am. Chem. Soc.* **1989**, *111*, 6861.
(19) Cain, C. M.; Cousins, R. P. C.; Combarides, G.; Simpkins, N. S. *Tetrahedron* **1990**, *46*, 523.
(20) Rubottom, G. M.; Gruber, J. M. *J. Org. Chem.* **1978**, *43*, 1599.
(21) (a) Parker, K. A.; Dermatakis, A. *J. Org. Chem.* **1997**, *62*, 6692. (b) Parker, K. A.; Kim, H.-J. *J. Org. Chem.* **1992**, *57*, 752.
(22) (a) Lambert, J. B. In *The Conformation Analysis of Cyclohexenes, Cyclohexadienes, and Related Hydroaromatic Compounds*; Rabideau, P., Ed.; VCH: Weinheim, 1989; Chapter 2. (b) Denmark, S. E.; Dappen, M. S.; Sear, N. L.; Jacobs, R. T. *J. Am. Chem. Soc.* **1990**, *112*, 3466.
(23) The stereochemical course of this reduction was established on the strength of NOE experiments performed on **13**. The key interactions are illustrated here:



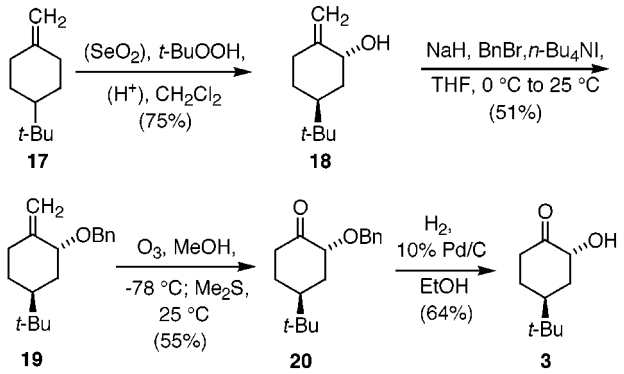
Scheme 3



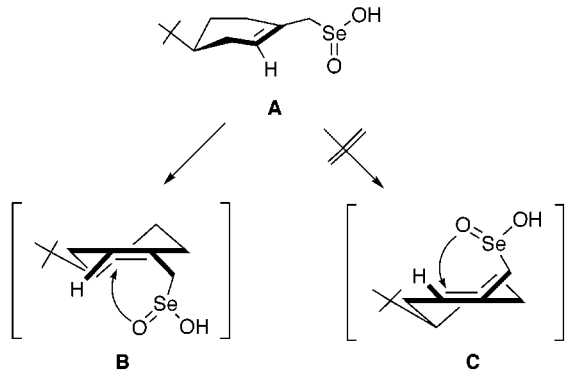
Scheme 4



Scheme 5



chairlike character develop in the transition state. Sequential ozonolysis and hydrogenolysis of **19** afforded **3**. Our normal practice was to transform **20** into **3** on an as-needed basis.



favorable 1.7:1 ratio of **15** and **16**, which epimers were readily amenable to chromatographic separation. However, all attempts to remove the acetal group in **15** without being disruptive of stereochemistry (including conditions specifically recommended for this purpose[24−26]) returned only **2** and **6** (in varying proportions) without any evidence for **3**.[27]

These complications were bypassed by Wittig olefination[28] of 4-*tert*-butylcyclohexanone and submission of **17** to allylic oxidation with *tert*-butyl hydroperoxide in the presence of catalytic levels of selenium dioxide[29] (Scheme 5). The high diastereoselectivity accompanying introduction of the hydroxyl group in **18**[29] (>97:3 by ^{1}H NMR integration) is attributed to the strong kinetic preference of ene product **A** for [2,3]-sigmatropic rearrangement[30] via **B** rather than **C**. Only in the first instance does

2-Hydroxycyclohexanones **4** and **5** were prepared by a modification of the procedure originally devised by Vedejs,[31a] and by Aubé and Wang.[31b] Monomethylation of the anion resulting from deprotonation of the dimethylhydrazone of 4-*tert*-butylcyclohexanone, with subsequent periodate cleavage,[32] provided the pair of diastereomeric ketones **21** (Scheme 6). Epoxidation of the thermodynamic silyl enol ether, generated by the Krafft−Holton protocol,[33] and ensuing desilylation afforded **4** and **5** in a 2.8:1 ratio. Pure samples were readily acquired through combined application of chromatographic and crystallization methods.

Last, the 3-hydroxycyclohexanones **7** and **8** were synthesized according to the directives given by Evans, Chapman, and Carreira,[34,35] except that the final ketal

(24) Carreño, M. C.; Ruano, J. L. G.; Garrido, M.; Ruiz, M. P.; Solladié, G. *Tetrahedron Lett.* **1990**, *31*, 6653.

(25) Lipshutz, B. H.; Pollart, D.; Monforte, J.; Kotsuki, H. *Tetrahedron Lett.* **1985**, *26*, 705.

(26) (a) Still, I. W.; Shi, Y. *Tetrahedron Lett.* **1987**, *28*, 2489. (b) Kim, K. S.; Song, Y. H.; Lee, B. H.; Hahn, C. S. *J. Org. Chem.* **1986**, *51*, 404.

(27) The readiness with which axial α-alkyl groups experience epimerization has been previously documented: Cross, B.; Whitham, G. H. *J. Chem. Soc.* **1961**, 1650.

(28) (a) Wittig, G.; Schoellkopf, U. *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol. V, p 751. (b) Greenwald, G.; Chaykovsky, M.; Corey, E. J. *J. Org. Chem.* **1963**, *28*, 1128.

(29) The axial disposition of the hydroxyl was clearly evident on the basis of the appearance of the H-2 methine proton as a doublet of doublets (J = 2.6, 2.6 Hz) at δ 3.99. The two small coupling constants arise from neighboring equatorial−equatorial and equatorial−axial spin interactions.

(30) Sharpless, K. B.; Lauer, R. F. *J. Am. Chem. Soc.* **1972**, *94*, 7154.

(31) (a) Vedejs, E.; Dent, W. H., III.; Kendall, J. T.; Oliver, P. A. *J. Am. Chem. Soc.* **1996**, *118*, 3556. (b) Wang, Y. Ph.D. Thesis, University of Kansas, 1993. We thank Professor J. Aubé for making part of this thesis available to us.

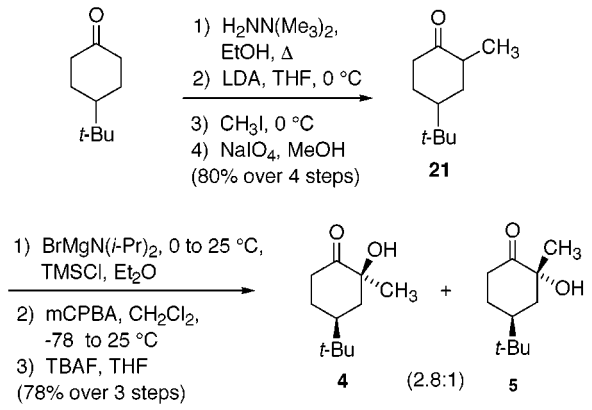
(32) Corey, E. J.; Enders, D. *Tetrahedron Lett.* **1976**, 3.

(33) Krafft, M. E.; Holton, R. A. *Tetrahedron Lett.* **1983**, *24*, 1345.

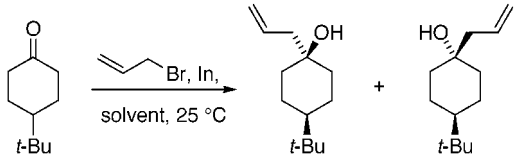
(34) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560.

(35) In view of certain discrepancies noted between our ^{1}H and ^{13}C NMR data for **7** and **8** and those reported in ref 34 (note the identity of the carbon shifts); our data for these two compounds are given here in full. For **7**: mp 118−119 °C.; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.61 (br s, 1 H), 2.55−2.38 (m, 4 H), 2.37−2.24 (m, 1 H), 2.07 (dddd, J = 12.8, 12.8, 12.8, 4.6 Hz, 1 H), 1.97−1.87 (m, 1 H), 1.91 (br s, 1 H), 1.53 (ddd, J = 12.5, 3.4, 1.5 Hz, 1 H), 1.01 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 211.8, 70.2, 50.9, 50.0, 41.5, 32.6, 28.8, 21.4. For **8**: mp 67.5−68.5 °C.; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.15 (dd, J = 8.8, 3.9 Hz, 1 H), 2.54 (dd, J = 15.4, 4.0 Hz, 1 H), 2.44 (dd, J = 15.5, 5.0 Hz, 1 H), 2.38−2.25 (m, 2 H), 1.55−1.40 (m, 2 H), 0.98 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 211.9, 68.6, 52.3, 47.8, 38.5, 32.8, 27.7, 21.6.

Scheme 6



Scheme 7

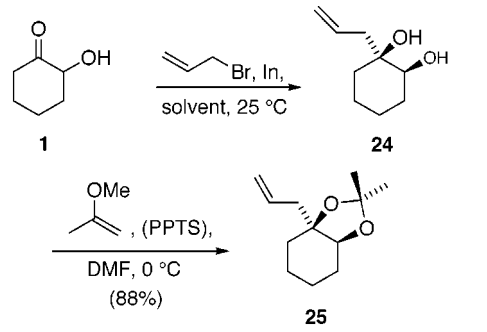


entry	solvent	time, h	**22/23**	yield, %
1	H_2O	3	4.6 : 1	75
2	THF-H_2O (1:1)	4	5.2 : 1	79
3	THF	see text	10.2 : 1	73

hydrolysis was accomplished with pyridinium *p*-toluenesulfonate in refluxing aqueous acetone.

Comparative Behavior of 4-*tert*-Butylcyclohexanone and 1−3. To provide useful calibration, 4-*tert*-butylcyclohexanone was initially treated with allyl bromide and powdered indium metal in three different media (Scheme 7). The strong equatorial bias provided by this tertiary alkyl substituent has the utilitarian role of strongly biasing conformational population while serving as a stereochemical marker. Irrespective of whether the reaction medium was pure water, dry THF, or a 1:1 mixture thereof, alcohol **22** was found to predominate. The preferred equatorial approach of the allylindium reagent conforms to the stereoselectivity previously noted for other allylmetal reagents.[3,36] The preparation of **22** was greatest in THF, a finding suggestive of the possibility that solvation in water has the effect of facilitating axial attack to some degree. Another notable feature is the reaction time in THF. When commercial indium powder was utilized in entry 3 as it was in the aqueous experiments, consumption of the ketone was complete only after 48 h. However, when the indium was produced by the electrolysis of $InCl_3$ with platinum electrodes,[37] the requisite reaction time was dramatically reduced to 4 h. Since comparable rate enhancements have previously been reported for zinc produced in a similar

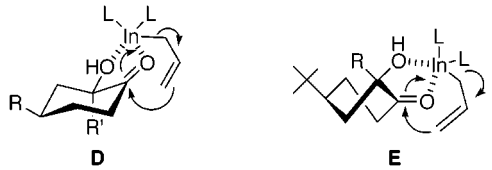
Scheme 8



entry	solvent	time, h	chelate/ non-chelate	yield, %
4	H_2O	1	>97 : 3	54
5	THF-H_2O (1:1)	1	>97 : 3	63
6	THF	48	>97 : 3	51

manner,[38] studies involving this activated form of indium were not pursued further at this time.

Comparable coupling of 2-hydroxycyclohexanone (**1**) to allyl bromide in the presence of indium afforded exclusively diastereomer **24** irrespective of the reaction conditions (Scheme 8, entries 4−6). The diastereoselectivity was determined by ^1H NMR integration of unpurified reaction mixtures.[39] The considerably more extended reaction time required for the allylation performed in THF constitutes a trend that was observed throughout this study. The high diastereoselectivity exhibited by **1** warrants direct comparison with 2-methoxycyclohexanone for which a maximum 14:1 kinetic preference for attack anti to the alkoxy substituent has been reported.[9] These findings conform to a mechanistic model in which the indium atom coordinates simultaneously to the ketonic carbonyl and the adjacent oxygenated center as depicted in **D** (R = R′ = H). Chelation in this fashion simultaneously activates the ketone toward nucleophilic attack, locks the cyclohexanone into a specific chair conformation (if this feature is not already incorporated into the substrate), and sets the stage for equatorial delivery of the allyl unit. The improved chelating ability of OH relative to OCH_3 can be traced to improved steric accessibility by the metal atom.[8]



Full stereochemical assignment to **24** was made possible following conversion to acetonide **25**. The added

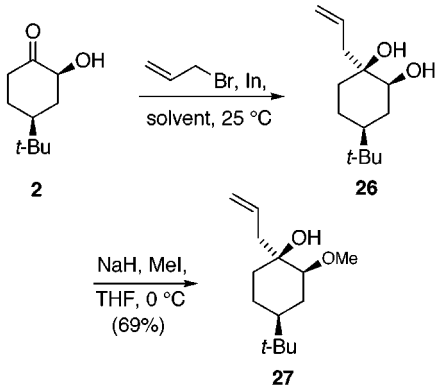
(36) (a) Aluminum, magnesium, lithium, potassium, and sodium: Gaudemar, M. *Tetrahedron*, **1976**, *32*, 1689. (b) Chromium: Hiyama, T.; Okude, Y.; Kimura, K.; Nozaki, H. *Bull. Chem Soc. Jpn.* **1982**, *55*, 561. (c) Tin: Naruta, Y.; Ushida, S.; Maruyama, K. *Chem. Lett.* **1979**, 919. (d) Indium: Reetz, M. T.; Haning, H. *J. Organomet. Chem.* **1997**, *541*, 117. (e) Indium: Araki, S.; Ito, H.; Butsugan, Y. *J. Org. Chem.* **1988**, *53*, 1831. (f) Zinc: Wilson, S. R.; Guazzaroni, M. E. *J. Org. Chem.* **1989**, *54*, 3087.

(37) (a) Tokuda, M.; Satoh, S.; Katoh, Y.; Suginome, H. In *Electroorganic Synthesis*; Little, R. D., Weinberg, N. L., Eds.; Dekker: New York, 1991; p 83. (b) Tanaka, H.; Yamashita, S.; Hamatani, T.; Nakahara, T.; Torii, S. In *Recent Advances in Electroorganic Synthesis*; Torii, S., Ed.; Elsevier: New York, 1987; p 307. (c) Habeeb, J. J.; Tuck, D. G. *J. Organomet. Chem.* **1977**, *134*, 363. (d) Habeeb, J. J.; Said, F. F.; Tuck, D. G. *J. Organomet. Chem.* **1980**, *190*, 325.

(38) Tokuda, M.; Kurono, N.; Mimura, N. *Chem. Lett.* **1996**, 1091.

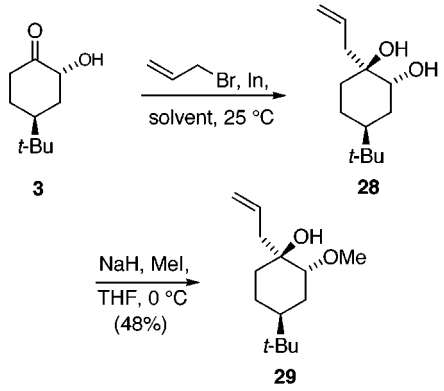
(39) A diastereoselectivity of >97:3 represents the perceived detection limit of the instrument.

Scheme 9



entry	solvent	time, h	chelate/ non-chelate	yield, %
7	H_2O	1.5	>97:3	80
8	THF-H_2O (1:1)	1.5	>97:3	76
9	THF	25	>97:3	86

Scheme 10



entry	solvent	time, h	chelate/ non-chelate	yield, %
10	H_2O	1.5	>97:3	53
11	THF-H_2O (1:1)	1.5	>97:3	48
12	THF	no reaction (5 days)	----	----

structural rigidification accompanying this transformation allowed for the successful implementation of NOE difference experiments. Particularly revealing in this instance was the enhancement of the signals due to allyl protons H-7, H-7′, and H-8 upon irradiation of axial proton H-2 (see Experimental Section).

The fact that the 2-hydroxy substituent in **2** is equatorially disposed suggested that transition state **D** (R = *t*-Bu, R′ = H) should again be operational. Indeed, the allylindation of **2** delivered only **26** in each instance (entries 7−9, Scheme 9). Comparable efficiency was realized throughout, although the elapsed time necessary to attain this level of conversion was again much slower in THF. The identification of **26** was established by chemical means. Its selective O-methylation with sodium hydride and methyl iodide at 0 °C gave rise to the known ether alcohol **27**.[9]

With attention now focused on **3**, its remarkable propensity for facile tautomeric equilibration was manifested again. During the course of reaction with the allylindium reagent, 23% of the product mixture generated in water arose from attack on **2** and **6**. In 50% aqueous THF, the extent of these side reactions dropped only modestly to the 18% level. Contrastingly, allylations performed in pure THF were free of this complication. The yields provided in Scheme 10 have been adjusted to reflect the efficiency with which **3** itself is engaged in allylindation. The stereochemical course of this process is such that only **28** is produced (entries 10−12). The trans disposition of the hydroxyl group in **28** was confirmed by conversion into the known **29**.[9] The formation of a lone diastereomeric product further attests to the powerful chelating ability of hydroxy substituents in aqueous media. In the present circumstances, complexation of the indium reagent to **3** is thought to foster adoption of a twist-boat conformation as in **E** (R = H) in order to maximize the level of the two O- - -In interactions. This structural arrangement allows for ready delivery of the allyl unit from the pseudoequatorial direction. For comparison, the methyl ether of **3** exhibits a chelate/nonchelate ratio of 9.6:1.[9]

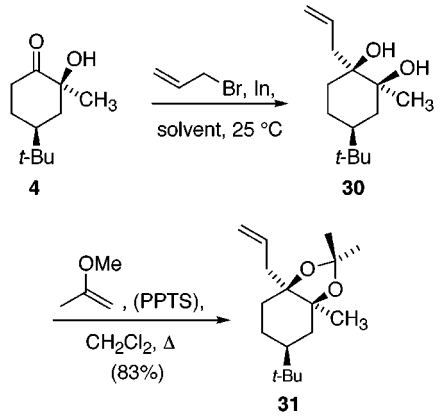
Evaluation of the Stereoisomeric Tertiary α-Ketols 4 and 5. An earlier investigation has demonstrated that incorporation of an ether oxygen into a neighboring spirotetrahydrofuran ring can be met with a significant dropoff in chelation to an allylindium reagent.[9] This phenomenon has been attributed to an enhancement in local steric shielding, a structural feature toward which this organometallic reagent is quite responsive. As a logical extension of possible steric variants, we became particularly interested in the rather different functional group assembly resident in **4** and **5**. Both cyclohexanones carry an unprotected α-alcohol, although the tertiary status of these OH groups is guaranteed to reduce their accessibility to some degree. Our concern was whether complete chelation control would continue to be operational, particularly in water. Clearly, **4** and **5** are not subject to potential complications stemming from tautomeric equilibration.

The experiments undertaken with **4** uniformly gave rise to **30** as the only detectable product (Scheme 11). In contrast to the earlier examples, no reaction was observed in THF when the reaction components were admixed in the usual way. However, preformation of the allylindium reagent did lead to rapid and efficient coupling to deliver **30**. The dramatic reduction in reaction time seen in entry 16 is noteworthy as it likely merits consideration when preparative-scale experiments are contemplated.

The equatorial orientation of the allyl group in **30** was established by way of NOE difference experiments performed on both the free diol and its acetonide **31** (see Experimental Section). In the latter instance, the enhanced rigidification provided by the fused dioxolane ring was met with considerable enhancement of the NOE response in every instance.

A reversal in the relative configuration of the carbinol carbon as in **5** provided complementary results demonstrating the superiority of the aqueous indium protocol for controlling the stereoselectivity of C-allylation (Scheme 12). In H_2O or aqueous THF, the reaction is complete in 2−2.5 h and only diol **32** is formed. The couplings in THF afforded approximately 2:1 mixtures of **32** and **33**, with the product distribution proving to be relatively insensi-

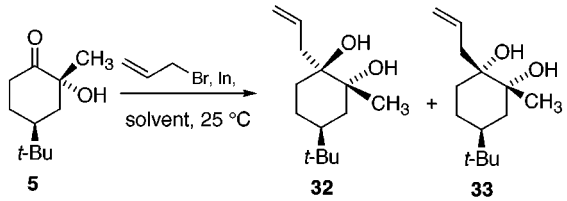
Scheme 11



entry	solvent	time, h	chelate/ non-chelate	yield, %
13	H_2O	2.5	>97:3	64
14	THF-H_2O (1:1)	2.5	>97:3	58
15	THF	no reaction (5 days)	----	----
16	THF[a]	0.5	>97:3	82

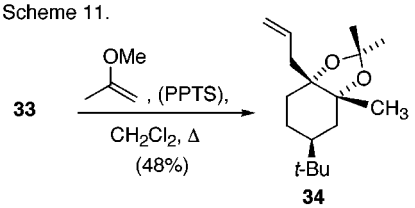
[a] Allyl bromide and indium powder were refluxed in THF for 0.5 h, then cooled to 25 °C before the addition of **4**.

Scheme 12



entry	solvent	time, h	chelate/ non-chelate	yield, %
17	H_2O	2.5	>97:3	66
18	THF-H_2O (1:1)	2.0	>97:3	67
19	THF	120	2.1:1	90
20	THF[a]	0.5	1.7:1	96

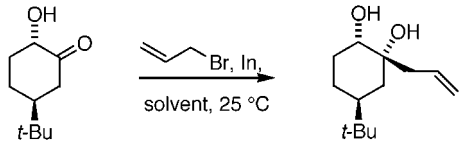
[a] See Scheme 11.



tive to the mode of generation of the allylindium reagent. Evidently, the anhydrous conditions and not the reaction time are controlling of competing axial and equatorial attack.

The stereodisposition of the allyl groups in **32** and **33** was defined by NOE difference and long-range semiselective DEPT experiments.[40] The axially oriented H-6a

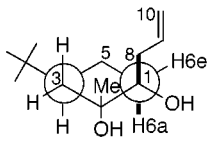
Scheme 13



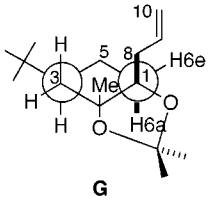
entry	solvent	time, h	chelate/ non-chelate	yield, %
21	H_2O	1.25	>97:3	87
22	THF-H_2O (1:1)	1.25	>97:3	88
23	THF	16	>97:3	88

of trans diol **32** displays significant enhancements to the protons resident on the equatorial allylic substituent, interactions that would not be observed if the allyl side chain was axial as in **33**. Conversely, as a consequence of the 1,3-diaxial relationships involving the allyl group, H-3a, and H-5a in cis diol **33**, enhancements at the 3−5% level were seen upon appropriate double irradiation of the associated signals. The relevant data are compiled in the Experimental Section.

The DEPT 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 **33**, models show the dihedral angle between H-6a and C-8 to be approximately 180° (see **F**) such that significant $^{1,3}J$ interaction should be seen for this isomer but not for **32**, which lacks this trans-diaxial relationship. Such was indeed the case. In addition, acetonide **34** generated conventionally from **33**[41] gave similar evidence for strong heteronuclear coupling between H-6a and C-8, indicating its ground-state conformation to be that given by **G**.



F



G

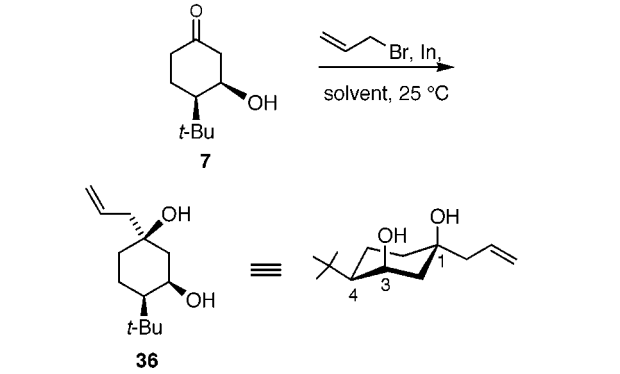
The excellent control of diastereofacial selectivity reflected in entries 17 and 18 together with the axial nature of the tertiary hydroxyl in **32** conforms to the ready adoption by α-ketol **5** of twist-boat conformation **E** (R = CH_3) when water is present. This chelation-controlled pathway clearly does not enjoy a comparable overwhelming kinetic advantage when the reaction medium is anhydrous. The data show that the allylindium reagent exhibits a bonding affinity for tertiary hydroxyl groups in water that is strong and measurably in excess over that exhibited toward hindered ethereal oxygen centers.[9]

Stereochemical Course of the Allylation of 6. The results obtained for the allylation of **6** are summarized in Scheme 13. To our delight, this transposed system also underwent nucleophilic attack cleanly and exclu-

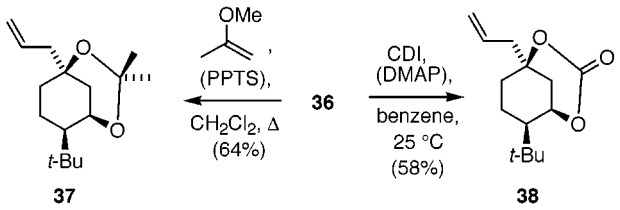
(40) (a) Bax, A. *J. Magn. Reson.* **1983**, *52*, 330; **1983**, *53*, 517. (b) Rutar, V. *J. Am. Chem. Soc.* **1983**, *105*, 4095. (c) Rutar, V. *J. Magn. Reson.* **1984**, *56*, 87. (d) Wimperis, S.; Freeman, R. *J. Magn. Reson.* **1984**, *58*, 348. (e) Lin, L.-J.; Cordell, G. A. *J. Chem. Soc.,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

(41) Diol **32** was completely unreactive to these conditions.

Scheme 14



entry	solvent	time, h	chelate/ non-chelate	yield, %
24	H_2O	2.5	>97:3	89
25	THF-H_2O (1:1)	1.5	>97:3	89
26	THF	72	>97:3	39

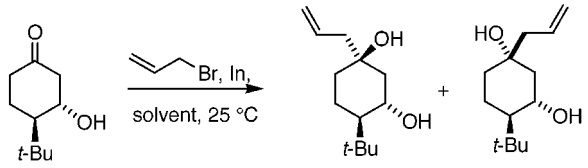


sively from the equatorial direction to give **35**. Entries 21−23 reveal that the equatorial status of the differently positioned α-hydroxyl substituent remains ideally situated for coupling via a chelation-controlled transition state related to that described by **D**. As in preceding examples, the stereochemistry of **35** was unambiguously defined by NOE difference experiments.

Couplings Involving the 3-Hydroxycyclohexanones 7 and 8. The conventional allylindation of **7** led uniquely to production of diastereomer **36** irrespective of the reaction medium (entries 24−26, Scheme 14). In this instance, the experiment performed in THF was allowed to proceed for 3 days and resulted in only 39% conversion to **36**. The structural definition of **36** was initially made by means paralleling those utilized earlier. Thus, when NOE difference experiments were performed (see Experimental Section), the independent irradiation of allylic protons H-7 and H-7′ as well as vinylic proton H-8 was found to induce no transfer to H-5a as would be expected of a diaxial relationship. On the other hand, H-2e, H-2a, H-6e, and H-6a proved responsive, indicating that the allyl group was equatorially disposed. This conclusion was ultimately confirmed by the conversion of **36** into **37** and **38** under conditions sufficiently mild to preclude the possibility that the trans diol would react with equal efficiency, if at all. The atom connectivity in **38**, established by ^{1}H,^{1}H COSY NMR analysis, eliminated the possibility that a rearrangement may have materialized during its formation. Particularly diagnostic were the W-plan couplings observed between H-2e/H-6e and H-3e/H-5e.

The allylindation of **8** proceeded smoothly with formation of two homoallylic alcohols (Scheme 15). The ratios of **39** to **40** reported in entries 27−29 parallel very closely those obtained earlier with 4-*tert*-butylcyclohexanone

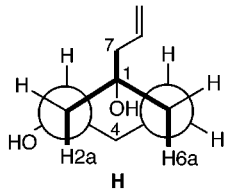
Scheme 15



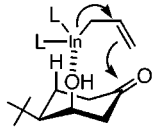
entry	solvent	time, h	chelate/ non-chelate	yield, %
27	H_2O	2.5	6.6:1	73
28	THF-H_2O (1:1)	1.5	7.2:1	76
29	THF	60	5.8:1	74

(Scheme 7). The axial orientation of the allyl unit in **40** was clearly apparent from NOE difference data, particularly when direct comparison was made with **39**. In the latter instance, the effect of irradiating H-3 on the intensity of the H-7,H-7′ signal is particularly diagnostic of a 1,3-diaxial interaction. Long-range semiselective DEPT studies also conclusively established the axial nature of the allyl group in **40**. Thus, independent irradiation of H-2a and H-6a resulted in pronounced transfer to C-7 (see **H**).

Competition Experiments. In the absence of kinetic studies, it is not possible to distinguish between chelation as a product-determining event or an unproductive reversible process.[42,43] However, if chelated transition states are responsible for providing a lower energy pathway to products, it must also be true that this process must take place more rapidly than others not involving chelation. Presently, this important parameter



H



I

has been probed by means of a series of competition experiments. At issue is whether those processes that exhibit highly controlled diastereoselectivity toward the allylindium reagent are indeed mediated by more reactive indium chelates. To simplify matters, we have assumed that chelation/nonchelation phenomena and conformational factors are the only relevant kinetic considerations. Although strictly speaking this need not be so,[44] it can be argued that the correlation is reasonable because of the close structural similarity of the ketones.

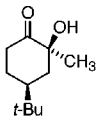
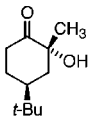
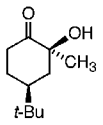
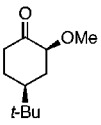
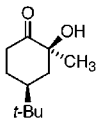
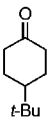
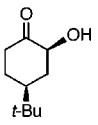
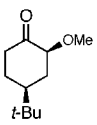
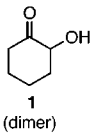
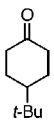
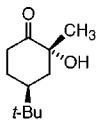
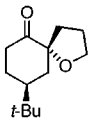
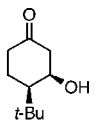
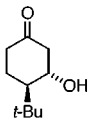
Several important facts can be culled from the data compiled in Table 1. First, an equatorial α-hydroxy group exerts a significant accelerating effect not available to its axial counterpart. Inspection of entries 30−32, particularly the 8.5-fold greater reactivity of **4** relative to 4-*tert*-butylcyclohexanone, is most informative. Since

(42) (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.

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

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

Table 1. Competitive Indium-Promoted Allylations in Water at 25 °C

entry	first ketone	second ketone	reaction time, h	relative rate ratio[a]
30	 **4**	 **5**	8	4.1 : 1[b]
31	 **4**	 **41**	5	6.1 : 1[c]
32	 **4**		5	8.5 : 1[c]
33	 **2**	 **41**	8	6.9 : 1[c]
34	 **1** (dimer)		6 6	1.7 : 1[c,d] 1.5 : 1[c,e]
35	 **5**	 **42**	8	1.6 : 1[c]
36	 **7**	 **8**	5.5	1.4 : 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 unreacted ketones remaining. [c] The relative rate ratio was ascertained by quantitative analysis of the alcohol products formed. [d] The reaction was performed at an initial pH of 7.0 as in all of the other cases. [e] The reaction was performed in water at an initial pH of 4.0.

2 and **4** exhibit comparable kinetic advantages over **41** (entries 31 and 33), support is gained for the contention that the effects of steric screening in the vicinity of equatorial OH groups on the reactivity of the allylindium reagent in water is virtually inconsequential. The appreciably diminished reactivity of **5** toward **4** (entry 30) and **42** (entry 35) makes evident in direct competition the fact that the axial α-hydroxyls are not similarly advantaged. In this sterically more demanding environment, the distinction between free OH groups and ethereal oxygen centers is seen to be leveled (entry 40). Since excellent allylation diastereoselectivity is exhibited by **3** and **5** in water, the implication is that complexation likely operates as well in these circumstances. The absence of significant kinetic acceleration may reside in the need to involve a twist-boat conformation of the reactant as in **E**. Consequently, the pathway to product for the axial alcohols involves the crossing of an energy barrier[45] having no parallel in the equatorial diastereomers.

Caution must be exercised in evaluating the data for entry 34 because of the requirement for dimer to monomer conversion in **1** prior to its availability for reaction. Notwithstanding, the results illustrate the greater reactivity of **1**.

At the outset of this study, a modest amount of information was available concerning the ability of OH groups in β-hydroxy aldehydes to effectively chelate the allylindium reagent under aqueous conditions.[8a,b] In fact, these observations prompted our examination of **7** and **8** in the present context. While it is obvious that the equatorial orientation of the hydroxyl in **8** precludes the possible operation of remote chelation of any type, isomer **7** has the option of undergoing allylation via the complexed transition state **I**. As pointed out previously, the diastereoselectivity exhibited by **8** expectedly conforms closely to that shown by the parent 4-*tert*-butylcyclohexanone. In addition, it is marginally less reactive than **7** (entry 36) which, however, gives rise exclusively to **36** (Scheme 14). The equatorial disposition of the allyl group in **36** unequivocally excludes the involvement of transition state **I**, which must culminate in axial allylation. The data are totally inconsistent with the notion that the indium reagent experiences dual coordination to both oxygen atoms in **7**. The substantial steric congestion at play in **I** may be contributory to its nonoperability. The origin of the strong preference for equatorial attack exhibited by **7** is less clear. The possibility exists that the size and electronegativity of the axial OH substituent serve singly[46] or in combination to disfavor axial entry of the allylindium reagent.

Conclusions

Our investigation into the facial selectivity of the indium-promoted allylation of 2-hydroxycyclohexanones provides experimental evidence for possible chelation control in these carbonyl addition reactions, particularly in water. Coordination of the unprotected OH to the nucleophilic allylindium reagent is notably effective when it is projected into equatorial space. As demonstrated by competition experiments, rate accelerations are manifested irrespective of the secondary or tertiary nature of the neighboring hydroxyl. The stereoselectivity demonstrated by the axial α-ketols remains exceptionally high. In these examples, kinetic effects are not as dramatic. This phenomenon is attributed to the possible involvement of twist-boat conformations for realizing effective chelation by In(III) to both oxygen centers. The need to cross this added energy barrier does not appear to be inhibitory of stereocontrol, which is excellent in water.

The present work establishes further that 3-hydroxycyclohexanones are not subject to chelation-controlled diastereoselection. Although they are not activated toward allylation by precoordination, stereocontrol is not

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

(46) (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.

necessarily precluded. The response of **7** is particularly instructive in this respect.

It will be noted that equatorial attack operates regardless of the equatorial or axial orientation of the hydroxyl group. This fact leaves open the possibility that stereocontrol in these cyclohexyl systems is dictated in part by the rather large diameter of indium, such that axial approach of the allylindium reagent is not sterically tolerated. To the extent that this phenomenon operates, the rate acceleration for equatorial hydroxy groups might be attributable to other factors such as hydrogen bridging to the neighboring carbonyl group. Notwithstanding the overall balance of forces including chelation effects, their combined contribution leads to high stereocontrol from the equatorial side.

Experimental Section[47]

***cis*-4-*tert*-Butyl-2-(*tert*-butyldimethylsiloxy)cyclohexanone (9) and *trans*-5-*tert*-Butyl-2-(*tert*-butyldimethylsiloxy)cyclohexanone (10).** A cold (−78 °C) solution of diisopropylamine (3.64 mL, 26.0 mmol) in dry THF (100 mL) was blanketed with N_2, treated via syringe with *n*-butyllithium (18.5 mL of 1.3 M in hexanes, 24.0 mmol), allowed to warm to 0 °C during 1 h, and recooled to −78 °C prior to the sequential addition of 4-*tert*-butylcyclohexanone (3.08 g, 20.0 mmol) dissolved in dry THF (100 mL) and of chlorotrimethylsilane (3.81 mL, 30.0 mmol) via syringe. The reaction mixture was slowly warmed to 0 °C over 4 h, diluted with triethylamine (100 mL), and concentrated in vacuo. The residue was dissolved in pentane, filtered through Celite (pentane wash), and evaporated. Distillation gave the silyl enol ether (bp 55 °C/0.6 Torr) as a pale yellow viscous oil (3.85 g, 85%).

A 2.26 g (10.0 mmol) sample of the above product was dissolved in CH_2Cl_2 (100 mL), treated portionwise with purified *m*-chloroperbenzoic acid (2.07 g, 12.0 mmol), stirred for 8 h, and diluted with saturated $NaHCO_3$ solution. The separated organic phase was dried, concentrated, dissolved in dry THF (90 mL), and treated directly with tetra-*n*-butylammonium chloride (10 mL of 1.0 M in THF, 10 mmol). The reaction mixture was stirred for 8 h and partitioned between saturated $NaHCO_3$ solution and ether. The aqueous phase was extracted with ether and the combined organic phases were dried and carefully concentrated on a rotary evaporator.

To a 340 mg (2.0 mmol) sample of this material in dry DMF (4 mL) was added imidazole (361 mg, 2.40 mmol). The reaction mixture was stirred for 2 h and diluted with brine. After repeated extraction of the aqueous phase with ether, the combined organic layers were dried and concentrated. Chromatography of the residue on silica gel (elution with 6% ethyl acetate in hexanes) afforded 80 mg (14%) of the less polar **10** and 111 mg (20%) of **9**, both as colorless oils.

For **9**: IR (neat, cm^{-1}) 1732; ^1H NMR (300 MHz, $CDCl_3$) δ 4.18 (ddd, J = 11.6, 6.4, 1.0 Hz, 1 H), 2.40 (ddd, J = 13.8, 4.3, 2.7 Hz, 1 H), 2.27 (ddd, J = 13.8, 5.9, 1.1 Hz, 1 H), 2.25−2.19 (m, 1 H), 2.02 (dddd, J = 15.7, 3.0, 3.0, 3.0 Hz, 1 H), 1.60 (dddd, J = 12.2, 12.2, 2.6, 2.6 Hz, 1 H), 1.47 (dd, J = 12.0, 12.0 Hz, 1 H), 1.37 (dddd, J = 13.4, 13.4, 13.4, 4.3 Hz, 1 H), 0.91 (s, 9 H), 0.89 (s, 9 H), 0.12 (s, 3 H), 0.01 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 209.4, 76.7, 46.0, 39.4, 38.5, 32.3, 28.0, 27.6, 25.8, 18.5, −4.6, −5.4; HRMS (EI) m/z (M^+) calcd 284.2172, obsd 284.2145.

Anal. Calcd for $C_{16}H_{32}O_2Si$: C, 67.55; H, 11.34. Found C, 67.68; H, 11.43.

For **10**: IR (neat, cm^{-1}) 1731; ^1H NMR (300 MHz, $CDCl_3$) δ 4.14 (ddd, J = 12.0, 6.6, 1.0 Hz, 1 H), 2.46 (ddd, J = 12.9, 2.9, 2.9 Hz, 1 H), 2.14 (dddd, J = 12.7, 3.3, 3.3, 3.3 Hz, 1 H), 2.04 (ddd, J = 13.0, 13.0, 1.1 Hz, 1 H) 1.91 (dddd, J = 12.7, 3.0, 3.0, 3.0 Hz, 1 H), 1.67−1.36 (series of m, 3 H), 0.89 (s, 9 H), 0.88 (s, 9 H), 0.13 (s, 3 H), 0.02 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 209.6, 77.0, 49.8, 42.2, 35.8, 32.6, 27.3, 25.8, 25.2, 18.5, −4.6, −5.4; HRMS (EI) m/z (M^+) calcd 284.2172, obsd 284.2169.

Anal. Calcd for $C_{16}H_{32}O_2Si$: C, 67.55; H, 11.34. Found C, 67.67; H, 11.39.

Desilylation of 9 and 10. A solution of **9** (1.40 g, 4.95 mmol) in dry THF (5.5 mL) was treated with tetra-*n*-butylammonium fluoride (5.44 mL of 1.0 M in THF, 5.44 mmol), stirred for 2 h at 20 °C, and diluted with brine. The separated aqueous layer was extracted with ether, and the combined organic phases were dried and evaporated. The residue was quickly eluted through a column of silica gel with 10% ethyl acetate in hexanes to furnish 400 mg (48%) of **2**. The semisolid was used immediately without further characterization. High-field ^1H NMR analysis showed that 11% of **2** had isomerized to **6**.

Comparable treatment of **10** (761 mg, 2.67 mmol) afforded 268 mg (59%) of **6** as a semisolid containing 9% of **2**. This material was utilized without delay.

***trans*-2-[(*E*)-Benzylidene]-4-*tert*-butylcyclohexanol (12).** A solution of **11** (1.0 g, 3.5 mmol) in 75% aqueous acetone (20 mL) containing concentrated hydrochloric acid (0.10 mL) was refluxed for 2 h, diluted with brine, and extracted with ether. The combined organic layers were dried and concentrated to provide the ketone, which was taken up in THF (9 mL) and added to a cold (0 °C), freshly prepared solution of lithium trimethoxyaluminum hydride [from 0.53 g (14 mmol) of lithium aluminum hydride and 1.69 mL (42 mmol) of anhydrous methanol in 11 mL of dry THF]. After 1 h at this temperature, the reaction mixture was treated dropwise with H_2O (0.53 mL), 15% sodium hydroxide solution (0.53 mL), and H_2O (1.59 mL), and extracted several times with ether. The combined ethereal layers were washed with brine, dried, and concentrated. Purification of the residue by chromatography on silica gel (elution with 10% ethyl acetate in hexanes) afforded 0.54 g (63% overall) of **12** as a white solid: mp 101−102 °C; IR (KBr, cm^{-1}) 3284; ^1H NMR (300 MHz, $CDCl_3$) δ 7.29−7.12 (m, 5 H), 6.50 (s, 1 H), 4.08−4.04 (m, 1 H), 2.98 (dt, J = 13.0, 2.5 Hz, 1 H), 2.23−2.17 (m, 1 H), 1.87−1.82 (m, 1 H), 1.70 (br s, 1 H), 1.44−1.14 (series of m, 4 H), 0.82 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 144.9, 137.9, 128.8, 128.0, 126.0, 118.1, 73.3, 49.3, 37.6, 32.8, 29.5, 27.4, 25.9; HRMS (EI) m/z (M^+) calcd 244.1827, obsd 244.1830.

Anal. Calcd for $C_{17}H_{24}O$: C, 83.55; H, 9.90. Found C, 83.39; H, 9.84.

[[*trans*-2-[(*E*)-Benzylidene]-4-*tert*-butylcyclohexyl]oxy]-*tert*-butyldimethylsilane (13). A solution of **12** (484 mg, 1.98 mmol), imidazole (230 mg, 3.38 mmol), and *tert*-butyldimethylsilyl chloride (358 mg, 2.37 mmol) in dry DMF (4 mL) was stirred for 12 h, diluted with brine, and extracted with ether. After the predescribed workup and chromatography on silica gel (elution with 5% ethyl acetate in hexanes), there was obtained 506 mg (71%) of **13** as a colorless oil: IR (neat, cm^{-1}) 1130, 1108; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34−7.17 (m, 5 H), 6.61 (s, 1 H), 4.08 (ddd, J = 11.0, 4.9, 1.6 Hz, 1 H), 3.03 (ddd, J = 13.0, 2.5, 2.5 Hz, 1 H), 2.15−2.06 (m, 1 H), 1.90−1.86 (m, 1 H), 1.55−1.19 (series of m, 4 H), 0.98 (s, 9 H), 0.89 (s, 9 H), 0.16 (s, 3 H), 0.14 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 144.4, 138.5, 128.8, 127.9, 125.8, 119.0, 74.2, 49.3, 37.9, 32.8, 29.6, 27.5, 26.0, 26.0, 18.5, −4.8, −4.8; HRMS (EI) m/z (M^+) calcd 358.2692, obsd 358.2707.

Anal. Calcd for $C_{23}H_{38}OSi$: C, 77.03; H, 10.68. Found C, 77.14; H, 10.71.

Ozonolytic Cleavage of 13. A cold (−78 °C) solution of **13** (506 mg, 1.41 mmol) in a 1:1 mixture of CH_2Cl_2 and methanol (14 mL) containing 1% triethylamine was ozonolyzed until a faint blue color appeared. The reaction mixture was purged with oxygen, treated with dimethyl sulfide (0.65 mL), warmed to room temperature, diluted with 1% $NaHCO_3$ solution, and extracted with CH_2Cl_2. The combined organic layers were dried and concentrated to leave a residue, puri-

(47) For generic experimental details, see ref 9.

fication of which by chromatography on silica gel (elution with 6% ethyl acetate in hexanes) gave 306 mg (76%) of **10**.

Hydride Reduction of 14. Diisobutylaluminum hydride (6.82 mL of 1.0 M in hexanes, 6.82 mmol) was added via syringe to a cold (−78 °C), magnetically stirred solution of **14** (1.11 g, 5.25 mmol) in hexanes (14 mL) under N_2. The reaction mixture was warmed to room temperature during 4 h, quenched with saturated Rochelle salt solution, stirred overnight, and extracted with ether. The combined organic layers were dried and concentrated to leave a residue which was subjected to chromatography on silica gel (gradient elution with 17 → 33% ethyl acetate in hexanes). There was isolated 662 mg (57%) of the less polar axial isomer **15** and 370 mg (33%) of the more polar **16**.

For **15**: colorless crystals, mp 57−58 °C: IR (KBr, cm^{-1}) 3510; ^1H NMR (300 MHz, $CDCl_3$) δ 3.98−3.90 (m, 4 H), 3.63 (s, 1 H), 2.20 (s, 1 H), 1.96−1.86 (m, 2 H), 1.72−1.64 (m, 1 H), 1.56 (dddd, J = 13.1, 3.4, 3.4, 1.8 Hz, 1 H), 1.48−1.35 (m, 2 H), 1.22 (dddd, J = 12.9, 12.9, 12.9, 3.5 Hz, 1 H), 0.85 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 109.0, 70.0, 65.3, 64.3, 39.3, 31.8, 30.3, 30.2, 27.5, 24.1; HRMS (EI) m/z (M^+) calcd 214.1569, obsd 214.1566.

Anal. Calcd for $C_{12}H_{22}O_3$: C, 67.26; H, 10.35. Found C, 67.36; H, 10.43.

For **16**: colorless crystals, mp 55−56 °C; IR (KBr, cm^{-1}) 3493; ^1H NMR (300 MHz, $CDCl_3$) δ 4.12−3.94 (series of m, 4 H), 3.64−3.57 (m, 1 H), 2.03−1.92 (series of m, 2 H), 1.82 (ddd, J = 13.1, 13.1, 3.0 Hz, 1 H), 1.67−1.60 (m, 1 H), 1.36 (ddd, J = 13.1, 13.1, 3.7 Hz, 1 H), 1.29−1.09 (series of m, 3 H), 0.86 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 109.5, 73.5, 65.5, 65.3, 45.9, 33.6, 33.5, 32.2, 27.6, 24.1; HRMS (EI) m/z (M^+) calcd 214.1569, obsd 214.1552.

Anal. Calcd for $C_{12}H_{22}O_3$: C, 67.26; H, 10.35. Found C, 67.33; H, 10.42.

Hydrolysis of 15. Major ketal **15** (241 mg, 1.00 mmol) was refluxed in 75% aqueous acetone (20 mL) containing concentrated hydrochloric acid (0.01 mL) for 10 h, cooled to 20 °C, diluted with brine, and partitioned several times with ether. The combined organic extracts were dried and concentrated to afford 120 mg (71%) of a mixture of **2** and **6** but none of **3**, as determined by ^1H NMR at 300 MHz.

***trans*-2-(Benzyloxy)-4-*tert*-butylmethylenecyclohexane (19).** A mixture of sodium hydride (4.90 g, 0.20 mmol) and freshly distilled DMSO (100 mL) was heated to 75−80 °C for 45 min and then cooled to 0 °C. Freshly prepared methyltriphenylphosphonium iodide (80.85 g, 0.20 mmol) was introduced as a solution in warm DMSO (200 mL) via a pressure-equalized addition funnel. The reaction mixture was warmed to 20 °C during 1 h and the product was separated from most of the DMSO by fractional distillation under reduced pressure. Residual DMSO in the higher boiling fractions was removed by flash column chromatography on silica gel (elution with hexanes) to afford 26.84 g (80%) of **17** which was directly oxidized.

tert-Butyl hydroperoxide (32 mL) was added to a mixture of selenium dioxide (441 mg, 3.98 mmol) and salicyclic acid (1.10 g, 7.95 mmol) in CH_2Cl_2 (40 mL), to be followed by **17** (12.11 g, 79.5 mmol). The reaction mixture was stirred for 40 h, diluted with brine, and extracted with CH_2Cl_2. The combined organic layers were washed with 10% KOH solution, dried, and concentrated. Chromatographic purification (silica gel, gradient elution with 5 → 20% ethyl acetate in hexanes) provided 10.05 g (75%) of **18** as the only observed product. This material was stirred with benzyl bromide (8.48 mL, 71.7 mmol), sodium hydride (1.94 g, 77.6 mmol), and tetra-*n*-butylammonium iodide (2.21 g, 5.98 mmol) in dry THF (300 mL) at 0 °C for 2 h and at room temperature overnight. After careful dilution with brine, the product was extracted into ether, dried, and concentrated prior to chromatographic purification (silica gel, elution with 2.5% ethyl acetate in hexanes). There were isolated 7.84 g (51%) of **19** as a faint yellow oil: IR (neat, cm^{-1}) 1365, 1086, 1065; ^1H NMR (300 MHz, $CDCl_3$) δ 7.45−7.26 (m, 5 H), 4.96 (dd, J = 2.0, 2.0 Hz, 1 H), 4.85 (dd, J = 1.6, 1.6 Hz, 1 H), 4.58 (d, J = 12.3 Hz, 1 H), 4.35 (d, J = 12.3 Hz, 1 H), 3.99 (dd, J = 2.6, 2.6 Hz, 1 H), 2.46−2.35 (m, 1 H), 2.30−2.16 (series of m, 2 H), 1.99−1.91 (m, 1 H), 1.80 (dddd, J = 12.4, 12.4, 3.2, 3.2 Hz, 1 H), 1.34 (ddd, J = 13.0, 13.0, 3.0 Hz, 1 H), 1.14 (ddd, J = 25.4, 12.4, 4.1 Hz, 1 H), 0.94 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 147.9, 139.2, 128.2, 127.4, 127.1, 110.7, 78.8, 68.8, 40.9, 34.3, 32.0, 30.7, 28.6, 27.5; HRMS (EI) m/z (M^+) calcd 258.1984, obsd 258.1980.

***trans*-2-(Benzyloxy)-4-*tert*-butylcyclohexanone (20).** A cold solution of **19** (1.29 g, 5.0 mmol) in methanol (50 mL) was ozonolyzed in the predescribed manner to give 714 mg (55%) of **20** after silica gel chromatography (elution with 5% ethyl acetate in hexanes): colorless oil; IR (neat, cm^{-1}) 1719, 1455, 1367; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40−7.27 (m, 5 H), 4.51 (d, J = 11.9 Hz, 1 H), 4.41 (d, J = 11.9 Hz, 1 H), 3.72 (dd, J = 2.7, 2.7 Hz, 1 H), 2.82 (ddd, J = 13.6, 13.6, 6.0 Hz, 1 H), 2.31−2.23 (m, 2 H), 2.12−2.03 (m, 1 H), 1.96 (dddd, J = 12.4, 12.4, 3.4, 3.4 Hz, 1 H), 1.52 (ddd, J = 14.1, 12.6, 3.1 Hz, 1 H), 1.42 (dddd, J = 12.7, 12.7, 12.7, 4.0 Hz, 1 H), 0.91 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 212.6, 137.5, 128.3, 127.6 (2C), 80.9, 71.0, 40.3, 37.7, 34.2, 31.9, 28.1, 27.4; HRMS (EI) m/z (M^+) calcd 260.1776, obsd 260.1780.

Anal. Calcd for $C_{17}H_{24}O_2$: C, 78.42; H, 9.29. Found C, 78.57; H, 9.32.

Debenzylation of 20. A solution of **20** (714 mg, 2.74 mmol) in ethanol (9 mL) containing 275 mg of 10% palladium on carbon was stirred under an atmosphere of hydrogen for 1.5 h. The reaction mixture was filtered through Celite, concentrated, and subjected to flash chromatography (silica gel, elution with 20% ethyl acetate in hexanes). There was obtained 302 mg (64%) of **3** as a semisolid that was used immediately. ^1H NMR analysis indicated that modest levels of **2** and **6** (ca. 20% combined) had been produced under these conditions.

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 room temperature 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 room temperature until ketone consumption was complete (TLC analysis). A workup identical to that in **B** was employed.

In all cases, product yields have been adjusted to discount those allylation products resulting from attack on contaminating tautomeric forms. The product distributions represent the average derived from duplicate runs.

Coupling Involving 4-*tert*-Butylcyclohexanone. Isomer separation accomplished on silica gel (elution with 10% ethyl acetate in hexanes).

For **22**:[36a] colorless oil, IR (neat, cm^{-1}) 3385 (br); ^1H NMR (300 MHz, C_6D_6) δ 5.84−5.75 (m, 1 H), 5.07−4.97 (m, 2 H), 2.04 (ddd, J = 7.4, 1.1, 1.1 Hz, 2 H), 1.56−1.33 (series of m, 6 H), 1.15−1.05 (m, 2 H), 0.87 (s, 9 H), 0.92−0.75 (m, 2 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 134.5, 118.0, 69.8, 49.1, 48.2, 37.7, 32.4, 27.8, 22.8.

For **23**:[36a] colorless solid, mp 59.5−60.5 °C; IR (KBr, cm^{-1}) 3312 (br); ^1H NMR (300 MHz, C_6D_6) δ 5.98−5.84 (m, 1 H),

5.10−5.01 (m, 2 H), 2.18 (d, J = 7.3 Hz, 2 H), 1.73−1.67 (m, 2 H), 1.52−1.45 (m, 2 H), 1.30 (ddd, J = 12.1, 12.1, 3.5 Hz, 2 H), 1.13 (s, 1 H), 0.99−0.86 (m, 3 H), 0.78 (s, 9 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 134.5, 118.0, 71.2, 47.6, 41.4, 38.9, 32.2, 27.7, 24.5.

Coupling Involving 1. Single product formed; purified by silica gel chromatography (elution with 50% ethyl acetate in hexanes).

For **24**: colorless solid, mp 73−74 °C; IR (KBr, cm^{-1}) 3405 (br), 3269 (br); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.94−5.80 (m, 1 H), 5.13−5.07 (m, 2 H), 3.42 (dd, J = 9.3, 3.9 Hz, 1 H), 2.37 (dd, J = 13.7, 7.5 Hz, 1 H), 2.27 (dd, J = 13.7, 7.4 Hz, 1 H), 2.19 (br s, 1 H), 1.72−1.16 (series of m, 8 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 133.8, 118.5, 73.2, 73.1, 43.5, 34.1, 30.2, 23.2, 21.0; HRMS (EI) m/z (M^+) calcd 156.1150, obsd 156.1160.

Anal. Calcd for $C_9H_{16}O_2$: C, 69.19; H, 10.32. Found C, 69.03; H, 10.25.

Coupling Involving 2. Single product formed; purified by chromatography on silica gel (elution with 20% ethyl acetate in hexanes).

For **26**: colorless solid, mp 99−100 °C; IR (KBr, cm^{-1}) 3288 (br); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.97−5.83 (m, 1 H), 5.15−5.10 (m, 2 H), 3.42 (dd, J = 11.2, 4.5 Hz, 1 H), 2.42 (dd, J = 13.6, 7.7 Hz, 1 H), 2.26 (dd, J = 13.6, 7.3 Hz, 1 H), 1.93 (br s, 2 H), 1.84−1.72 (m, 2 H), 1.51−1.44 (m, 1 H), 1.37−1.18 (m, 3 H), 1.06−0.91 (m, 1 H), 0.86 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 134.1, 118.6, 74.2, 72.4, 46.4, 44.3, 34.8, 32.2, 31.9, 27.5, 21.5; HRMS (EI) m/z ($M^+ - C_3H_5$) calcd 171.1385, obsd 171.1376.

Anal. Calcd for $C_{13}H_{24}O_2$: C, 73.54; H, 11.39. Found C, 73.57; H, 11.29.

Coupling Involving 3. Single product; purified by chromatography on silica gel (elution with 20% ethyl acetate in hexanes).

For **28**: colorless semisolid; mp 86−90 °C; IR (KBr, cm^{-1}) 3404 (br); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.94−5.80 (m, 1 H), 5.06−4.99 (m, 2 H), 3.43 (br s, 1 H), 2.35 (dd, J = 13.6, 7.4 Hz, 1 H), 2.13 (dd, J = 13.6, 7.6 Hz, 1 H), 1.73−1.56 (m, 3 H), 1.50−1.35 (m, 5 H), 1.06 (s, 1 H), 0.86 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 134.3, 118.7, 72.3, 71.7, 44.4, 40.5, 33.1, 32.0, 30.5, 27.6, 22.2; HRMS (EI) m/z ($M^+ - C_3H_5$) calcd 171.1385, obsd 171.1390.

Anal. Calcd for $C_{13}H_{24}O_2$: C, 73.54; H, 11.39. Found C, 73.72; H, 11.48.

Coupling Involving 4. Single diastereomer; purified by gradient elution (17−50% ethyl acetate in hexanes) on silica gel.

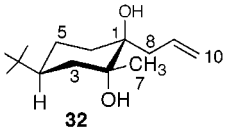
For **30**: colorless oil; IR (neat, cm^{-1}) 3450 (br); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.03−5.89 (m, 1 H), 5.19−5.10 (m, 2 H), 2.51 (dd, J = 13.7, 8.3 Hz, 1 H), 2.24 (s, 1 H), 2.15 (s, 1 H), 2.11 (dd, J = 13.7, 6.7 Hz, 1 H), 1.77 (ddd, J = 10.3, 2.8, 2.8 Hz, 1 H), 1.59−1.43 (m, 3 H), 1.40−1.23 (m, 2 H), 1.22 (s, 3 H), 1.08 (dddd, J = 12.1, 12.1, 3.5, 3.5 Hz, 1 H), 0.84 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 134.5, 119.1, 75.0, 74.1, 45.0, 40.7, 38.9, 33.9, 32.1, 27.4, 23.1, 21.7; HRMS (EI) m/z (M^+) calcd 226.1933, obsd 226.1929.

Anal. Calcd for $C_{14}H_{26}O_2$: C, 74.29; H, 11.57. Found C, 74.05; H, 11.63.

Coupling Involving 5. Note that **33** was produced only when anhydrous THF was the reaction medium. The products were purified by chromatography on silica gel (elution with 11% ethyl acetate in hexanes).

For **32**: colorless oil; IR (neat, cm^{-1}) 3490 (br); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.98−5.84 (m, 1 H), 5.17−5.10 (m, 2 H), 2.44 (dd, J = 13.7, 7.5 Hz, 1 H), 2.35 (dd, J = 13.7, 7.6 Hz, 1 H), 1.76−1.19 (series of m, 7 H), 1.38 (s, 1 H), 1.34 (s, 1 H), 1.24 (s, 3 H), 0.85 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 134.5, 119.0, 74.4, 73.6, 42.0, 40.3, 37.4, 32.7, 32.0, 27.5, 24.6, 21.5; HRMS (EI) m/z (M^+) calcd 226.1933, obsd 226.1936.

Anal. Calcd for $C_{17}H_{26}O_2$: C, 74.29; H, 11.57. Found C, 74.17; H, 11.60.

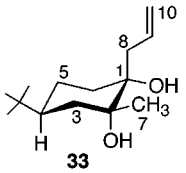


32

irradiate	observe	% NOE difference
H-6a	H-8	3.2
	H-8'	0.9
	H-9	1.9
H-7 (CH_3)	H-8	3.3
	H-8'	3.2
H-8	H-6a	2.3
	H7 (CH_3)	0.8
H-8'	H-6a	1.4
	H-7 (CH_3)	3.9

For **33**: colorless oil; IR (neat, cm^{-1}) 3430 (br); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.95−5.81 (m, 1 H), 5.17−5.07 (m, 2 H), 2.33 (dd, J = 14.0, 7.9 Hz, 1 H), 2.20 (dd, J = 14.0, 6.6 Hz, 1 H), 2.19 (s, 1 H), 1.94 (s, 1 H), 1.76−1.44 (series of m, 5 H), 1.24 (dd, J = 13.3, 13.3 Hz, 1 H), 1.18 (s, 3 H), 1.08−0.95 (m, 1 H), 0.85 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 133.7, 118.4, 75.2, 74.3, 41.7, 38.1, 36.9, 32.0, 31.9, 27.5, 24.5, 23.5; HRMS (EI) m/z (M^+) calcd 226.1933, obsd 226.1956.

Anal. Calcd for $C_{17}H_{30}O_2$: C, 74.29; H, 11.57. Found C, 74.13; H, 11.52.



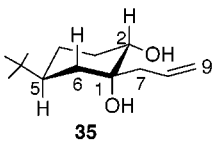
33

irradiate	observe	% NOE difference
H-3a	H-8	2.8
	H-8'	1.7
H-5a	H-8	3.7
	H-3a	4.8
H-8	H-5a	3.1

Coupling Involving 6. Single product; isolation accomplished by chromatography on silica gel (elution with 25% ethyl acetate in hexanes).

For **35**: colorless solid, mp 63−67 °C; IR (neat, cm^{-1}) 3381 (br); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.99−5.84 (m, 1 H), 5.16−5.10 (m, 2 H), 3.37 (dd, J = 11.4, 4.8 Hz, 1 H), 2.47 (dd, J = 13.6, 7.7 Hz, 1 H), 2.28 (dd, J = 13.6, 7.4 Hz, 1 H), 1.92 (bs, 1 H), 1.84−1.69 (series of m, 4 H), 1.61−1.47 (m, 1 H), 1.38 (dddd, J = 12.4, 12.4, 3.1, 3.1 Hz, 1 H), 1.09−0.89 (series of m, 2 H), 0.84 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 134.1, 118.7, 73.6, 73.2, 44.9, 41.6, 36.0, 32.0, 30.8, 27.5, 25.1; HRMS (EI) m/z ($M^+ - C_3H_5$) calcd 171.1385, obsd 171.1385.

Anal. Calcd for $C_{13}H_{24}O_2$: C, 73.54; H, 11.39. Found C, 73.54; H, 11.44.



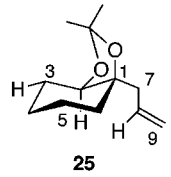
35

irradiate	observe	% NOE difference
H-2	H-7	0.6
	H-7'	1.7
	H-8	2.2
	H-4a, 6a	3.9
H-7	H-2	1.4
H-7'	H-2	2.5

(1*R,2*R**)-1-Allyl-1,2-(isopropylidenedioxy)cyclohexane (25).** A solution of diol **24** (156 mg, 1.0 mmol) in DMF (1 mL) was treated with 2-methoxypropene (0.19 mL, 2.0 mmol) and pyridinium *p*-toluenesulfonate (25 mg, 0.10 mmol), stirred at 0 °C for 45 min, diluted with brine, and extracted several times with ether. The combined organic layers were dried and concentrated, and the residue was purified chromatographically (elution with 9% ethyl acetate in hexanes). There was isolated 172 mg (88%) of **25** as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.98−5.84 (m, 1 H), 5.12−5.02 (m, 2 H), 3.90

(d, J = 2.6 Hz, 1 H), 2.37 (dddd, J = 14.4, 6.9, 1.2, 1.2 Hz, 1 H), 2.28 (dd, J = 14.4, 7.5 Hz, 1 H), 2.12−2.03 (m, 1 H), 1.71−1.44 (series of m, 6 H), 1.49 (s, 3 H), 1.33 (s, 3 H), 1.18−1.08 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 133.8, 117.7, 106.8, 80.1, 76.2, 40.1, 34.3, 28.5, 27.0, 26.2, 22.7, 19.8; HRMS (EI) m/z (M^+) calcd 196.1463, obsd 196.1464.

Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found C, 73.51; H, 10.20.



25

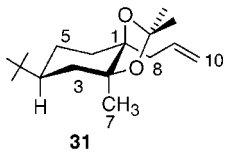
irradiate	observe	% NOE difference
H-2	H-3e	2.4
	H-7, 7'	3.2
	H-8	1.9
H-7	H-2	1.2
H-7'	H-2	3.2
H-8	H-2	1.7

(1*R,2*R**,4*R**)-1-Allyl-4-*tert*-butyl-2-methoxycyclohexanol (27).** A suspension of sodium hydride (4.0 mg, 0.17 mmol) and diol **26** (30 mg, 0.14 mmol) in dry THF (1.5 mL) was stirred under N_2 for 30 min prior to the addition of methyl iodide (0.18 mL, 2.8 mmol). The reaction mixture was warmed to room temperature during 12 h and then partitioned between brine and ether. The combined organic layers were dried and evaporated. Chromatography of the residue on silica gel (elution with 8% ethyl acetate in hexanes) gave 22 mg (69%) of **27** and returned 5 mg (17%) of unreacted **26**. The spectral data for **27** proved identical to those previously reported.[9]

(1*R,2*S**,4*R**)-1-Allyl-4-*tert*-butyl-2-methoxycyclohexanol (29).** Methylation of **28** (31 mg, 0.15 mmol) in the predescribed manner gave **29** (15 mg, 48%) while returning 11 mg (36%) of unreacted diol. The spectral data for **29** completely matched those previously reported.[9]

(1*S,2*S**,4*S**)-1-Allyl-4-*tert*-butyl-1,2-(isopropylidenedioxy)-2-methylcyclohexane (31).** Heating **30** (80 mg, 0.38 mmol) with 2-methoxypropene (0.15 mL, 1.5 mmol) and pyridinium *p*-toluenesulfonate (9 mg) in CH_2Cl_2 (3.8 mL) at the reflux temperature for 14 h followed by workup in the predescribed manner (elution with 2.5% ethyl acetate in hexanes) afforded 83 mg (83%) of **31** as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.99−5.85 (m, 1 H), 5.14−5.03 (m, 2 H), 2.72 (dd, J = 14.1, 5.4 Hz, 1 H), 2.19 (dd, J = 10.8, 3.4 Hz, 1 H), 1.91 (dd, J = 14.1, 8.6 Hz, 1 H), 1.74−1.61 (m, 3 H), 1.53 (s, 3 H), 1.47 (s, 3 H), 1.24 (s, 3 H), 1.21−1.14 (m, 2 H), 0.95−0.86 (m, 1 H), 0.84 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 134.2, 117.9, 106.6, 83.3, 82.5, 45.4, 41.7, 39.4, 32.8, 32.0, 30.3, 30.1, 27.3, 22.2, 21.6; HRMS (EI) m/z (M^+) calcd 266.2246, obsd 266.2285.

Anal. Calcd for $C_{17}H_{30}O_2$: C, 76.64; H, 11.35. Found C, 76.55; H, 11.31.



31

irradiate	observe	% NOE difference
H-7 (CH_3)	H-8	4.7
	H-8'	5.3
H-8	H-7 (CH_3)	3.7
H-8"	H-7 (CH_3)	2.2

(1*R,2*R**,4*S**)-1-Allyl-4-*tert*-butyl-1,2-(isopropylidenedioxy)-2-methylcyclohexane (34).** A solution of **33** (71 mg, 0.31 mmol), 2-methoxypropene (12 μL, 1.26 mmol), and pyridinium *p*-toluenesulfonate (8 mg) in CH_2Cl_2 (3 mL) was refluxed for 10 h and processed similarly (elution with 2.5% ethyl acetate in hexanes) to furnish 40 mg (48%) of **34** as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.96−5.82 (m, 1 H), 5.12−5.03 (m, 2 H), 2.44 (ddd, J = 14.1, 5.6, 1.2 Hz, 1 H), 2.19 (dd, J = 14.1, 8.7 Hz, 1 H), 2.00 (ddd, J = 14.3, 3.4, 2.6 Hz, 1 H), 1.83 (ddd, J = 13.8, 5.0, 5.0 Hz, 1 H), 1.76 (ddd, J = 14.7, 14.7, 4.1 Hz, 1 H), 1.66−1.57 (m, 1 H), 1.51 (s, 3 H), 1.46 (s, 3 H), 1.49−1.38 (m, 1 H), 1.28 (m, 3 H), 1.08 (dd, J = 14.3, 12.7, Hz, 1 H), 0.93 (dddd, J = 10.9, 10.9, 4.6, 4.6 Hz, 1 H), 0.84 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 134.7, 117.8, 106.7, 83.1, 82.7, 41.3, 39.7, 37.2, 32.8, 32.1, 30.5, 29.8, 27.4, 26.3, 23.4; HRMS (EI) m/z ($M^+ - CH_3$) calcd 251.2012, obsd 251.2012.

Anal. Calcd for $C_{17}H_{30}O_2$: C, 76.64; H, 11.35. Found C, 76.35; H, 11.33.

Coupling Involving 7. Single product formed; purified by chromatography on silica gel (elution with 20% ethyl acetate in hexanes).

For **36**: colorless oil; IR (neat, cm^{-1}) 3334 (br); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.92−5.78 (m, 1 H), 5.15−5.05 (m, 2 H), 4.26 (m, 1 H), 2.97 (br s, 2 H) 2.17−2.15 (m, 2 H), 1.88 (ddd, J = 14.4, 3.2, 3.2 Hz, 1 H), 1.81−1.72 (m, 2 H), 1.56−1.49 (m, 1 H), 1.44 (dd, J = 14.3, 3.0 Hz, 1 H), 1.39 (ddd, J = 13.4, 13.4, 3.9 Hz, 1 H), 1.00−0.92 (m, 1 H), 0.96 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 133.3, 118.9, 72.5, 69.1, 50.8, 48.1, 42.8, 37.8, 32.6, 28.6, 16.4; HRMS (EI) m/z (M^+) calcd 212.1776, obsd 212.1777.

Anal. Calcd for $C_{13}H_{24}O_2$: C, 73.54; H, 11.39. Found C, 73.44; H, 11.34.

(1*R,5*S**,6*S**)-1-Allyl-6-*tert*-butyl-3,3-dimethyl-2,4-dioxabicyclo[3.3.1]nonane (37).** A solution of **36** (0.101 g, 0.48 mmol), 2-methoxypropene (0.18 mL, 1.9 mmol), and PPTS (12 mg, 0.05 mmol) in CH_2Cl_2 (4.8 mL) was refluxed under N_2 for 12 h, cooled to 25 °C, and diluted with brine. The aqueous layer was separated and extracted with CH_2Cl_2. The combined organic layers were dried and concentrated to leave an oil that was purified by chromatography on silica gel (elution with 2.5% ethyl acetate in hexanes) to afford 77 mg (64%) of **37** as a colorless oil: IR (neat, cm^{-1}) 1377; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.90−5.76 (m, 1 H), 5.09−5.00 (m, 2 H), 4.50 (dd, J = 4.4, 0.9 Hz, 1 H), 2.51 (ddd, J = 14.1, 5.3, 3.1 Hz, 1 H), 2.29−2.12 (m, 2 H), 1.86 (dddd, J = 12.9, 12.9, 12.9, 4.5 Hz, 1 H), 1.71−1.64 (m, 1 H), 1.59−1.53 (m, 1 H), 1.57 (s, 3 H), 1.36 (s, 3 H), 1.25 (ddd, J = 13.1, 13.1, 4.7 Hz, 1 H), 1.25−1.20 (m, 1 H), 0.94 (s, 9 H), 0.87 (ddd, J = 12.6, 3.7, 1.0 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 134.1, 117.7, 96.8, 72.4, 68.2, 52.7, 47.5, 38.3, 33.3, 32.6, 31.9, 31.5, 28.7, 19.2; HRMS (EI) m/z (M^+) calcd 252.2089, obsd 252.2089.

(1*R,5*S**,6*S**)-1-Allyl-6-*tert*-butyl-2,4-dioxabicyclo[3.3.1]nonan-3-one (38).** A solution of **36** (30 mg, 0.14 mmol), 1,1′-carbonyldiimide (22 mg, 0.014 mmol), and a catalytic amount of DMAP in benzene (1.4 mL) was heated to reflux under N_2 for 12 h. TLC analysis showed the continued presence of starting material, and therefore a second equivalent of 1,1′-carbonyldiimide was added and heating was continued under N_2 for an additional 12 h. The reaction mixture was concentrated and the residue was purifed by chromatography on silica gel (elution with 20% ethyl acetate in hexanes) to yield 20 mg (58%) of **38** as a white solid, mp 90−91 °C: IR (KBr, cm^{-1}) 1718; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.86−5.72 (m, 1 H), 5.19−5.09 (m, 2 H), 4.91−4.90 (m, 1 H), 2.46−2.31 (m, 2 H), 2.16−2.00 (m, 2 H), 1.86−1.76 (m, 1 H), 1.72−1.51 (series of m, 3 H), 1.28−1.23 (m, 1 H), 0.98 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 150.0, 131.1, 119.9, 81.9, 75.6, 50.8, 44.9, 35.4, 34.0, 32.5, 28.2, 17.9; HRMS (EI) m/z ($M^+ + H$) calcd 239.1647, obsd 239.1666.

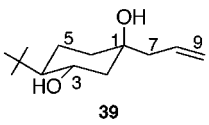
Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.56; H, 9.30. Found C, 70.40; H, 9.36.

Coupling Involving 8. Diols **39** and **40**, produced in ratios which differed with the reaction solvent (Scheme 15), were separated by gradient elution chromatography on silica gel (20−33% ethyl acetate in hexanes).

For **39**: colorless solid; mp 118−119 °C; IR (KBr, cm^{-1}) 3381 (br); ^{1}H NMR (300 MHz, C_6D_6) δ 5.82−5.68 (m, 1 H), 5.07−4.96 (m, 2 H), 3.85−3.80 (m, 1 H), 1.99−1.97 (m, 2 H), 1.63 (ddd, J = 12.8, 4.2, 2.9 Hz, 1 H), 1.52−1.41 (m, 1 H), 1.38−1.28 (m, 2 H), 1.11 (s, 9 H), 1.08−0.83 (series of m, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 134.0, 118.5, 72.1, 69.7, 53.4, 48.7,

48.2, 37.0, 33.1, 29.6, 22.2; HRMS (EI) m/z ($M^+ - C_3H_5$) calcd 171.1385, obsd 171.1373.

Anal. Calcd for $C_{13}H_{24}O_2$: C, 73.54; H, 11.39. Found C, 73.47; H, 11.27.

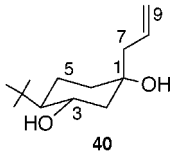


39

irradiate	observe	% NOE difference
H-8	H-2e	0.9
	H-6e	0.8
H-7,7"	H-2e	1.1
	H-6e	0.8
H-2e	H-8	1.3
	H-7,7"	1.5
	H-3	4.6

For **40**: colorless solid, mp 105−106 °C; IR (KBr, cm^{-1}) 3296 (br); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.95−5.81 (m, 1 H), 5.19−5.10 (m, 2 H), 3.84−3.78 (m, 1 H), 2.23−2.21 (m, 2 H), 2.16 (br s, 1 H), 1.98 (br s, 1 H), 1.88−1.67 (series of m, 2 H), 1.60 (dd, J = 13.2, 7.9 Hz, 1 H), 1.50−1.40 (m, 1 H), 1.29−1.11 (series of m, 3 H), 0.98 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 133.1, 119.2, 71.9, 69.7, 52.4, 45.0, 44.6, 36.6, 32.8, 29.1, 21.1; HRMS (EI) m/z ($M^+ - C_3H_5$) calcd 171.1385, obsd 171.1382.

Anal. Calcd for $C_{13}H_{24}O_2$: C, 73.54; H, 11.39. Found C, 73.39; H, 11.26.



40

irradiate	observe	% NOE difference
H-3	H-7,7'	2.7
	H-2a	3.0
	H-2e	1.3
	H-5a	1.4
H-7,7'	H-3	2.4
	H-2e	1.0
	H-5a	1.2

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