Intramolecular Cyclization of Tethered Phenyl Ketones. Complementary Stereochemical Results Arising from the Indium-Promoted Ring Closure of Allyl Bromides and the Fluoride Ion-Induced Desilylation of Allylsilanes

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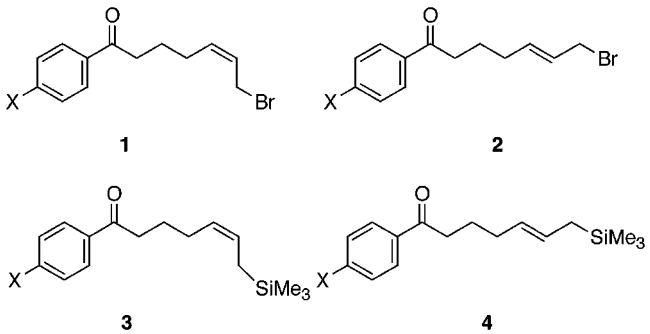
The intramolecular indium-promoted cyclization of 4′-substituted (*Z*)- and (*E*)-7-bromo-5-heptenophenones has been examined in aqueous tetrahydrofuran. In every instance, ring closure occurred to deliver the *syn*-2-vinylcyclopentanol exclusively. The corresponding allylsilanes have been prepared as well, and the course of their fluoride ion-induced cyclization was also studied. In these systems, a kinetic bias for formation of the *anti*-2-vinylcyclopentanol is observed, although not with the same exclusivity. Accordingly, complementarity in product diastereoselectivity can be realized in purposeful fashion. The data acquired in this investigation suggest that the indium-catalyzed reactions involve intramolecularly coordinated transition states where development of a cis 5/6-bicyclic framework is most energetically feasible. In contrast, the silanes appear to utilize open-chain antiperiplanar transition states. While the latter are not particularly sensitive to double-bond geometry, they are responsive to steric compression involving the aryl group.

Anionic cyclization reactions continue to be ranked among the premier ring-forming transformations in organic synthesis.[1] Significant effort has been expended in order to elucidate the stereochemical aspects of these processes. During the past several years, our research group has been probing the fundamental mechanistic issues and synthetic potential of the indium-promoted coupling of allyl bromides to open-chain aldehydes under aqueous conditions.[2] A major focus of this thrust has been to account for the impact of heteroatomic substituents positioned either α or β to the reacting carbonyl functionality on product stereochemistry. This work has provided a strong indication for transition-state chelate organization, notwithstanding the presence of vast amounts of water.[3] In the case of substrates lacking the potential for chelate organization, stereoinduction appears to be achieved by adherence to the Felkin−Ahn paradigm.[4]

In addition to the sensitivity to aldehyde structure, reaction diastereoselection was found to be controlled by oxophilic coordination of the In(III) atom to the carbonyl oxygen. This preorganization is seemingly necessary for activation of the carbonyl center to S_N2' attack. Should this mechanistic deduction be generally true, cyclization reactions carried out in this manner would be expected to proceed via "closed" transition states and to differ stereochemically from related processes that utilize "open" geometries to accomplish ring formation.

The present purpose was therefore to examine the stereochemical course of the intramolecular cyclization of allylic bromides **1** and **2** with indium metal in water and to make proper comparison with the fluoride ion-promoted ring closure of **3** and **4** in organic media.[5] If no constraints are applied to any of the four phenyl ketones, each reactant has available to it one or more distinctive limiting transition states. Options to modify the double-bond geometry on demand and to vary the electronic character of the carbonyl by substitution at X have been implemented. The collective results clearly show a significant difference between **1/2** on one hand and **3/4** on the other. The important product-determining features of these reactions are elucidated and shown to hold considerable synthetic potential for stereocontrolled 2-vinylcyclopentanol production.



Intramolecular anionic allylations of carbonyl compounds that use indium as the activating metal have been accorded little attention. The only example reports the conversion of **5** in highly selective fashion to cis-fused

(1) Thebtaranoth, C.; Thebtaranoth, Y. *Cyclization Reactions*; CRC Press: Boca Raton, FL; 1994.

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(3) (a) Paquette, L. A.; Mitzel, T. M. *J. Am. Chem. Soc.* **1996**, *118*, 1931. (b) Paquette, L. A.; Lobben, P. C. *J. Am. Chem. Soc.* **1996**, *118*, 1917. (c) Paquette, L. A.; Mitzel, T. M.; Isaac, M. B.; Crasto, C. F.; Schomer, W. W. *J. Org. Chem.* **1997**, *62*, 4293. (d) Paquette, L. A.; Lobben, P. C. *J. Org. Chem.* **1998**, *63*, 5604. (e) Lobben, P. C.; Paquette, L. A. *J. Org. Chem.* **1998**, *63*, 6990. (f) Paquette, L. A.; Rothhaar, R. R.; Isaac, M.; Rogers, L. R.; Rogers, R. D. *J. Org. Chem.* **1998**, *63*, 5463. (g) Paquette, L. A.; Rothhaar, R. R. *J. Org. Chem.* **1998**, *63*, in press.

(4) (a) Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199. (b) Ahn, N. T.; Eisenstein, O. *Nouv. J. Chim.* **1977**, *1*, 61.

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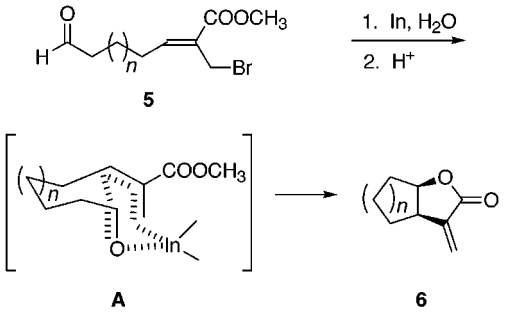
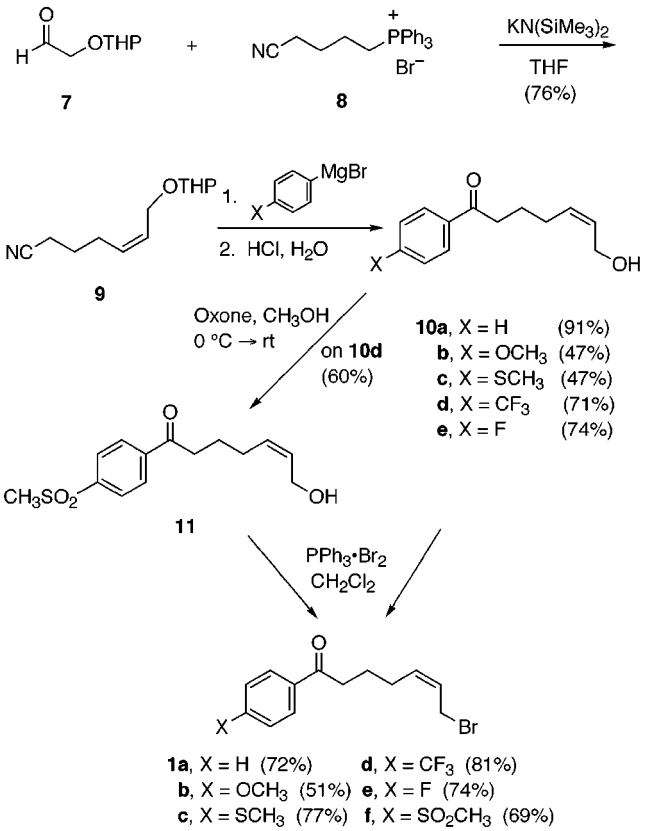
lactone **6**, presumably because of a preference for the pseudo-chair−chair conformation **A** over the alternative chair−boat option.[6]



Results

Synthesis of the Starting Materials. The *Z* allylic bromides of type **1** were prepared as shown in Scheme 1. Aldehyde **7**, readily available from inexpensive *cis*-2-

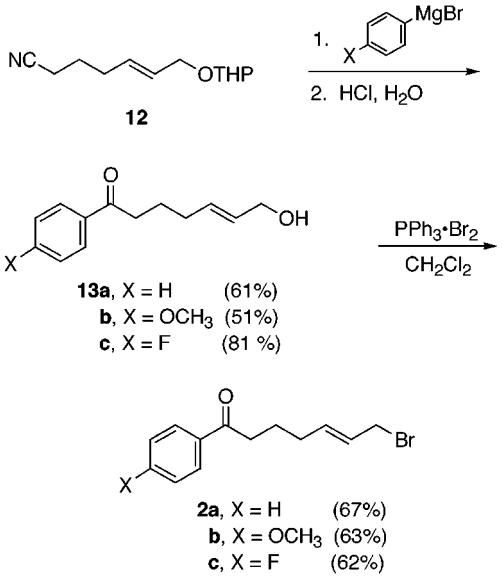
Scheme 1



butene-1,4-diol,[7] was coupled to the known phosphonium salt **8**[8] in tetrahydrofuran with potassium hexamethyldisilazide serving as the base. The resulting Wittig product **9** proved to be a versatile intermediate, lending itself suitably to condensation with five differently substituted arylmagnesium bromides. For direct conversion to keto alcohols **10**, the reaction mixtures were routinely processed through a mild acidic workup. The acquisition of the *p*-methanesulfonyl derivative **11** required only that **10c** be regioselectively oxidized with Oxone.[9] Treatment of **10a**−**e** and **11** with triphenylphosphine dibromide furnished **1** without detectable loss of double-bond configuration.

The *E* allylic bromides **2** were obtained in a comparable manner from the unsaturated nitrile **12** (Scheme 2).

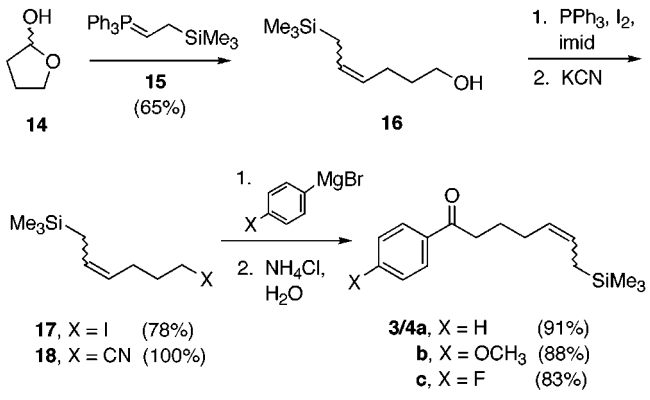
Scheme 2



While this substrate could not be formed from 5-oxopentanenitrile,[10] it proved particularly convenient to produce it from **9** by thiophenol-mediated olefin inversion.[11] Upon heating **9** with 0.5 equiv of thiophenol and 0.3 equiv of AIBN in benzene for 5−6 h, a 10:1 *E*/*Z* mixture was formed reproducibly and carried directly into coupling with the aryl Grignard reagents. The purification of **13a**−**c** was facilitated by the fact that they are low-melting solids amenable to recrystallization from ligroin/CH_2Cl_2 mixtures at 0 to −30 °C.

When it was recognized early on that both stereoisomeric allylsilanes underwent cyclization to the same product alcohol, the decision was made to generate **3** and **4** most simply as 2.5:1 *Z*/*E* mixtures. In this instance,

Scheme 3



the route began by Wittig reaction of γ-butyrolactol (**14**)[12] with ylide **15**[5b] (Scheme 3). Neither isomer of **16** pre-

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Table 1. Indium-Promoted Cyclizations of Allylic Bromides 1 and 2 in THF/H_2O (1:4) at 25 °C[a]

compd	X	reaction time, h	% conversion[a]	yield,[b] %	product ratio syn	product ratio anti
A. *Z* series						
1a	H	24	75	70	>98:2	
1b	OCH_3	20	77	73	>98:2	
1c	SCH_3	24	83	67	>98:2	
1d	CF_3	36	86	79	>98:2	
1e	F	24	91	87	>98:2	
1f	SO_2CH_3	9	50	38	>98:2	
B. *E* series						
2a	H	24	86	82	>98:2	
2b	OCH_3	21	80	70	>98:2	
2c	F	25	89	86	>98:2	

[a] Determined by integration of 300 MHz ^{1}H NMR spectra. [b] Yields are based on the amount of material obtained after chromatographic separation.

Table 2. Comparison of ^{1}H Chemical Shifts in 19 and 20 (δ Values at 300 MHz (C_6D_6 Solution)[a]

compd	X	H_a	H_b/H_c	H_d
19a	H	5.74−5.63	4.96−4.88	2.68−2.60
19b	OCH_3	5.81−5.70	5.01−4.92	2.65−2.62
19c	SCH_3	5.78−5.66	5.15−5.04	2.91−2.83
19d	CF_3[a]	5.58−5.46	4.92−4.80	2.49−2.41
19e	F	5.65−5.54	4.94−4.81	2.50−2.42
19f	SO_2CH_3	5.63−5.52	4.91−4.89	2.48−2.40
20a	H	5.32−5.21	4.83−4.67	2.74−2.67
20b	OCH_3	5.42−5.30	4.90−4.75	2.80−2.73
20c	F	5.25−5.14	4.81−4.70	2.67−2.60

[a] Data recorded in $CDCl_3$ solution.

sented any special handling problems in that they underwent ready conversion to iodides **17** in 78% yield upon reaction with triphenylphosphine and iodine. Treatment of **17** with potassium cyanide in DMF gave nitriles **18** quantitatively. These substances were readily converted to **3/4a**−**c** via the process employed above.

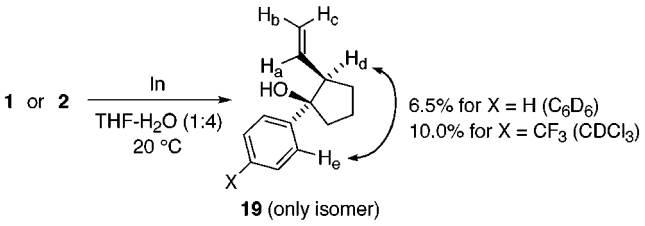
Cyclization Reactions Involving Bromides 1 and 2. Reactants **1a**−**f** and **2a**−**c** were uniformly subjected to the action of powdered indium metal (3 equiv) in a solvent system constituted of 20% THF and 80% water. In each instance, the progress of reaction was monitored by thin-layer chromatography. When the rate of cyclization slowed visibly, product isolated was undertaken. The global results are compiled in Table 1. The methylsulfonyl derivative **1f** behaves in somewhat anomalous fashion, with ring closure occurring relatively rapidly at the outset but coming to a virtual stop after approximately 50% consumption of the reactant. As is customary for these processes, the purposeful introduction of more indium at this point has no obvious effect, particularly in advancing the ring closure. The phenomenon is due in large part to the enhanced acidity of the reaction mixtures at this stage (pH ~4),[3a] one consequence of which is to promote rapid solvolysis of the bromide to its corresponding alcohol (**10** or **11**). The latter were routinely isolated during the chromatographic purification step.

Carbinols **19a**−**f** were readily obtained in isomerically pure form. The structural assignment to **19a** rests on NOE data as indicated and chemical shift values recorded in C_6D_6 solution. Both parameters distinguish this isomer clearly from **20a**. As is evident in Table 2, the vinyl proton H_a in **19a** (δ 5.74−5.63) appears well downfield of its counterpart in **20a** (δ 5.32−5.21), this ordering being invariant through the series. This distinction applies as well to the terminal vinyl protons H_b and H_c, which are clearly visible in the range δ 4.96−4.88 in **19a** and δ 4.83−4.67 in **20a**. Finally, the allylic proton H_d is also distinctive in the two series, that in syn isomer **19a** (δ 2.68−2.60) appearing upfield of the **20a** example (δ 2.74−2.67). In none of the cases studied was more than a trace of **20** produced from **1** and **2** as judged by 300 MHz ^{1}H NMR analysis.

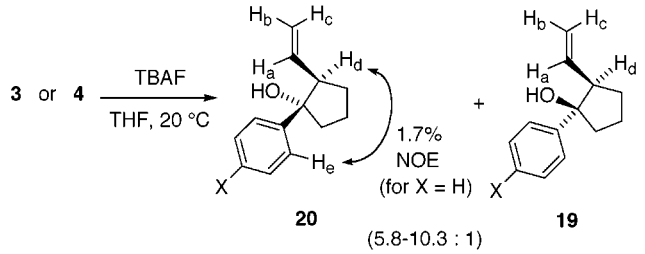
Table 3. Fluoride Ion-Promoted Cyclizations of Allylsilanes 3 and 4 in THF at 25 °C

compd	X	reaction time, h	% conversion[a]	syn product yield,[b] %	anti product yield,[b] %	ratio syn/anti
3/4a	H	16	>97	8	82	1:10.3
3/4b	OCH_3	16	95	8	76	1:9.5
3/4c	F	16	82	11	11	1:5.8

[a] Determined by integration of 300 MHz ^{1}H NMR spectra. [b] Yields are based on the amount of material obtained after chromatographic purification.



Ring Closure of the Allylsilanes. Results for the cyclization of **3** and **4** are tabulated in Table 3. Carbinol production occurred with isolated yields in the 75−90% range. In all three examples, the anti isomer was significantly favored but never formed exclusively. Quite



obviously, the response of the allylsilanes toward fluoride ion is not as diastereoselective as that of the allylic bromides toward indium metal. Nonetheless, the pair of reactions are usefully complementary in their ability to produce tertiary cyclopentanols having vicinal stereogenic centers with good to excellent control of the stereochemical outcome.

Discussion of Results

Indium-Mediated Cyclizations. The ring closure of bromides **1** and **2** induced by stirring with indium powder in aqueous THF gave the *syn*-2-vinylcyclopentanols **19** irrespective of the double-bond geometry in the starting material. The good yields realized in these intramolecular 1,2-additions (Table 1) indicate that both isomers react with comparable efficiency under conditions that have been held constant. The accepted mechanism for

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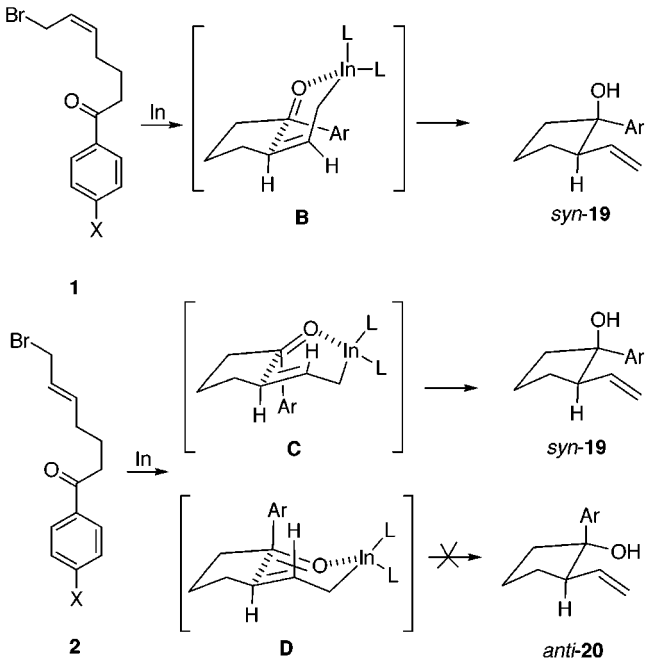
Scheme 4. Cyclic Allylindium Transition State Models for the *Z*- and *E*-Isomers



the activation of allylic bromides by indium,[2,13] which involves oxidative addition of the metal into the C−Br bond with formation of a reactive In(III) species, is assumed to be operative presently. Under these circumstances, the heavy predominance of *syn*-**19** resulting from the *Z*-isomers **1** can be explained in terms of transition state **B** (Scheme 4). This cis-fused bicyclic arrangement, an equivalent to which has been invoked in allylstannane chemistry,[14] allows for unconstrained intramolecular coordination of the In(III) center with the carbonyl oxygen while predisposing the aryl substituent in a quasiequatorial orientation. No other structural option offers so many comparable advantages. In fact, **B** represents the only possibility if coordination of In to the carbonyl oxygen atom is as important as we consider it to be.

When the double bond is of the *E* geometry as in **2**, the two reasonable transition states labeled as **C** and **D** are worthy of consideration. The facts are that the cyclizations of **2** proceed as smoothly as those involving **1**, and with an equally strong and overriding preference for the delivery of syn product. This is as expected for the cis-fused bicyclic transition state **C** but is incompatible with the utilization of **D**. One distinction between these two options is the boatlike arrangement of the developing organometallic ring in **C**, in contrast to its chairlike character in **D**. In view of the relatively large size of indium, these energetic considerations appear to pale in importance relative to the issue of cis (as in **C**) or trans ring junction (as in **D**). The trans-fused model gives evidence of not serving as a viable pathway for product formation, perhaps because it shares in the thermodynamic instability associated with trans-fused 5−6 ring systems.

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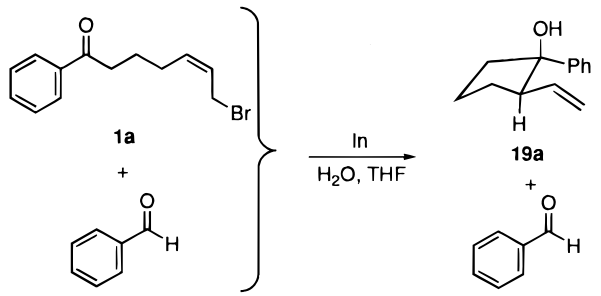
(14) Kadota, I.; Kawada, M.; Gevorgyan, V.; Yamamoto, Y. *J. Org. Chem.* **1997**, *62*, 7439.

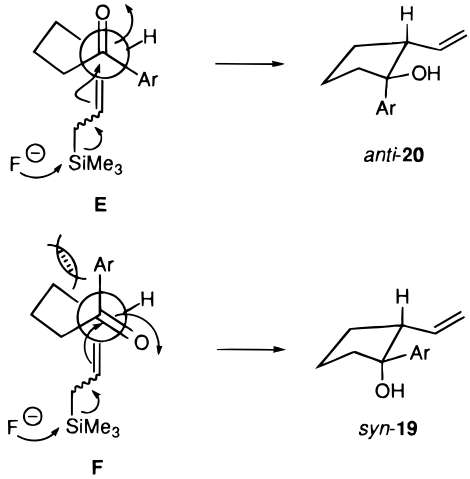
Competition Studies. In early studies, ketones were regarded to be minimally reactive toward allylindium reagents. Many deviations from this generic assumption have since been recognized, including the results recorded here. Since aldehydes are unquestionably more reactive than ketones in the absence of steric factors, we were attracted to examine whether the indium reagent derived from **1a** would capture benzaldehyde in an intermolecular progress more rapidly than undergo intramolecular cyclization. Although first-order reactions are rarely observed to be intercepted by higher-order alternatives, the structural circumstances in this instance could not be ignored.



In actual fact, when equimolar amounts of **1a** and benzaldehyde were admixed with a comparable quantity of indium, only ring closure to **19a** was observed. This kinetic preference provides strong supportive evidence for intramolecular coordination as shown in Scheme 4.

Fluoride Ion-Induced Cyclizations. The closely comparable ring closures of **3** and **4**, when performed with TBAF in THF at room temperature, show the opposite stereoselectivity, giving rise instead to the *anti*-cyclopentanols **20** predominantly. This group of reactions is not stereocontrolled to the extent observed in the indium examples but provides direct entry into the opposite configurational series. In line with convention,[5] it is most probable that anionic intermediates generated by the attack of F^- at silicon intervene in a so-called "push−pull" process (Scheme 5). The antiperiplanar transition-

Scheme 5



state models **E** and **F** explain satisfactorily the preference exhibited by the keto allylsilanes under study. Thus, the limiting reactive conformation in all six examples corresponds to **E**. This may be because in **F** steric compression develops between the aryl substituent and the

interconnective trimethylene chain. Since **3a** and **4a** generate the same product distribution, a phenomenon likewise reflected in the para-substituted derivatives, the *Z* or *E* character of the double bond is clearly a noninfluential factor on product stereochemistry. We do see, however, that the syn/anti ratio increases from 1:10.3 when X = H to 1:5.8 when X = F.

The more competitive nature of the **E/F** options as the para substituent is made increasingly more electron withdrawing may reflect increased electrophilicity at the carbonyl carbon in **3/4c**, with resultant leveling of the rates of cyclization along both reaction trajectories.

Summary

The intramolecular cyclization of allylic bromo ketones **1** and **2** as promoted by indium in water proceeds with exceptionally high discrimination for the *syn*-2-vinylcyclopentanol irrespective of the *E* or *Z* double-bond geometry and the electronic character of para substituent X. This notable stereoselectivity is believed to be achieved because of the adoption of transition states **B** and **C**, which share a distinctive cis-fused 5/6-bicyclic nature. Ring closure of the structurally related allylsilanes **3** and **4** also proceeds without concern for starting double-bond geometry. For this series of compounds, however, *anti*-cyclopentanol formation is dominant. The stereochemical bias for the production of **20** is not wholesale, reaching a maximum level of 10.3:1 in the parent system (X = H). Therefore, utilization of acyclic transition state **E** is kinetically preferred, but ground is lost to the somewhat more congested option **F** as X is made increasingly electronegative. Nevertheless, the complementary diastereocontrol exhibited by these two classes of reactions holds synthetic potential as they provide the means for controlling stereoinduction at a fully substituted carbon atom. The present reactions bear an overall relationship to select samarium(II)-promoted cyclizations.[15]

Experimental Section

General Information. Yields were calculated for material judged to be homogeneous by TLC and NMR. Magnetic stirring was used for all reactions. Thin-layer chromatography was performed on Merck Kieselgel 60 F_{254} aluminum-backed plates. Flash column chromatography was accomplished in glass columns with Woelm silica gel (230−400 mesh). NMR spectra were acquired at 300 MHz for ^{1}H and 75 MHz for ^{13}C. Melting points are uncorrected. Solvents were reagent grade and in most cases dried prior to use. The high-resolution mass spectra were obtained at The Ohio State University Chemical Instrumentation Center. Elemental analyses were performed by Atlantic Microlab, Norcross, GA.

(*Z*)-7-[(Tetrahydro-2*H*-pyran-2-yl)oxy]-5-heptenenitrile (9). A solution of **8**[8] (38.3 g, 90.2 mmol) in dry THF (500 mL) was treated with potassium hexamethyldisilazide (198 mL of 0.5 M in toluene, 90.2 mmol) and stirred for 1.5 h. Aldehyde **7**[7] (10.0 g, 69.4 mmol) was dissolved in dry THF (30 mL) and introduced dropwise. After 4 h, the solvent was evaporated under reduced pressure, and the residue was taken up in ether prior to filtration through a pad of silica gel. After the pad was rinsed several times with ether, the filtrate was concentrated under reduced pressure. The residue was chromatographed on silica gel (elution with 20% ethyl acetate in petroleum ether) to give 11.0 g (76%) of **9** as a colorless liquid: IR (neat, cm^{-1}) 2245, 1656, 1077; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.68−5.60 (m, 1 H), 5.52−5.44 (m, 1 H), 5.47 (m, 1 H), 4.23 (ddd, J = 12.3, 6.1, 0.3 Hz, 1 H), 4.04 (dd, J = 12.3, 7.1 Hz, 1 H), 3.83 (m, 1 H), 3.48 (m, 1 H), 2.31 (t, J = 7.2 Hz, 1 H), 2.22 (q, J = 7.3 Hz, 1 H), 1.87−1.62 (m, 4 H), 1.61−1.46 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 130.4, 128.2, 119.4, 97.9, 62.4, 62.1, 30.5, 26.2, 25.3, 25.0, 19.4, 16.3; HRMS *m*/*z* (M^+) calcd 209.1416, obsd 209.1406.

Anal. Calcd for $C_{12}H_{19}NO_2$: C: 68.86; H, 9.15. Found: C, 68.74; H, 9.15.

(*Z*)-7-Hydroxy-5-heptenophenone (10a). A 2.03 g (9.69 mmol) sample of **9** was added dropwise to a solution of phenylmagnesium bromide in ether (110 mL of 0.17 M, 18.7 mmol) at 0 °C. The reaction mixture turned cloudy, and a white solid precipitated. After 15 min, water (20 mL) was added, and stirring was maintained for another 15 min. The ether was evaporated under reduced pressure, and the remaining material was taken up in 100 mL of water/methanol (1:3), cooled to 0 °C, and treated slowly with 15 mL of 10% HCl. The mixture was allowed to warm to room temperature, and deprotection with liberation of the allylic alcohol was monitored by TLC. The product was extracted into CH_2Cl_2 (4×), and the combined organic phases were washed with brine, dried, and evaporated. The concentrate was chromatographed on silica gel (elution with 20% ethyl acetate in petroleum ether) to give 1.80 g (91%) of **10a** as a colorless oil: IR (neat, cm^{-1}) 3419, 1682, 1597, 1448; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (d, J = 8.0 Hz, 2 H), 7.56−7.40 (m, 3 H), 5.69−5.47 (m, 2 H), 4.16 (d, J = 6.7 Hz, 2 H), 2.95 (t, J = 7.2 Hz, 2 H), 2.25 (br s, 1 H), 2.15 (q, J = 7.3 Hz, 2 H), 1.81 (quintet, J = 7.2 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.4, 136.8, 133.0, 131.6, 129.6, 128.5, 128.0, 58.2, 37.5, 26.6, 23.9; HRMS *m*/*z* (M^+) calcd 204.1150, obsd 204.1141.

Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.33; H, 7.86.

(*Z*)-7-Hydroxy-4′-methoxy-5-heptenophenone (10b). Compound **10b** was formed as above in 47% yield: colorless oil; IR (neat, cm^{-1}) 3422, 1672, 1600; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (d, J = 8.8 Hz, 2 H), 6.91 (d, J = 8.8 Hz, 2 H), 5.65 (m, 1 H), 5.51 (m, 1 H), 4.15 (d, J = 6.7 Hz, 2 H), 3.84 (s, 3 H), 2.90 (t, J = 7.2 Hz, 2 H), 2.15 (q, J = 7.3 Hz, 2 H), 2.04 (br s, 1 H), 1.80 (quintet, J = 7.2 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.0, 163.4, 131.8, 130.3, 130.2, 129.9, 129.5, 113.6, 58.2, 55.4, 37.2, 26.6, 24.2; HRMS *m*/*z* (M^+) calcd 234.126, obsd 234.125.

(*Z*)-7-Hydroxy-4′-(methylthio)-5-heptenophenone (10c). Compound **10c** was formed as above in 47% yield: colorless crystals; mp 77−78 °C; IR ($CHCl_3$, cm^{-1}) 3614, 3492, 1675, 1589; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 (d, J = 8.5 Hz, 2 H), 7.24 (d, J = 8.5 Hz, 2 H), 5.70−5.62 (m, 1 H), 5.56−5.50 (m, 1 H), 4.17 (d, J = 6.7 Hz, 2 H), 2.92 (t, J = 7.2 Hz, 2 H), 2.50 (s, 3 H), 2.16 (q, J = 7.2 Hz, 2 H), 1.85−1.76 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.3, 145.8, 133.1, 131.8 (2 C), 129.5, 128.4, 125.0, 58.3, 37.3, 26.6, 24.1, 14.7; HRMS *m*/*z* (M^+) calcd 250.103, obsd 250.106.

Anal. Calcd for $C_{14}H_{18}O_2S$: C, 67.17; H, 7.25. Found: C, 67.30; H, 7.30.

(*Z*)-7-Hydroxy-4′-(trifluoromethyl)-5-heptenophenone (10d). A solution of [4-(trifluoromethyl)phenyl]magnesium bromide (47.8 mmol) in 4:1 benzene/ether (100 mL) was vigorously refluxed while **9** (5.00 g, 23.9 mmol) was introduced dropwise. After 15 min of additional heating, the reaction mixture was cooled to room temperature, quenched with water (20 mL), and stirred for 15 min. After application of the predescribed workup, there was isolated 4.65 g (71%) of **10d** as a pale yellow oil: IR (neat, cm^{-1}) 3372, 1691, 1410; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (d, J = 8.1 Hz, 2 H), 7.72 (d, J = 8.1 Hz, 2 H), 5.68 (m, 1 H), 5.53 (m, 1 H), 4.18 (d, J = 6.8 Hz, 2 H), 3.00 (t, J = 7.1 Hz, 2 H), 2.19 (q, J = 7.3 Hz, 2 H), 1.84 (quintet, J = 7.3 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.2, 139.5, 134.6, 131.7, 129.7, 128.4, 125.7, 121.8, 58.4, 37.9, 26.6, 23.7; HRMS *m*/*z* (M^+) calcd 272.1024, obsd 272.0997.

Anal. Calcd for $C_{14}H_{15}F_3O_2$: C, 61.76; H, 5.55. Found: C, 61.61; H, 5.56.

(*Z*)-4′-Fluoro-7-hydroxy-5-heptenophenone (10e). Compound **10e** was prepared as for **10a** in 74% yield: colorless oil; IR (neat, cm^{-1}) 3415, 1684, 1597, 1506; ^{1}H NMR (300 MHz,

(15) (a) Kan, T.; Nara, S.; Ito, S.; Matsuda, F.; Shirahama, H. *J. Org. Chem.* **1994**, *59*, 5111. (b) Molander, G. A.; Shakya, S. R. *J. Org. Chem.* **1996**, *61*, 5885. (c) Curran, D. P.; Gu, X.; Zhang, W.; Dowd, P. *Tetrahedron* **1997**, *53*, 9023.

$CDCl_3$) δ 7.99−7.94 (m, 2 H), 7.15−7.08 (m, 2 H), 5.70−5.62 (m, 1 H), 5.57−5.47 (m, 1 H), 4.16 (d, J = 6.7 Hz, 2 H), 2.94 (t, J = 7.2 Hz, 2 H), 2.17 (q, J = 7.2 Hz, 2 H), 1.86−1.77 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.7, 165.7 (d, J = 255 Hz), 133.3, 131.8, 130.7 (d, J = 8.8 Hz), 129.6, 115.6 (d, J = 22 Hz), 58.3, 37.5, 26.6, 23.9; HRMS m/z (M^+) calcd 222.1056, obsd 222.1026.

Anal. Calcd for $C_{13}H_{15}FO_2$: C, 70.25; H, 6.80. Found: C, 70.52; H, 6.87.

(*Z*)-7-Hydroxy-4′-(methylsulfonyl)-5-heptenophenone (11). Half of a solution of Oxone (730 mg, 1.19 mmol) in 8 mL of potassium dihydrogen phosphate buffer (pH = 4.5) was added dropwise to a solution of **10c** (198 mg, 0.79 mmol) in methanol (8 mL) at 0 °C. The reaction mixture was warmed to room temperature, and the remainder of the oxidant was added in four portions during 30 min. Upon completion of this process, stirring was maintained for 1 h prior to dilution with water and extraction with $CHCl_3$. The combined extracts were dried and concentrated to leave a residue that was purified chromatographically on silica gel (elution with 50% ethyl acetate in petroleum ether). There was isolated 134 mg (60%) of **11** as a colorless crystalline solid: mp 70−71 °C; IR ($CHCl_3$, cm^{-1}) 3615, 1693, 1321; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11 (d, J = 8.4 Hz, 2 H), 8.04 (d, J = 8.5 Hz, 2 H), 5.72−5.66 (m, 1 H), 5.55−5.52 (m, 1 H), 4.18 (d, J = 6.7 Hz, 2 H), 3.08 (s, 3 H), 3.02 (t, J = 7.1 Hz, 2 H), 2.20 (q, J = 7.3 Hz, 2 H), 1.85 (quintet, J = 7.2 Hz, 2 H), 1.52 (br s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.7, 144.1, 140.8, 131.7, 129.7, 128.9, 127.8, 58.4, 44.3, 38.1, 26.6, 23.6; HRMS m/z (M^+ − OH) calcd 265.090, obsd 265.090.

Anal. Calcd for $C_{14}H_{18}O_4S$: C, 59.55; H, 6.43. Found: C, 59.43; H, 6.44.

(*Z*)-7-Bromo-5-heptenophenone (1a). Alcohol **10a** (0.95 g, 4.6 mmol) was dissolved in dry CH_2Cl_2 (50 mL), cooled to −20 °C, treated with triphenylphosphine (1.34 g, 5.1 mmol), and stirred for 30 min. Bromine (0.26 mL, 5.1 mmol) was introduced dropwise, and the reaction mixture was quenched with methanol after 30 min. The solvent was evaporated under reduced pressure, and the residue was chromatographed on Florisil (elution with 5% ether in petroleum ether) to afford 0.89 g (72%) of **1a** as a yellowish oil: IR (neat, cm^{-1}) 1684, 1602, 1443, 1360; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (d, J = 7.2 Hz, 2 H), 7.54 (t, J = 7.2 Hz, 1 H), 7.44 (t, J = 7.2 Hz, 2 H), 5.80−5.74 (m, 1 H), 5.65−5.57 (m, 1 H), 3.99 (d, J = 8.3 Hz, 2 H), 3.00 (t, J = 7.3 Hz, 2 H), 2.25 (q, J = 7.2 Hz, 2 H), 1.87 (quintet, J = 7.3 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.8, 136.9, 134.8, 132.9, 128.5, 126.2, 37.6, 27.1, 26.2, 23.3; HRMS m/z (M^+) calcd 265.0228, obsd 265.0197.

(*Z*)-7-Bromo-4′-methoxy-5-heptenophenone (1b). Compound **1a** was obtained from **10b** as described above in 51% yield: colorless oil; IR (neat, cm^{-1}) 1674, 1600, 1258, 1170; ^{1}H NMR (300 MHz, C_6D_6) δ 7.88 (d, J = 8.9 Hz, 2 H), 6.67 (d, J = 8.9 Hz, 2 H), 5.57−5.47 (m, 1 H), 5.30−5.22 (m, 2 H), 3.63 (d, J = 8.4 Hz, 2 H), 3.22 (s, 3 H), 2.53 (t, J = 7.1 Hz, 2 H), 1.89 (q, J = 7.5 Hz, 2 H), 1.67 (quintet, J = 7.1 Hz, 2 H); ^{13}C NMR (75 MHz, C_6D_6) δ 197.1, 163.5, 135.0, 130.7, 130.4, 126.4, 113.9, 54.9, 37.3, 27.1, 26.4, 23.6; HRMS m/z (M^+) calcd 296.0142, obsd 296.1379.

(*Z*)-7-Bromo-4′-(methylthio)-5-heptenophenone (1c). Compound **1c** was prepared in the manner described above in 77% yield: colorless oil; IR ($CHCl_3$, cm^{-1}) 1677, 1556, 1437; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (d, J = 8.6 Hz, 2 H), 7.24 (d, J = 8.6 Hz, 2 H), 5.81−5.71 (m, 1 H), 5.63−5.55 (m, 1 H), 3.98 (d, J = 8.3 Hz, 2 H), 2.93 (t, J = 7.4 Hz, 2 H), 2.50 (s, 3 H), 2.23 (q, J = 7.4 Hz, 2 H), 1.84 (q, J = 7.4 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.8, 145.6, 134.8, 133.2, 128.3, 126.2, 124.9, 37.4, 27.1, 26.2, 23.3, 14.7; HRMS m/z (M^+) calcd 312.0183, obsd 312.0142.

(*Z*)-7-Bromo-4′-(trifluoromethyl)-5-heptenophenone (1d). Compound **1d** was produced in 81% yield according to the predescribed protocol: colorless oil; IR (neat, cm^{-1}) 1693, 1410, 1326, 1128; ^{1}H NMR (300 MHz, C_6D_6) δ 7.63 (d, J = 8.2 Hz, 2 H), 7.31 (d, J = 8.2 Hz, 2 H), 5.59−5.48 (m, 1 H), 5.29−5.20 (m, 1 H), 3.63 (d, J = 8.4 Hz, 2 H), 2.39 (t, J = 7.2 Hz, 2 H), 1.87 (q, J = 7.2 Hz, 2 H), 1.58 (quintet, J = 7.2 Hz, 2 H); ^{13}C NMR (75 MHz, C_6D_6) δ 197.6, 139.9, 134.7, 128.4, 126.6, 125.64, 125.59, 125.54, 37.8, 26.9, 26.2, 23.1; HRMS m/z (M^+) calcd 334.0189, obsd 334.0152.

(*Z*)-7-Bromo-4′-fluoro-5-heptenophenone (1e). Compound **1e** was prepared in the manner described above in 81% yield: colorless oil; IR (neat, cm^{-1}) 1685, 1598, 1506; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01−7.94 (m, 2 H), 7.15−7.07 (m, 2 H), 5.83−5.73 (m, 1 H), 5.64−5.56 (m, 1 H), 3.99 (d, J = 8.3 Hz, 2 H), 2.97 (t, J = 7.3 Hz, 2 H), 2.24 (q, J = 7.3 Hz, 2 H), 1.86 (quintet, J = 7.3 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.8, 133.3, 130.6 (d, J = 9.6 Hz), 126.3, 115.6 (d, J = 21.8 Hz), 37.6, 27.0, 26.2, 23.2; HRMS m/z (M^+) calcd 286.0192, obsd 286.0218.

(*Z*)-7-Bromo-4′-(methylsulfonyl)-5-heptenophenone (1f). Compound **1f** was prepared in the manner described above in 69% yield: colorless oil; IR (neat, cm^{-1}) 1691, 1438, 1398, 1153; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08 (d, J = 8.4 Hz, 2 H), 7.99 (d, J = 8.4 Hz, 2 H), 5.80−5.71 (m, 1 H), 5.61−5.52 (m, 1 H), 3.96 (d, J = 8.3 Hz, 2 H), 3.04−2.99 (m, 5 H), 2.22 (q, J = 7.2 Hz, 2 H), 1.84 (quintet, J = 7.2 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.5, 148.7, 143.9, 134.5, 128.7, 127.6, 126.3, 44.1, 38.0, 27.0, 26.0, 22.8; HRMS m/z (M^+) calcd 344.0082, obsd 344.0037.

(*E*)-7-[(Tetrahydro-2*H*-pyran-2-yl)oxy]-5-heptenenitrile (12). To a solution of **9** (2.0 g, 9.5 mmol) and thiophenol (0.49 mL, 4.25 mmol) in refluxing benzene (200 mL) was added AIBN (500 mg, 3.0 mmol) in three portions over a 6-h period. The solvent was evaporated, and the 10:1 *E*/*Z* mixture (^{1}H NMR analysis) was purified by flash chromatography on silica gel (elution with 20% ethyl acetate in ligroin) to provide 1.59 g (81%) of **12** as a yellowish oil: IR (neat, cm^{-1}) 2245, 1669, 1455; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.65 (m, 2 H), 4.62 (m, 1 H), 4.19 (m, 1 H), 3.90 (m, 2 H), 3.50 (m, 1 H), 2.34 (t, J = 7.2 Hz, 2 H), 2.20 (m, 2 H), 1.89−1.67 (m, 4 H), 1.66−1.50 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 130.9, 128.7, 119.5, 98.0, 67.4, 62.3, 31.0, 30.6, 25.4, 24.7, 19.5, 16.4 HRMS m/z (M^+) calcd 209.1416, obsd 209.1390.

Anal. Calcd for $C_{12}H_{19}NO_2$: C, 68.87; H, 9.15. Found: C, 68.94; H, 9.22.

(*E*)-7-Hydroxy-5-heptenophenone (13a). Compound **13a** was prepared as described above for **10a** in 61% yield and crystallized from CH_2Cl_2/petroleum ether at −30 °C to yield a colorless oil at room temperature: IR (neat, cm^{-1}) 3409, 1682, 1597, 1580; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (dd, J = 8.5, 1.4 Hz, 2 H), 7.56−7.50 (m, 1 H), 7.42 (dd, J = 8.5, 7.1 Hz, 2 H), 5.73−5.53 (m, 2 H), 4.07−4.05 (m, 2 H), 2.95 (t, J = 7.3 Hz, 2 H), 2.16−2.09 (m, 2 H), 1.82 (quintet, J = 7.3 Hz, 2 H), 1.78 (br s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) 200.3, 136.9, 132.9, 131.8, 129.9, 128.5, 127.9, 63.4, 37.6, 31.6, 23.5; HRMS m/z (M^+) calcd 204.1150, obsd 204.1142.

Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.15; H, 7.93.

(*E*)-7-Hydroxy-4′-methoxy-5-heptenophenone (13b). Compound **13b** was obtained as a thick colorless oil at room temperature, obtained by crystallization from CH_2Cl_2/petroleum ether at 0 °C in 51% yield: IR (neat, cm^{-1}) 3425, 1666, 1595; ^{1}H NMR (300 MHz, C_6D_6) δ 8.36 (d, J = 8.9 Hz, 2 H), 6.68 (d, J = 8.9 Hz, 2 H), 5.60 (m, 2 H), 4.04 (s, 2 H), 3.28 (s, 3 H), 2.76 (s, 1 H), 2.62 (t, J = 7.3 Hz, 2 H), 1.99 (m, 2 H), 1.77 (quintet, J = 7.2 Hz, 2 H); ^{13}C NMR (75 MHz, C_6D_6) δ 198.2, 163.6, 131.2, 130.9, 130.7, 130.5, 113.9, 63.4, 55.0, 37.5, 32.0, 24.2; HRMS m/z (M^+) calcd 234.1256, obsd 234.1247.

Anal. Calcd for $C_{14}H_{18}O_4S$: C, 59.55; H, 6.43. Found: C, 59.43; H, 6.44.

(*E*)-4′-Fluoro-7-hydroxy-5-heptenophenone (13c): white crystals; mp 56−57 °C (from CH_2Cl_2/petroleum ether at 0 °C) in 81% yield; IR ($CHCl_3$, cm^{-1}) 3609, 1679, 1599; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (dd, J = 8.6, 5.4 Hz, 2 H), 7.11 (t, J = 8.6 Hz, 2 H), 5.67 (m, 2 H), 4.08 (d, J = 4.1 Hz, 2 H), 2.93 (t, J = 7.3 Hz, 2 H), 2.14 (m, 2 H), 1.84 (q, J = 7.3 Hz, 2 H), 1.63 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.5, 165.6 (d, J = 254 Hz), 133.4, 131.9, 130.6 (d, J = 9.5 Hz), 130.0, 115.6 (d, J = 21.9 Hz), 63.5, 37.6, 31.6, 23.5; HRMS m/z (M^+) calcd 222.1056, obsd 222.1052.

Anal. Calcd for $C_{13}H_{15}FO_2$: C, 70.25; H, 6.80. Found: C, 70.52; H, 6.87.

(*E*)-7-Bromo-5-heptenophenone (2a): colorless oil (67%); IR (neat, cm^{-1}) 1683, 1597, 1448; ^1H NMR (300 MHz, C_6D_6) δ 7.86 (dd, J = 8.0, 1.6 Hz, 2 H), 7.22−7.12 (m, 3 H), 5.49−5.32 (m, 2 H), 3.58 (d, J = 7.2 Hz, 2 H), 2.52 (t, J = 7.2 Hz, 2 H), 1.84 (q, J = 7.2 Hz, H), 1.66 (m, 2 H); ^{13}C NMR (75 MHz, C_6D_6) δ 198.5, 137.6, 135.5, 132.7, 128.6, 128.2, 127.4, 37.4, 33.1, 31.5, 23.3; HRMS m/z (M^+) calcd 266.0306, obsd 266.0324.

(*E*)-7-Bromo-4′-methoxy-5-heptenophenone (2b): colorless oil (63%); IR (neat, cm^{-1}) 1674, 1599, 1510; ^1H NMR (300 MHz, C_6D_6) δ 7.86 (d, J = 8.8 Hz, 2 H), 6.88 (d, J = 8.8 Hz, 2 H), 5.47−5.27 (m, 2 H), 3.55 (d, J = 7.2 Hz, 2 H), 3.25 (s, 3 H), 2.52 (t, J = 7.1 Hz, 2 H), 1.84 (q, J = 7.1 Hz, 2 H), 1.67 (q, J = 7.1 Hz, 2 H); ^{13}C NMR (75 MHz, C_6D_6) δ 197.2, 163.5, 135.7, 130.7, 130.4, 127.3, 113.9, 54.9, 37.1, 33.2, 31.6, 23.5; HRMS m/z (M^+) calcd 296.0412, obsd 296.0430.

(*E*)-7-Bromo-4′-fluoro-5-heptenophenone (2c): colorless oil (62%); IR (neat, cm^{-1}) 1682, 1597, 1505; ^1H NMR (300 MHz, C_6D_6) δ 7.62 (dd, J = 8.9, 5.5 Hz, 2 H), 6.68 (t, J = 8.9 Hz, 2 H), 5.44−5.25 (m, 2 H), 3.51 (d, J = 7.3 Hz, 2 H), 2.33 (t, J = 7.1 Hz, 2 H), 1.77 (q, J = 7.1 Hz, 2 H), 1.58 (quintet, J = 7.1 Hz, 2 H); ^{13}C NMR (75 MHz, C_6D_6) δ 198.6, 165.7 (d, J = 253 Hz), 135.3, 133.9 (d, J = 3 Hz), 130.7 (d, J = 9 Hz), 127.5, 115.5 (d, J = 2 Hz), 37.2, 32.9, 31.4, 23.2; HRMS m/z (M^+) calcd 284.0212, obsd 284.0258.

6-(Trimethylsilyl)-4-hexen-1-ol (16). A stirred suspension of methyltriphenylphosphonium bromide (29.47 g, 82.5 mmol) in dry THF (100 mL) was cooled to 0 °C, treated with *n*-butyllithium (56.7 mL of 1.6 M in hexanes, 90.7 mmol), warmed to room temperature, stirred for 1 h, and recooled to 0 °C. After the addition of (iodomethyl)trimethylsilane (17.67 g, 82.5 mmol), the mixture was again allowed to warm to room temperature, stirred for 1 h, cooled to −78 °C, and treated again with *n*-butyllithium (56.7 mL of 1.6 M in hexanes, 90.7 mmol). The dark red solution was stirred for 1.5 h at 20 °C, cooled to 0 °C, and treated during 20 min with a solution of γ-butyrolactol (3.30 g, 37.5 mmol) in dry THF (20 mL). The mixture was allowed to warm slowly to room temperature, stirred overnight, and quenched with saturated NH_4Cl solution (100 mL). The aqueous phase was extracted with ether (3 × 50 mL), and the combined organic layers were washed with brine (75 mL), dried, and concentrated in vacuo. The residue was taken up in ligroin (100 mL), filtered, again freed of solvent, and chromatographed on silica gel (elution with 10−20% ethyl acetate in ligroin). There was isolated 4.18 g (65%) of **16** as a colorless oil consisting of a 2.5:1 mixture of *E* and *Z* isomers: IR (neat, cm^{-1}) 3325, 1645, 1248; ^1H NMR (300 MHz, C_6D_6) δ 5.49−5.23 (m, 2 H), 3.49 (t, J = 6.4 Hz, 2 H), 2.43 (s, 1 H), 2.06 (m, 2 H), 1.60−1.37 (m, 4 H), −0.01 and −0.03 (2 s, total 9 H); ^{13}C NMR (75 MHz, C_6D_6) δ 128.7, 127.4, 126.7, 126.0, 62.3, 62.1, 33.4, 33.2, 29.5, 23.8, 22.8, 18.5, −1.8, −1.9; HRMS m/z (M^+) calcd 172.1283, obsd 172.1297.

Anal. Calcd for $C_9H_{20}OSi$: C, 62.72; H, 11.70. Found: C, 62.77; H, 11.61.

(6-Iodo-2-hexenyl)trimethylsilane (17). A mixture of **16** (936 mg, 5.44 mmol), triphenylphosphine (3.55 g, 13.5 mmol), imidazole (920 mg, 13.5 mmol), and iodine (2.75 g, 10.8 mmol) in benzene (60 mL) was stirred for 20 min at 20 °C. After the addition of saturated $NaHSO_3$ solution (30 mL), the reaction mixture was stirred for 10 min longer and extracted with ethyl acetate (2 × 60 mL). The combined organic layers were washed with brine, dried, and concentrated. The residue was chromatographed on silica gel (elution with ligroin) to give 1.20 g (78%) of **17** as a colorless liquid: IR (neat, cm^{-1}) 1648, 1425, 1248; ^1H NMR (300 MHz, C_6D_6) δ 5.48−5.38 (m, 1 H), 5.13−4.98 (m, 1 H), 2.80−2.72 (m, 2H), 1.94−1.85 (m, 2 H), 1.60−1.49 (m, 2 H), 1.43 (d, J = 8.0 Hz, 0.75 × 2 H), 1.33 (d, J = 8.0 Hz, 0.25 × 2 H), −0.03 and −0.06 (2 s, total 9 H); ^{13}C NMR (75 MHz, C_6D_6) δ 128.1, 127.2, 126.7, 125.5, 33.8, 33.54, 33.45, 28.0, 22.8, 18.8, 6.5, 6.4, −1.7, −1.9; HRMS m/z (M^+) calcd 282.0301, obsd 282.0311.

Anal. Calcd for $C_9H_{19}ISi$: C, 38.30; H, 6.79. Found: C, 38.43; H, 6.81.

7-(Trimethylsilyl)-5-heptenenitrile (18). A mixture of **17** (1.20 g, 4.26 mmol), potassium cyanide (0.83 g, 12.8 mmol), and DMF (10 mL) was stirred overnight, diluted with ether (200 mL), washed with dilute $NaHCO_3$ solution (3 × 50 mL), dried, and filtered. The filtrate was concentrated, and the residue was chromatographed on silica gel (elution with 5−10% ether in ligroin) to give 770 mg (100%) of **18** as a colorless oil (E/Z = 2.5:1): IR (neat, cm^{-1}) 2246, 1646, 1456; ^1H NMR (300 MHz, C_6D_6) δ 5.48−5.26 (m, 1 H), 5.01−4.87 (m, 1 H), 1.85−1.75 (m, 2 H), 1.54−1.44 (m, 2 H), 1.39−1.26 (m, 2 H), 1.17−1.04 (m, 2 H), −0.03 (s, 9 H); ^{13}C NMR (75 MHz, C_6D_6) δ 128.6, 127.7, 126.4, 125.1, 119.3, 31.6, 25.9, 25.5, 22.8, 18.6, 16.1, 15.9, −1.8, −2.0; HRMS m/z (M^+) calcd 181.1287, obsd 181.1279.

Anal. Calcd for $C_{10}H_{19}NSi$: C, 66.23; H, 10.56. Found: C, 66.50; H, 10.71.

General Procedure for Grignard Coupling to 18. Nitrile **18** (1.0 g, 5.5 mmol) was added to a solution of the aryl Grignard reagent in ether (approximately 0.5 M, 3 equiv), stirred for 20 min, cooled in an ice bath, quenched with saturated NH_4Cl solution (15 mL), and diluted with ether (40 mL) and water (15 mL). The separated aqueous phase was extracted with ether (2 × 50 mL), and the combined organic layers were dried, filtered, and concentrated. The residue was chromatographed on silica gel (elution with 0−10% ether in ligroin) to give the **3/4** ketone mixtures as colorless oils.

For **3a/4a** (91%): IR (neat, cm^{-1}) 1688, 1598; ^1H NMR (300 MHz, C_6D_6) δ 7.88 (d, J = 7.0 Hz, 2 H), 7.22−7.09 (m, 3 H), 5.56−5.24 (m, 2 H), 2.68 (t, J = 7.2 Hz, 2 H), 2.07 (quintet, J = 7.2 Hz, 2 H), 1.83 (quintet, J = 7.2 Hz, 2 H), 1.49 (d, J = 8.5 Hz, 0.75 × 2 H), 1.42 (d, J = 7.8 Hz, 0.25 × 2 H), 0.03 (s, 0.75 × 9 H), 0.02 (0.25 × 9 H); ^{13}C NMR (75 MHz, C_6D_6) δ 198.7, 137.7, 132.6, 128.6, 128.2, 127.2, 126.4, 37.9, 37.7, 32.6, 26.8, 24.7, 24.5, 22.8, 18.6, −1.8, −1.9; HRMS m/z (M^+) calcd 260.1596, obsd 260.1575.

Anal. Calcd for $C_{16}H_{24}OSi$: C, 73.79; H, 9.29. Found: C, 74.02; H, 9.20.

For **3b/4b** (88%): IR (neat, cm^{-1}) 1681, 1601; ^1H NMR (300 MHz, C_6D_6) δ 7.87 (d, J = 8.9 Hz, 2 H), 6.66 (d, J = 8.9 Hz, 2 H), 5.53−5.20 (m, 2 H), 3.23 (s, 3 H), 2.67 (t, J = 7.2 Hz, 2 H), 2.06 (quintet, J = 7.2 Hz, 2 H), 1.83 (quintet, J = 7.2 Hz, 2 H), 1.46 (d, J = 8.5 Hz, 0.75 × 2 H), 1.38 (d, J = 7.7 Hz, 0.25 × 2 H), −0.01 (s, 0.75 × 9 H), −0.02 (s, 0.25 × 9 H); ^{13}C NMR (75 MHz, C_6D_6) δ 197.4, 163.4, 130.4, 128.7, 127.3, 127.1, 126.4, 113.8, 54.9, 54.8, 37.7, 37.5, 32.7, 26.9, 24.7, 22.8, 18.6, −1.8, −1.9; HRMS m/z (M^+) calcd 290.1702, obsd 290.1684.

Anal. Calcd for $C_{17}H_{26}O_2Si$: C, 70.29; H, 9.02. Found: C, 70.45; H, 9.09.

For **3c/4c** (83%): IR (neat, cm^{-1}) 1688, 1599; ^1H NMR (300 MHz, C_6D_6) δ 7.66 (m, 2 H), 6.70 (t, J = 8.7 Hz, 2 H), 5.53−5.18 (m, 2 H), 2.53 (t, J = 7.3 Hz, 2 H), 2.03 (quintet, J = 7.3 Hz, 2 H), 1.77 (quintet, J = 7.3 Hz, 2 H), 1.46 (d, J = 8.5 Hz, 0.75 × 2 H), 1.40 (d, J = 7.8 Hz, 0.25 × 2 H), 0.00 (s, 0.75 × 9 H), −0.02 (s, 0.25 × 9 H); ^{13}C NMR (75 MHz, C_6D_6) δ 197.2, 165.7 (d, J = 253 Hz), 134.0 (d, J = 2 Hz), 130.7 (d, J = 9 Hz), 128.5, 127.3, 127.1, 126.5, 115.5 (d, J = 22 Hz), 37.7, 37.6, 32.6, 26.8, 24.6, 24.4, 22.8, 18.6, −1.8, −2.0; HRMS m/z (M^+) calcd 278.1502, obsd 278.1481.

Anal. Calcd for $C_{16}H_{23}FOSi$: C, 69.02; H, 8.33. Found: C, 69.30; H, 8.31.

General Procedure for the Indium-Promoted Cyclizations of 1 and 2. The allylic bromide (0.4 mmol) was dissolved in 4.0 mL of THF/water (1:4), treated with powdered indium metal (1.2 equiv), and stirred vigorously for the indicated reaction time. After the cyclization was judged to be complete (TLC analysis), the reaction mixture was diluted with ether or chloroform, transferred to a separatory funnel, and extracted several times with the same solvent. The combined extracts were dried and concentrated under reduced pressure to leave a residue, which was analyzed by ^1H NMR. This material was next chromatographed. The yield of ring-closed product was ascertained after the purification step.

For **1a** → **19a**: 24 h, silica gel (elution with 5% ether in petroleum ether), 70% yield; colorless oil; IR (neat, cm^{-1}) 3474, 1493, 1334; ^1H NMR (300 MHz, C_6D_6) δ 7.48 (d, J = 7.9 Hz, 2 H), 7.36 (t, J = 7.3 Hz, 2 H), 7.27−7.22 (m 1 H), 5.74 (ddd, J = 17.1, 10.7, 6.0 Hz, 1 H), 5.11 (dd, J = 17.4, 10.5 Hz, 2 H),

2.97−2.89 (m, 1 H), 2.19−1.80 (series of m, 7 H); ^{13}C NMR (75 MHz, C_6D_6) δ 145.8, 135.8, 128.1, 126.5, 125.0, 117.7, 83.4, 54.5, 42.7, 27.9, 21.8; HRMS *m/z* (M^+) calcd 188.1201, obsd 188.1207.

Anal. Calcd for $C_{13}H_{16}O$: C, 82.94; H, 8.57. Found: C, 82.90; H, 8.56.

For **1b** → **19b**: 20 h, silica gel (elution with 5−10% ether in petroleum ether), 73% yield; colorless oil; IR (neat, cm^{-1}) 3492, 1611, 1249, 1179; ^{1}H NMR (300 MHz, C_6D_6) δ 7.32 (d, J = 8.8 Hz, 2 H), 6.83 (d, J = 8.8 Hz, 2 H), 5.81−5.70 (m, 1 H), 5.01−4.92 (m, 2 H), 3.35 (s, 3 H), 2.65−2.62 (m, 1 H), 1.99−1.75 (m, 5 H), 1.62−1.58 (m, 1 H), 1.34 (s, 1 H); ^{13}C NMR (75 MHz, C_6D_6) δ 158.6, 138.2, 136.5, 127.9, 127.6, 126.4, 116.9, 113.5, 83.0, 54.7, 54.5, 42.7, 28.4, 21.7; HRMS *m/z* (M^+) calcd 218.1307, obsd 218.1306.

Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 77.21; H, 8.58.

There was also isolated alcohol **10b** in 15% yield.

For **1c** → **19c**: 24 h, silica gel (elution with 5% ether in petroleum ether), 67% yield; colorless oil; IR (neat, cm^{-1}) 3474, 1494, 1096; ^{1}H NMR (300 MHz, C_6D_6) δ 7.24 (d, J = 8.5 Hz, 2 H), 7.17 (d, J = 8.5 Hz, 2 H), 5.84−5.63 (m, 1 H), 4.99−4.89 (m, 2 H), 2.62−2.04 (m, 2 H), 1.9−1.54 (series of m, 6 H), 1.39 (br s, 1 H); ^{13}C NMR (75 MHz, C_6D_6) δ 143.4, 137.0, 136.4, 126.8, 126.1, 117.3, 83.3, 55.0, 42.9, 28.6, 22.0, 15.6; HRMS *m/z* (M^+) calcd 234.1078, obsd 234.1083.

Anal. Calcd for $C_{14}H_{18}OS$: C, 71.75; H, 7.74. Found: C, 71.54; H, 7.83.

For **1d** → **19d**: 36 h, Florisil (elution with 5% ether in petroleum ether), 79% yield; colorless oil; IR (neat, cm^{-1}) 3472, 1615, 1325; ^{1}H NMR (300 MHz, C_6D_6) δ 7.41 (d, J = 8.4 Hz, 2 H), 7.20 (d, J = 8.4 Hz, 2 H), 5.58−5.46 (m, 1 H), 4.92−4.80 (m, 2 H), 2.49−2.41 (m, 1 H), 1.98−1.48 (series of m, 6 H), 1.27 (br s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.1, 135.1, 125.5, 125.1, 125.0, 118.4, 83.2, 54.9, 42.8, 27.9, 21.9; HRMS *m/z* (M^+) calcd 256.1075, obsd 256.1084.

Anal. Calcd for $C_{14}H_{15}F_3O$: C, 65.62; H, 5.90. Found: C, 65.72; H, 5.88.

For **1e** → **19e**: 24 h, silica gel (elution with 5% ether in petroleum ether), 87% yield; colorless oil; IR (neat, cm^{-1}) 3476, 1509, 1227; ^{1}H NMR (300 MHz, C_6D_6) δ 7.12 (dd, J = 8.8, 5.3 Hz, 2 H), 6.81 (t, J = 8.7 Hz, 2 H), 5.59 (ddd, J = 17.2, 10.6, 6.6 Hz, 1 H), 4.94−4.81 (m, 2 H), 2.50−2.42 (m, 1 H), 1.91−1.48 (series of m, 6 H), 1.33 (br s, 1 H); ^{13}C NMR (75 MHz, C_6D_6) δ 162.1 (d, J = 244 Hz), 142.1, 136.2, 127.2 (d, J = 8.2 Hz), 117.4, 114.9 (d, J = 20.9 Hz), 83.1, 55.1, 42.9, 28.6, 21.9; HRMS *m/z* (M^+) calcd 206.1107, obsd 206.1109.

There was also isolated alcohol **10e** in 6% yield.

For **1f** → **19f**: 9 h, silica gel (elution with 25% ethyl acetate in petroleum ether), 38% yield; colorless solid; mp 90−91 °C; IR (neat, cm^{-1}) 3516, 1310, 1149; ^{1}H NMR (300 MHz, C_6D_6) δ 7.78 (d, J = 8.3 Hz, 2 H), 7.27 (d, J = 8.3 Hz, 2 H), 5.63−5.52 (m, 1 H), 4.91 (d, J = 10.5 Hz, 1 H), 4.83 (d, J = 17.3 Hz, 1 H), 2.48−2.40 (m, 1 H), 2.29 (s, 3 H), 1.89−1.51 (m, 7 H); ^{13}C NMR (75 MHz, C_6D_6) δ 152.4, 139.8, 135.8, 127.4, 126.3, 117.7, 83.3, 55.6, 43.8, 43.0, 28.8, 22.1; HRMS *m/z* (M^+) calcd 266.0977, obsd 266.0959.

Anal. Calcd for $C_{14}H_{18}O_3S$: C, 63.13; H, 6.81. Found: C, 63.03; H, 6.77.

There was also isolated alcohol **11** in 18% yield.

For **2a** → **19a**: 24 h, 82% yield, spectroscopically identical to the material described above.

For **2b** → **19b**: 21 h, 70% yield, spectroscopically identical to the material described above.

For **2c** → **19c**: 25 h, 86% yield, spectroscopically identical to the material described above.

Competition Studies. A mixture of **1b** (57.8 mg, 0.20 mmol), benzaldehyde (21.5 mg, 0.20 mmol), and powdered indium (27.1 mg, 0.20 mmol) in 2.0 mL of 1:3 THF/H_2O was vigorously stirred overnight and diluted with ether (2 mL). The aqueous phase was extracted with ether (3 × 5 mL), and the combined organic solutions were dried (Na_2SO_4) and evaporated to leave 85.1 mg of crude product. This material was dissolved in 1:3 ether/petroleum ether and eluted through a small pipet of Florisil with 50% ether in petroleum ether. The filtrate was concentrated. After the residue was examined by ^{1}H NMR, separation was effected chromatographically (silica gel, 5−10% ether in petroleum ether), and the yields were determined at this stage.There was recovered 15.2 mg (71%) of unreacted benzaldehyde, 26.6 mg (63%) of **19b**, and 3.7 mg (6%) of **10b**.

General Procedure for Fluoride Ion-Promoted Cyclizations. Molecular sieves (4 Å, 10 mg) were placed in a 25 mL round-bottomed flask together with 1 mL of dry THF under nitrogen. A solution of tetra-*n*-butylammonium fluoride (100 μL of 1.0 M in THF, 0.25 equiv) was introduced, and the mixture was stirred for 15 min prior to the introduction of the **3/4** sample (0.4 mmol) dissolved in dry THF (1 mL). After overnight agitation, water (3 mL) was introduced, and the product was extracted into ether (3 × 7 mL). The combined organic phases were dried, filtered, and concentrated. After the residue was examined by ^{1}H NMR, diastereomer separation was effected chromatographically and the yields determined at this stage.

For **3/4a** → **20a**: >97% conversion, silica gel (elution with 10% ether in petroleum ether), 82% anti/8% syn; colorless oil; IR (neat, cm^{-1}) 3466, 1507, 1224; ^{1}H NMR (300 MHz, C_6D_6) δ 7.31−7.27 (m, 2 H), 7.16−7.11 (m, 2 H), 7.08−7.02 (m, 2 H), 5.32−5.21 (m, 1 H), 4.75 (m, 2 H), 2.70 (dd, J = 13.1, 7.2 Hz, 1 H), 2.15−2.05 (m, 2 H), 1.95−1.74 (m, 1 H), 1.70−1.50 (m, 4 H); ^{13}C NMR (75 MHz, C_6D_6) δ 145.0, 140.0, 128.0, 127.1, 127.0, 114.5, 85.0, 55.9, 38.0, 29.9, 21.8; HRMS *m/z* (M^+) calcd 188.1201, obsd 188.1205.

Anal. Calcd for $C_{13}H_{16}O$: C, 82.94; H, 8.57. Found: C, 82.69; H, 8.59.

For **3/4b** → **20b**: 95% conversion, silica gel (elution with 15% ether in petroleum ether), 76% anti/8% syn; colorless oil; IR (neat, cm^{-1}) 3418, 1613, 1296, 1250; ^{1}H NMR (300 MHz, C_6D_6) δ 7.27 (d, J = 8.8 Hz, 2 H), 6.79 (d, J = 8.8 Hz, 2 H), 5.42−5.30 (m, 1 H), 4.90−4.75 (m, 1 H), 3.34 (s, 3 H), 2.80−2.73 (m, 1 H), 2.23−2.10 (m, 2 H), 1.98−1.81 (m, 1 H), 1.77−1.54 (m, 4 H); ^{13}C NMR (75 MHz, C_6D_6) δ 159.1, 140.3, 137.2, 128.1, 114.3, 113.4, 84.7, 55.8, 54.7, 38.0, 29.9, 21.8; HRMS *m/z* (M^+) calcd 218.1307, obsd 218.1312.

Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31 Found: C, 76.93; H, 8.30.

For **3/4c** → **20c**: 82% conversion, silica gel (elution with 10% ether in petroleum ether), 64% anti/11% syn; colorless oil; IR (neat, cm^{-1}) 3389, 1602, 1510; ^{1}H NMR (300 MHz, C_6D_6) δ 7.14−7.07 (m, 2 H), 6.87−6.72 (m, 2 H), 5.25−5.14 (m, 2 H), 4.81−4.70 (m, 2 H), 2.63 (dd, J = 13.1, 7.0 Hz, 1 H), 2.15−1.94 (m, 2 H), 1.68−1.46 (m, 3 H), 1.22 (s, 1 H); ^{13}C NMR (75 MHz, C_6D_6) δ 162.2 (d, J = 245 Hz), 140.8 (d, J = 3 Hz), 139.7, 128.6 (d, J = 8 Hz), 114.64, 114.63 (d, J = 21 Hz), 84.5, 55.9, 38.1, 29.9, 21.7; HRMS *m/z* (M^+) calcd 206.1107, obsd 206.1135.

Anal. Calcd for $C_{13}H_{15}FO$: C, 75.70; H, 7.33. Found: C, 75.22; H, 7.37.

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Supporting Information Available: Copies of the high-resolution ^{1}H and ^{13}C NMR spectra of those new compounds for which elemental analyses are not reported (22 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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