Synthesis, Equilibration, and Coupling of 4-Lithio-1,3-dioxanes: Synthons for *syn*- and *anti*-1,3-Diols

Scott D. Rychnovsky,* Alexandre J. Buckmelter, Vilas H. Dahanukar, and Donald J. Skalitzky

Department of Chemistry, University of California, Irvine, California 92697-2025

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Configurationally defined α-alkoxylithium reagents were prepared by reductive lithiation of 4-(phenylthio)-1,3-dioxanes. A new and more general synthesis of 4-(phenylthio)-1,3-dioxanes has been developed on the basis of the reduction and in situ acetylation of 1,3-dioxan-4-ones. For each of the substitution patterns examined (**23a**−**d**), reductive lithiation gave the axial alkyllithium (**24a**−**d**) with 99:1 stereoselectivity. Equilibrations of these alkyllithium reagents were possible with unhindered substrates to give the equatorial alkyllithiums **26a** and **26b** with excellent stereoselectivities. The more hindered axial alkyllithium reagents (**24c**, **24d**) did not equilibrate efficiently. The equilibrium between alkyllithium reagents **24c** and **26c** strongly favors the equatorial isomer **26c**. The inefficient equilibration with this hindered substrate is attributed to a slow rate of equilibration rather than insufficient driving force. These alkyllithium reagents could be coupled with a variety of electrophiles with retention of configuration by direct addition, copper-mediated coupling, or transmetalation to the corresponding alkylzinc reagent followed by copper-mediated coupling.

Introduction

Since Still's seminal report on their configurational stability,[1] chiral α-alkoxylithium reagents have been of interest to synthetic chemists. Chiral α-alkoxylithium reagents were originally prepared by transmetalation of diastereomerically[1b] or optically pure alkylstannanes.[2] Enantioselective deprotonation in the presence of (−)-sparteine is a valuable new route to chiral α-alkoxylithium reagents.[3] Diastereoselective lithiations introduce the new α-alkoxy ether with a defined stereochemical relationship to a preexisting stereogenic center. Reductive lithiation of alkyl phenyl sulfides is an attractive alternative for the synthesis of alkyllithium reagents.[4,5] Cohen used this approach to synthesize configurationally defined α-alkoxylithium reagents, such as axial 2-lithiotetrahydropyrans, with excellent diastereoselectivities.[6] We extended this method to the preparation of axial 4-lithio-1,3-dioxanes, which are useful 1,3-diol synthons.[7] Reports from Cohen's group[6] and ours[7] demonstrated that the kinetically preferred axial alkyllithium reagents could be equilibrated to equatorial alkyllithium reagents. Thus, both axial and equatorial 4-lithio-1,3-dioxanes arise from a common precursor, as depicted in Scheme 1. Herein we describe in full the preparation, equilibration, and coupling of configurationally defined 4-lithio-1,3-dioxanes.

Axial alkyllithium reagents are the kinetic products in the reductive lithiation of 4-(phenylthio)-1,3-dioxanes (Scheme 1). The preference for the axial product reflects the greater stability of the intermediate axial radical compared with the equatorial radical, a manifestation of anomeric stabilization.[8] Still showed that acyclic α-alkoxylithium reagents are unstable above −30 °C,[1] but *cyclic* α-alkoxylithium reagents isomerize rather than decompose at this temperature.[6,7] An example from our lab is shown in Scheme 1.[7] The axial 4-lithio-1,3-dioxane **2** was prepared by reductive lithiation at −78 °C with lithium di-*tert*-butylbiphenylide (LiDBB)[9] and could be trapped with acetone with retention of configuration[1b,5] to give **4** in 78% yield as a 98:2 mixture of isomers. Equilibration to the more stable equatorial alkyllithium reagent **3** and trapping with acetone gave compound **5** as a 95:5 mixture of isomers in 52% yield. Thus, both diastereomers **4** and **5** could be prepared with reasonable selectivities and in good yields from a common precursor, (phenylthio)-dioxane **1**.

Unfortunately, the original preparation of the 4-(phenylthio)-1,3-dioxane **1**, illustrated in eq 1, left much to be desired. The 4-(phenylthio)-1,3-dioxane **1** is unstable under the conditions of its formation, and the reaction solution slowly evolves to a mixture of the desired product, the phenylthio acetal of aldehyde **6**, the phenylthio acetal of acetone, and a variety of unidentified

(1) (a) Still, W. C. *J. Am. Chem. Soc.* **1978**, *100*, 1481−7. (b) Still, W. C.; Sreekumar, C. *J. Am. Chem. Soc.* **1980**, *102*, 1201−2.

(2) (a) Chan, P. C.-M.; Chong, J. M. *J. Org. Chem.* **1988**, *53*, 5584−6. (b) Chong, J. M.; Mar, E. K. *Tetrahedron Lett.* **1990**, *31*, 1981−4. (c) Chan, P. C. M.; Chong, J. M. *Tetrahedron Lett.* **1990**, *31*, 1985−8.

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(5) Cohen, T.; Bhupathy, M. *Acc. Chem. Res.* **1989**, *22*, 152−61.

(6) (a) Cohen, T.; Matz, J. R. *Synth. Commun.* **1980**, *10*, 311−7. (b) Cohen, T.; Lin, M. T. *J. Am. Chem. Soc.* **1984**, *106*, 1130−1. (c) Boeckman, R. K.; Enholm, E. J.; Demko, D. M.; Charette, A. B. *J. Org. Chem.* **1986**, *51*, 4743−5.

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(8) Rychnovsky, S. D.; Powers, J. P.; Lepage, T. J. *J. Am. Chem. Soc.* **1992**, *114*, 8375−84.

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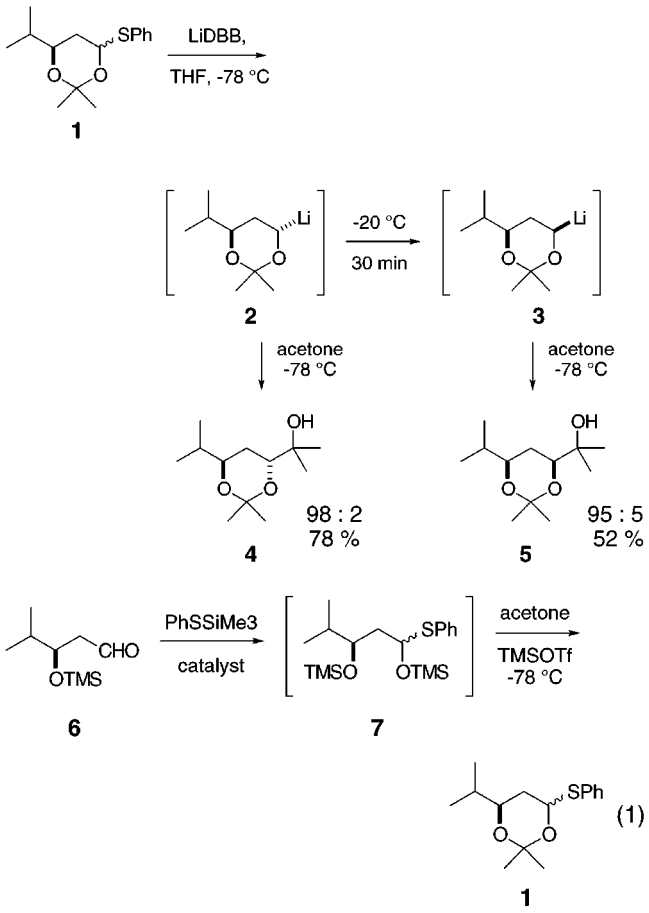
Scheme 1

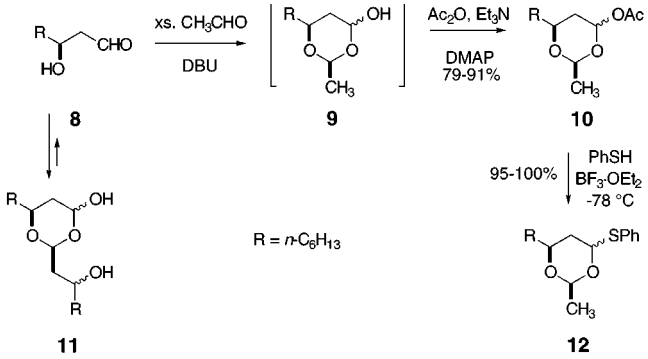


products. The desired product **1** could be isolated in reasonable yield if the reaction was quenched at the appropriate time, but the conversion was difficult to monitor. In practice, the procedure was not very reproducible. The 4-lithio-1,3-dioxanes were interesting 1,3-diol synthons, but their preparation was problematic. The two new syntheses of 4-(phenylthio)-1,3-dioxanes reported below overcome these difficulties and allow the chemistry of the derived axial and equatorial alkyllithium reagents to be fully explored.

Results

New Syntheses of 4-(Phenylthio)-1,3-dioxanes. The mode of decomposition of *β*-hydroxy aldehydes suggested one route to 4-(phenylthio)-1,3-dioxanes. On standing, *β*-hydroxy aldehydes decompose to mixtures of compounds that contain no aldehyde but do show a complex acetal region in the NMR spectra. These mixtures are predominantly unsymmetric dimers, **11**, of the *β*-hydroxy aldehyde containing a central 4-hydroxy-1,3-dioxane ring, as depicted in Scheme 2. Several 4-hydroxy-1,3-dioxanes of this type have been reported.[10] The 4-hydroxy-1,3-dioxane dimer **11** would appear to be a useful precursor for the desired 4-(phenylthio)-1,3-dioxane because (1) it forms spontaneously from *β*-hydroxy aldehydes and (2) one need only convert the hemiacetal to a phenylthio acetal, presumably a straightforward transformation. The problem is that 2 equiv of the precious aldehyde is incorporated into the 1,3-dioxane **11**. We found that the "acetal" aldehyde of the dimer can be exchanged with a simple aldehyde under DBU catalysis.[11] The new route to 4-(phenylthio)-1,3-dioxanes from *β*-hydroxy aldehydes is outlined in Scheme 2. The *β*-hydroxy aldehyde **8** (and **11**) was treated with an excess of acetaldehyde and 1.2 equiv of DBU. The reaction was monitored by TLC until the starting dimer was consumed, and the new hemiacetal **9** was trapped by in situ acetylation to give the 4-acetoxy-1,3-dioxane **10** in good yield. Lewis acid-promoted exchange of the acetate for thiophenol gave the 4-(phenylthio)-1,3-dioxane **12** in excellent yield. This procedure uses inexpensive reagents, works extremely well in simple systems, and has been used to prepare over 40 g of dioxane **33** (Scheme 6). The procedure is limited primarily by the structure of the acetal aldehyde. The aldehyde must be used in 5−10-fold excess to drive the equilibrium to completion, so inexpensive and easily separated, volatile aldehydes are preferred. The exchange reaction only works with carbonyl compounds that readily form geminal diols such as acetaldehyde; the reaction fails with unsaturated or aromatic aldehydes and most ketones. Thus, acetonide phenylthio acetal **1** could not be prepared by this method. The acetal-exchange route is very effective for the preparation of a limited range of 4-(phenylthio)-1,3-dioxanes.

Scheme 2



Attempts to extend the acetal exchange route to chains with alternating methyl and hydroxyl substituents led to unexpected difficulties. The α-methyl *β*-hydroxy aldehydes were prepared by way of enantioselective aldol reactions[12] or by Jung's rearrangement of epoxy alcohols.[13] The aldehydes were initially isolated as TMS ethers, and careful hydrolysis gave the expected *β*-hydroxy aldehydes. These compounds exist primarily as free aldehydes (Scheme 3) and are less susceptible to spontaneous dimerization than the acetate aldehydes described in Scheme 2. Aldehyde **13** is also prone to epimerization under the basic conditions of the reaction. Treatment of aldehyde **13** with 5−10 equiv of acetaldehyde and catalytic DBU generated 4-hydroxy-1,3-dioxane **14**, which was trapped by in situ acetylation in good yield

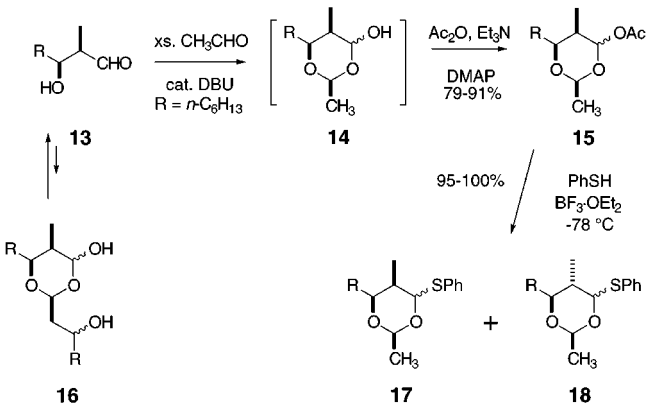
(10) (a) Saunders: R. H.; Murray, M. J.; Cleveland, F. F. *J. Am. Chem. Soc.* **1943**, *65*, 1714−7. (b) Spath, E.; Lorenz, R.; Fruend, E. *Chem. Ber.* **1943**, *76*, 1196−208. (c) Alexander, E. R.; Marvell, E. N. *J. Am. Chem. Soc.* **1950**, *72*, 1396. (d) Hine, J.; Houston, J. G.; Jensen, J. H. *J. Org. Chem.* **1965**, *30*, 1184−8. (e) Andersson, R.; Theander, O.; Westerlund, E. *Carbohydr. Res.* **1978**, *61*, 501−9. (f) Duke, C. C.; MacLeod, J. K.; Williams, J. F. *Carbohydr. Res.* **1981**, *95*, 1−26. (g) Cloux, R.; Schlosser, M. *Helv. Chim. Acta* **1984**, *67*, 1470−4.

(11) Rychnovsky, S. D.; Skalitzky, D. J. *J. Org. Chem.* **1992**, *57*, 4336−9.

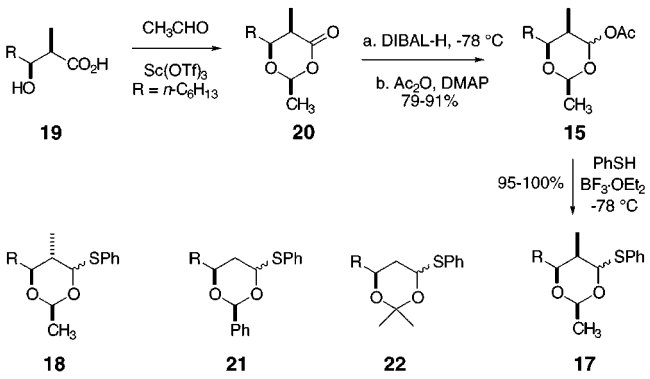
(12) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127−9.

(13) Jung, M. E.; D'amico, D. C. *J. Am. Chem. Soc.* **1993**, *115*, 12208−9.

Scheme 3



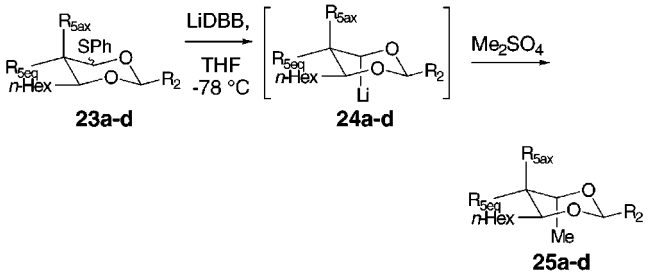
Scheme 4



(Scheme 3). Lewis acid-promoted exchange with thiophenol gave the 4-(phenylthio)-1,3-dioxane **17**. Unfortunately, **17** was contaminated with the C5 epimer **18**. Epimerization of aldehyde **13** competed with the formation of the 4-hydroxy-1,3-dioxane **14**. Different catalysts and solvents suppressed the epimerization but could not completely eliminate it. The best ratio of epimers **17** and **18** was about 5:1. The unavoidable epimerization rendered the acetal exchange route unsuitable for the preparation of 5-substituted 4-(phenylthio)-1,3-dioxanes.

A more general route to 4-(phenylthio)-1,3-dioxanes was developed on the basis of the reductive acetylation of 1,3-dioxan-4-ones,[14] which could be prepared from *β*-hydroxy acids by treatment with excess aldehyde and either a protic acid or a Lewis acid catalyst.[15] Conversion of 1,3-dioxan-4-ones to 4-acetoxy-1,3-dioxanes used our recently reported DIBAL-H reduction and in situ acetylation of esters to give α-acetoxy ethers.[14] This procedure is especially useful in cases where the hemiacetal is unstable with respect to the corresponding alcohol and aldehyde. As illustrated in Scheme 4, this procedure gave excellent yields of the 4-acetoxy-1,3-dioxane **15**. Acetal formation followed by DIBAL-H reduction and in situ acetalization converted **19** to **15** without epimerization. Treatment of the acetates **15** with thiophenol using $BF_3 \cdot OEt_2$ as a promoter gave the desired 4-(phenylthio)-1,3-dioxane **17**. The corresponding *anti*-aldol compound gave the expected 4-(phenylthio)-1,3-dioxane **18** in good yield without epimerization. This new synthesis of 4-(phenylthio)-1,3-dioxanes not only suppressed the C5 epimerization observed in the acetal exchange route, but also was successful with 1,3-dioxan-4-ones derived from aliphatic aldehydes, aromatic aldehydes (**21**), and even ketones (**22**). Several 4-(phenylthio)-1,3-dioxanes prepared by this route are shown in Scheme 4. The DIBAL-H reduction and in situ acetylation route is both more reliable and more general than the previously reported syntheses of 4-(phenylthio)-1,3-dioxanes, and can be used to prepare substrates for the reductive lithiation reactions discussed below.

Table 1. Kinetic Selectivity in Reductive Lithiation of 4-(Thiophenyl)-1,3-dioxanes



entry	R_2	R_{5ax}	R_{5eq}	protonated (%)	alkylated[a] (%)	ratio (ax/eq)[b]
a	*i*-Pr	H	H	*c*	79	99:1
b	Me	H	Me	8	77	99:1
c	Me	Me	H	17	75	99:1
d	Me	Me	Me	9	83	99:1

[a] Isolated yields. [b] Ratios by GC analysis. [c] Not measured.

Reductive Lithiation and Equilibration. The reductive lithiation of 4-(phenylthio)-1,3-dioxanes **23a**−**d** is summarized in Table 1. The C5 substituents were varied from unsubstituted (**23a**), through both equatorial and axial methyl (**23b** and **23c**, respectively) to geminal dimethyl (**23d**). Unsubstituted and monosubstituted dioxanes are relevant for the synthesis of polyacetate and polypropionate natural products, respectively, and the 5,5-dimethyldioxane **23d** could be useful for certain natural products such as the bryostatins.[16] The configurations of the alkyllithium reagents **24a**−**d** were assayed by alkylation with dimethyl sulfate, which has been shown to efficiently methylate α-alkoxylithium reagents with retention of configuration.[1] The structures of the methylated products were assigned by ^{1}H NMR analysis and NOE experiments, where appropriate. The reductive lithiation was carried out by adding a 0.4 M LiDBB solution by syringe to a solution of the 4-(phenylthio)-1,3-dioxane at −78 °C. The 4-(phenylthio)-1,3-dioxane solution was titrated with *n*-BuLi/1,10-phenanthroline before the reduction to remove residual water. Methylation of the alkyllithium intermediate at −78 °C led to the kinetic alkylation ratios shown in Table 1. The outcome is virtually identical for each substrate: 99:1 selectivity for the axial isomer and 75−83% isolated yields. The kinetic alkylation is an efficient and stereoselective process.

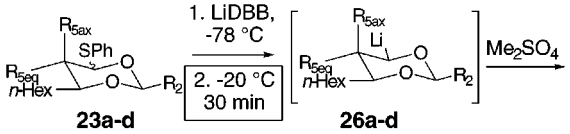
The equilibrations of the alkyllithium reagents are summarized in Table 2. Each axial alkyllithium reagent (**24a**−**d**) was generated as before and then warmed to −20 °C in a cryocool bath for 30 min to equilibrate it to the equatorial alkyllithium reagent (**26a**−**d**). The relative configurations of the alkyllithium reagents were evalu-

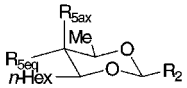
(14) Dahanukar, V. H.; Rychnovsky, S. D. *J. Org. Chem.* **1996**, *61*, 8317−20.

(15) (a) Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1980**, *21*, 71−4. (b) Seebach, D.; Sting, A. R.; Hoffmann, M. *Angew. Chem., Int. Ed. Engl.* **1997**, *35*, 2708−48.

(16) Pettit, G. R.; Herald, C. L.; Doubek, D. L.; Herald, D. L. *J. Am. Chem. Soc.* **1982**, *104*, 6846−8.

Table 2. Stereoselectivity in the Equilibration of 4-Lithio-1,3-dioxanes

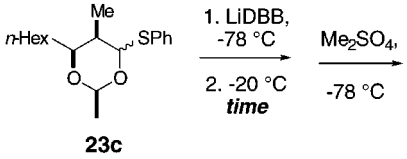


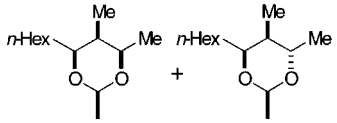


entry	R_2	R_{5ax}	R_{5eq}	protonated (%)	alkylated[a] (%)	ratio (ax/eq)[b]
a	*i*-Pr	H	H	*c*	79	>99:1
b	Me	H	Me	45	47	35:1
c	Me	Me	H	27	54	1:2
d	Me	Me	Me	49	31	1.5:1

[a] Isolated yields. [b] Ratios by GC analysis. [c] Not measured.

Table 3. Equilibration of *cis*-2,5-Dimethyl-6-hexyl-4-lithio-1,3-dioxane





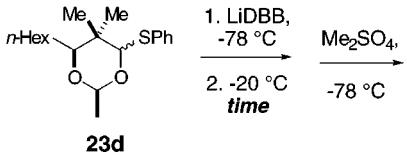
equilibration time (min)	yield[a] (%)	ratio (**27c**:**25c**)[b]	equilibration time (min)	yield[a] (%)	ratio (**27c**:**25c**)[b]
10	72	7:1	30	54	2.0:1
20	53	3.6:1	60	43	1.1:1

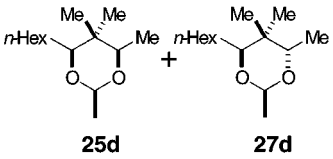
[a] Isolated yields. [b] Ratios by GC analysis.

ated by recooling to −78 °C and alkylating with dimethyl sulfate as before. The C5-unsubstituted acetal (entry a) equilibrates remarkably well, giving the desired equatorial product in >99:1 selectivity and 79% yield. This acetal equilibrates much more cleanly than the acetonide case (**2** to **3**) shown in Scheme 1. The 5eq-methyldioxane (entry b) also gave the equatorial product with good selectivity but lower yield. Unfortunately neither the 5ax-methyldioxane (entry c) nor the 5,5-dimethyldioxane (entry d) equilibrated effectively. In fact, the 5ax-methyldioxane gave predominantly the *axial* alkyllithium product after attempted equilibration! The 5-unsubstituted and 5eq-methyl-4-lithio-1,3-dioxanes **26a** and **26b** can be prepared effectively by equilibration and lead to the alkylated products **27a** and **27b** in good yield and high stereoselectivity.

Why does the alkyllithium equilibration break down in some cases? Two possibilities should be considered: the rate of equilibration may be much slower, or the position of equilibrium may no longer favor the equatorial alkyllithium. To shed light on this problem, the time course of the equilibration was investigated for the two problem cases (entries c and d, Table 2), and the results are shown in Tables 3 and 4. In both cases the axial/equatorial ratio continues to decrease throughout the course of the reaction. The yield of the alkylation products

Table 4. Equilibration of 6-Hexyl-4-lithio-2,5,5-trimethyl-1,3-dioxane

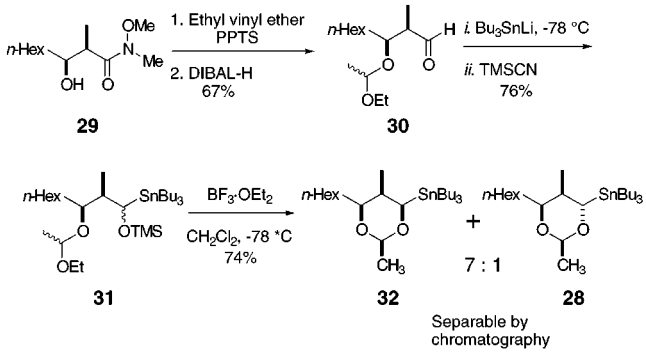




equilibration time (min)	yield[a] (%)	ratio (**27d**:**25d**)[b]	equilibration time (min)	yield[a] (%)	ratio (**27d**:**25d**)[b]
10	47	3:1	30	31	1:1.5
20	41	1.2:1	60	13	1:3.4

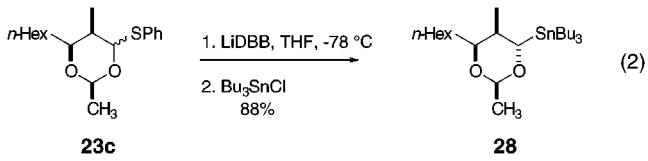
[a] Isolated yields. [b] Ratios by GC analysis.

Scheme 5



also decreases with longer equilibration times, especially for compound **23d** in Table 4. The mass balance on these equilibration reactions is good, with the protonated product making up the remainder of the material. The position of the equilibrium is still uncertain, but the rate of equilibration is certainly slower than for the unsubstituted acetal **23a** in Table 2.

We undertook the preparation of axial and equatorial tributylstannanes **28** and **32** to establish the position of equilibrium for the 5ax-methyl-1,3-dioxane system. The axial stannane **28** was prepared by reductive lithiation of **23c** and trapping of the resulting alkyllithium with tri-*n*-butyltin chloride (eq 2). Synthesis of the equatorial

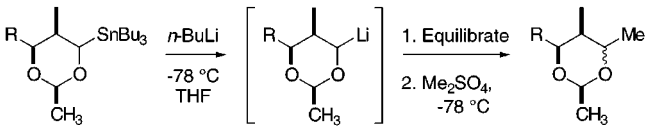


(2)

stannane **32** was more challenging. Ultimately we took advantage of Cram-selective addition of tri-*n*-butylstannyllithium to aldehyde **30** (Scheme 5). The addition and trapping were carried out as described by Linderman.[17] The ethoxyethyl protecting group in **31** was transformed into the cyclic acetaldehyde acetal **32** on treatment with $BF_3{\cdot}OEt_2$. The 4-(tributylstannyl)-1,3-dioxanes **32** and **28** were produced as a 7:1 mixture of isomers that could be

(17) Linderman, R. J.; Ghannam, A. *J. Am. Chem. Soc.* **1990**, *112*, 2392−8.

Table 5. Equilibration of 4-Lithio-1,3-dioxanes Generated from Stannane 28 or 32



28 or **32** **24c** or **26c** **25c** or **27c**

entry	stannane	equilibration temp (time)	protonated[a] (%)	alkylated[a] (%)	ratio (ax:eq)[b]
1	**32** (eq)	none	3	97	0:100
2	**29** (ax)	none	18	82	100:0
3	**32** (eq)	−30 °C (15 min)	12	88	0:100
4	**29** (ax)	−30 °C (15 min)	37	63	89:11
5	**32** (eq)	−20 °C (30 min)	63	37	0:100
6	**29** (ax)	−20 °C (30 min)	74	26	58:42

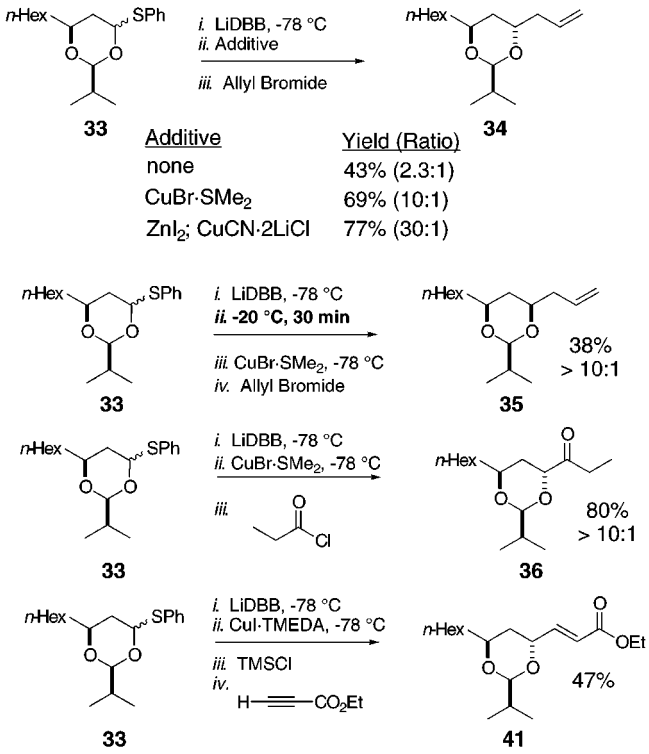
[a] Ratios and yields by GC analysis.

separated by chromatography. Thus, both the axial and equatorial 4-(tributylstannyl)-1,3-dioxanes **28** and **32** could be isolated as single isomers to evaluate the alkyllithium equilibration.[18]

The equilibrations of alkyllithiums **24c** and **26c** derived from stannanes **28** and **32** are summarized in Table 5. Transmetalation of the axial or equatorial stannanes **28** or **32** with 3.0 equiv of *n*-BuLi at −78 °C in THF, followed by alkylation with Me_2SO_4, gave the axial or equatorial 4-methyl-1,3-dioxanes **27c** and **25c** uncontaminated with the other isomer (entries 1 and 2).[18] Thus, the transmetalation and alkylation proceed with retention of configuration, and the only side product observed was a minor amount of the protonated product. Two conditions were investigated in the equilibration: warming to −30 °C for 15 min before alkylation with Me_2SO_4 at −78 °C (entries 3 and 4) or warming to −20 °C for 30 min before alkylation with Me_2SO_4 at −78 °C (entries 5 and 6). In both cases the axial stannane led to a mixture of axial and equatorial methylated products consistent with the results of previous equilibration studies (Table 3). The equatorial stannane **32** gave none of the axial methylated product under either condition. We conclude that (1) equilibration does take place under these conditions and (2) the equatorial alkyllithium **26c** is already at equilibrium. Thus, the position of equilibrium between **26c** and **24c** is essentially 100% toward the equatorial isomer **26c**. The preference for the equatorial isomer is entirely consistent with that observed in the equilibration of the 5-unsubstituted 4-lithio-1,3-dioxane **24a**. It is interesting to note that the yield of methylated product from the equatorial stannane **32** is greater than the yield from axial isomer **28** under each set of conditions. Thus, the axial alkyllithium is kinetically less stable than the equatorial alkyllithium, a result consistent with our conclusions about their relative thermodynamic stability.

Alkylation of 4-Lithio-1,3-dioxanes. Only a limited range of electrophiles reacts efficiently with α-alkoxylithium reagents. Aldehydes,[6b,19] ketones,[6c,19] some epoxides,[7] dimethyl sulfate,[1,2a] and CO_2[2c] all react with α-alkoxylithium reagents with retention of configuration. Simple alkyl halides usually react poorly and give mixtures of products with low stereoselectivity.[19] Both

Scheme 6



Linderman and Fuchs have shown that α-alkoxycopper and α-alkoxycuprate reagents react with a wider range of electrophiles, although the configurations of the reacting centers are not always retained.[20] A brief investigation of the alkylation using other electrophiles is shown in Scheme 6.

For the transmetalation of 4-lithio-1,3-dioxanes, employing CuCN·2LiCl as the additive to the alkyllithium, generally gave the best yields and showed the highest diastereoselectivity in coupling reactions. In practice, however, the use of CuBr·SMe_2 is most convenient as it can be added as a solid to the alkyllithium without any apparent deleterious effects on yield or selectivity. Both of these copper species must be thoroughly dried and be of the highest possible purity for successful transmetalation and subsequent coupling to occur. Employing CuCN (0.5 or 1 equiv) as the additive failed to generate coupled products, likely due to solubility problems of CuCN in THF. In addition, for the conjugate additions to proceed successfully, TMSCl was found to be essential.

Allyl bromide gives low yields and only 2.3:1 stereoselectivity when added directly to the axial 4-lithio-1,3-dioxane derived from **33**. Addition of stoichiometric CuBr·SMe_2 before reaction with allyl bromide gives a much better yield of axial allylated product **34** with 10:1 stereoselectivity. Addition of ZnI_2 followed by addition of CuCN·2LiCl according to Knochel's procedure[21] gave even better results with 30:1 selectivity and 77% isolated yield. Warming the intermediate alkylzinc solution to

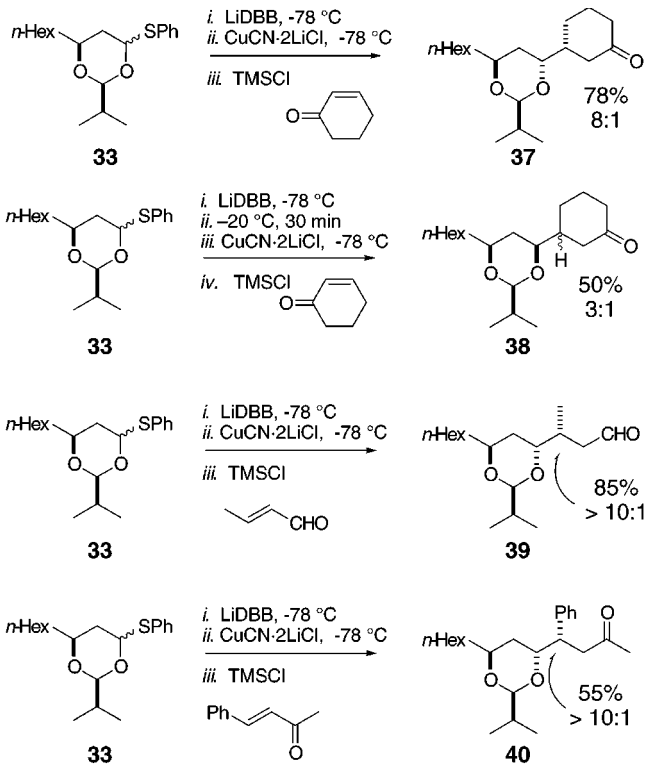
(18) NOE data for compounds **28**, **32**, **27c**, and **25c** are included in the Supporting Information, as is the preparation of **31**.

(19) (a) Sawyer, J. S.; Macdonald, T. L.; McGarvey, G. J. *J. Am. Chem. Soc.* **1984**, *106*, 3376−7. (b) Sawyer, J. S.; Kucerovy, A.; Macdonald, T. L.; McGarvey, G. J. *J. Am. Chem. Soc.* **1988**, *110*, 842−53.

(20) (a) Linderman, R. J.; Godfrey, A. *Tetrahedron Lett.* **1986**, *27*, 4553−6. (b) Hutchinson, D. K.; Fuchs, P. L. *J. Am. Chem. Soc.* **1987**, *109*, 4930−9. (c) Linderman, R. J.; Griedel, B. D. *J. Org. Chem.* **1990**, *55*, 5428−30. (d) Linderman, R. J.; Griedel, B. D. *J. Org. Chem.* **1991**, *56*, 5491−3. (c) Prandi, J.; Audin, C.; Beau, J.-M. *Tetrahedron Lett.* **1991**, *32*, 769−72.

(21) (a) Knochel, P.; Yeh, M. C. P.; Berk, S. C.; Talbert, J. *J. Org. Chem.* **1988**, *53*, 2390−2. (b) Knochel, P.; Chou, T.-S. *J. Org. Chem.* **1990**, *55*, 4791−3. (c) Knochel, P.; Singer, R. D. *Chem. Rev.* **1993**, *93*, 2117−88.

Scheme 7



−20 °C for 30 min lowered the yield to 55% but did not significantly reduce the ratio, demonstrating that the α-alkoxyzinc intermediate was configurationally stable under these conditions. The CuBr·SMe_2-promoted coupling with propionyl chloride gave the ketone **36** with good anti selectivity. Copper-mediated addition to ethyl propiolate gave the (*E*)-alkene **41** in satisfactory yield. Not surprisingly, equilibration of the alkyllithium reagent followed by addition of CuBr·SMe_2 and allyl bromide gave the expected equatorial adduct **35** in a modest 38% yield but with >10:1 selectivity. Thus, both axial and equatorial products can be prepared stereoselectively from the 4-(phenylthio)-1,3-dioxane **33** in one pot using copper-catalyzed reactions.

Stereoselective 1,4-Additions of Organocuprate Reagents. Addition of α-alkoxyalkyllithium or α-alkoxyalkylmagnesium bromide reagents to aldehydes or ketones leads to retention of configuration at the alkylmetal center, but shows very modest levels of stereochemical induction at the new stereogenic center.[22] Much higher stereochemical induction has been achieved by use of α-alkoxyorganolead reagents.[23] In contrast, 1,4-additions of α-alkoxyorganocuprates to enones can be very selective.[24] Higher order cuprate reagents prepared from the axial and equatorial alkyllithium reagents were added to several enones, and the results are shown in Scheme 7. TMSCl increased the yield of the 1,4-adduct and was used in each example.[25] The axial organocuprate derived from kinetic reductive lithiation of **33** gave a 8:1 mixture of stereoisomers at the newly formed center on addition to cyclohexenone. The configuration of the major product was 1,2-syn as expected from Linderman's work,[24] and was confirmed by an X-ray crystal structure of **37**.[26] The 1,2-syn selectivity complements the 1,2-anti selectivity observed in the Lewis acid-catalyzed addition of (*E*)-crotylstannane to 4-acetoxy-1,3-dioxanes such as **10**.[27] Addition to crotonaldehyde gave the syn 1,4-adduct **39** with >10:1 selectivity in 85% yield. Reaction with 4-phenyl-3-buten-2-one led to the 1,4-adduct **40** with >10:1 selectivity. NOE measurements were used to establish the configurations of 1,4-adducts **39** and **40**.[28] In each case, stereochemical induction using the axial organocuprate reagent favored the syn adduct.[24] The equatorial organocuprate reagent gave the expected adduct **38** with only 3:1 selectivity, however. The difference in selectivity is presumably due to the more sterically constrained environment around the axial organocuprate reagent.

Thermodynamic Stability of Alkyllithium Reagents. On the basis of the experiments described above, there is a significant energetic preference for equatorial alkyllithiums compared with their axial counterparts. Is this trend consistent with calculated energies?[29] Are nonchair conformations important in this equilibrium? We have investigated these questions by analyzing the conformation of alkyllithium reagents using ab initio and DFT methods.

The conformation of 4-lithio-1,3-dioxane was investigated. Initially PM3 was used to calculate conformational energies, but the results were useless. PM3 has been parametrized for lithium,[30] but it does not account for steric repulsion effectively. For example, PM3 (Spartan) predicts that the diaxial conformation of *cis*-2,4-dimethyl-1,3-dioxane will be favored over the diequatorial conformation by 1.70 kcal/mol. This is a nonsensical result. MM2 (Macromodel) predicts the diequatorial conformation will be favored by 8.7 kcal/mol, which is much more consistent with the expected thermodynamic preference.[31] We conclude that PM3 should never be used where steric influences may be a contributing factor.

The conformations of 4-lithio-1,3-dioxane were generated beginning with the MM2 minima for 1,3-dioxane. For the three dioxane conformations, the chair, 2,5-twist-boat, and 1,4-twist-boat, each of the nonequivalent C4−H atoms was replaced by lithium, and the resulting eight conformational isomers were minimized at HF/3-21G. This led to five distinct conformations that were further minimized at B3LYP/6-31+G(d), and the resulting structures and energies are shown in Figure 1.[32] In each of these compounds the lithium atom forms a three-membered ring with the carbon anion and the adjacent

(22) McGarvey, G. J.; Kimura, M. *J. Org. Chem.* **1982**, *47*, 5420−2.
(23) Yamada, J.-I.; Abe, H.; Yamamoto, Y. *J. Am. Chem. Soc.* **1990**, *112*, 6118−20.
(24) Linderman, R. J.; McKenzie, J. R. *Tetrahedron Lett.* **1988**, *29*, 3911−4.
(25) (a) Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.* **1984**, *106*, 3368−70. (b) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1985**, *26*, 6019−22. (c) Alexakis, A.; Berlan, J.; Besace, Y. *Tetrahedron Lett.* **1986**, *27*, 1047−50.
(26) The X-ray structure of **37** is illustrated in the Supporting Information. We thank Dr. Joseph Ziller from the University of California, Irvine, Department of Chemistry for determining the X-ray structure.
(27) Rychnovsky, S. D.; Sinz, C. J. *Tetrahedron Lett.* **1998**, *39*, 6811−4.
(28) Configurational assignments for compounds **39** and **40** are described in the Supporting Information.
(29) Lehn, J.-M.; Wipff, G. *J. Am. Chem. Soc.* **1976**, *98*, 7498−7505.
(30) Anders, E.; Koch, R.; Freunscht, P. *J. Comput. Chem.* **1993**, *14*, 1301−12.
(31) The pseudo-*A* value for methyl at the C2 position of a 1,3-dioxane is >3.55 kcal/mol, and this does not begin to account for the 1,3-diaxial interaction in the *cis*-2,4-dimethyl-1,3-dioxane. Eliel, E. L.; Knoeber, M. C. *J. Am. Chem. Soc.* **1968**, *90*, 3444−58.
(32) The coordinates for each calculated structure in Figures 1 and 2 are included in the Supporting Information.

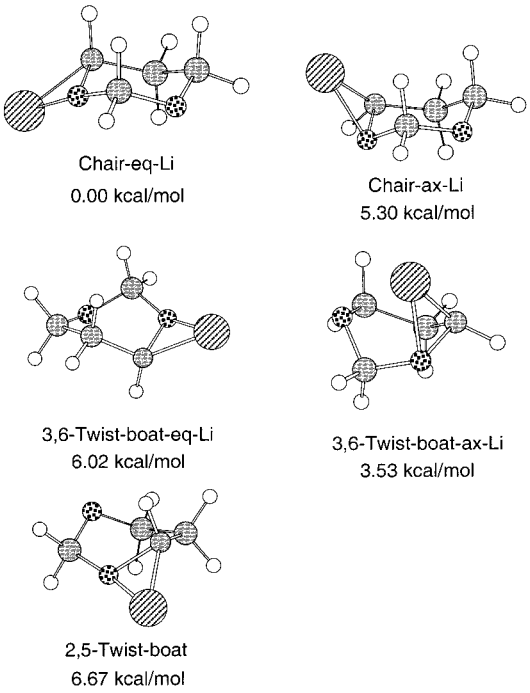


Figure 1. Conformations of 4-lithio-1,3-dioxane calculated at B3LYP/6-31+G(d)//B3LYP/6-31+G(d). The relative energies at this level are given in kcal/mol.

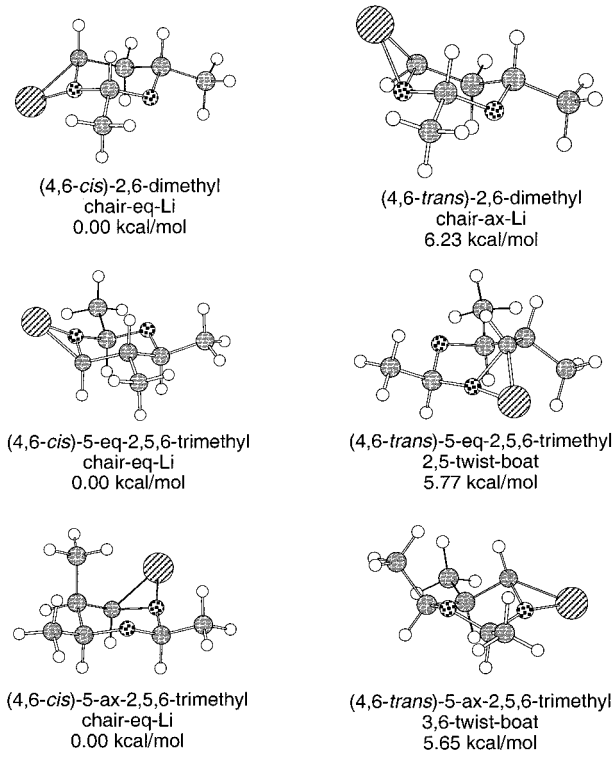


Figure 2. Conformations of substituted 4-lithio-1,3-dioxane calculated at B3LYP/6-31+G(d)//HF/3-21G. Only the lowest energy 4,6-*cis* and 4,6-*trans* conformation are listed, along with the relative energy for each pair. The (4,6-*cis*)-5-axial conformation is 1.81 kcal/mol higher in energy than the (4,6-*cis*)-5-equatorial conformation.

oxygen, and this ring dominates the stability of the system. The chair conformation with an equatorial lithium atom is the minimum, with the next lowest conformation at 3.53 kcal/mol higher. The chair axial Li is higher by 5.30 kcal/mol, and the two remaining twist-boat conformations are 6.02 and 6.67 kcal/mol above the minima. The 3,6-twist-boat conformation at 3.53 kcal/mol may be an artifact caused by neglecting solvation. The stability of the chair axial Li conformation is relatively close to the twist-boat conformations, and the relative energies can be interchanged by substitution, vide infra.

The relative energies of 4,6-*cis*- and 4,6-*trans*-6-alkyl-4-lithio-1,3-dioxanes are shown in Figure 2. In each case a Monte Carlo search was carried out in Macromodel on the corresponding protonated dioxane, and then each nonequivalent C4−H atom was replaced by Li. These alkyllithium structures were minimized using HF/3-21G, and the single-point energies were calculated using B3LYP/6-31+G(d).[33] For the simple dioxane in Figure 1 this procedure, B3LYP/6-31+G(d) energies evaluated at the 3-21G minima, led to the chair axial Li conformer being higher in energy than the 3,6-twist-boat equatorial Li conformer, but otherwise the relative energies were similar. The lowest energy 4,6-cis and 4,6-trans conformations are shown for each series. In each case the lowest energy cis conformation is a chair with the Li atom equatorial. For the 2,6-dimethyl case, the 4,6-trans conformation is a chair with the Li atom axial. The minimum for 5-equatorial 4,6-trans is a 2,5-twist-boat, whereas the minimum for 5-axial 4,6-trans is a 3,6-twist-boat.[34] In each case the 4,6-cis conformation is favored over 4,6-trans by approximately 5−6 kcal/mol. These calculations consistently favor the 4,6-cis (equatorial) alkyllithium reagent and are insensitive to substitution. The structure of the minimum energy 4,6-trans conformer varies with substitution, but to a first approximation the relative energies of the cis and trans conformations do not. Although these calculations ignore solvation, the general experimental trend, in which the equatorial alkyllithium reagents are strongly preferred over axial reagents regardless of substitution, is born out.

Conformation of Phenylthio Ethers and Ring Inversion. We recently discovered that reductive lithiation of 2-cyanotetrahydropyrans and decarboxylation of the corresponding Barton esters can be faster than ring inversion.[35] Thus, the two different chair conformers of a 2-tetrahydropyranyl radical are reduced competitively with ring inversion and lead to different ratios of products. Are variations in the conformations of the 4-(phenylthio)-1,3-dioxanes **23a**−**d** playing an important role in these reductive lithiations? To address this question, both of the phenylthio epimers for **23a**, **23b**, **23c**, and **23d** were modeled with Monte Carlo searches in Macromodel 5.5 using the MM2 force field.[36] In these

(33) For the 2,6-dimethyl series, seven cis and seven trans conformers were evaluated at HF/3-21G and led to three unique cis and five unique trans conformers. In the 5-equatorial 2,5,6-trimethyl series, eight cis and eight trans conformers were evaluated at HF/3-21G and led to four unique cis and six unique trans conformers. Finally, in the 5-axial 2,5,6-trimethyl series, six cis and six trans conformers were evaluated at HF/3-21G and led to three unique cis and five unique trans conformers.

(34) On an absolute scale, the 4,6-cis 5-axial conformation is 1.81 kcal/mol higher than the 4,6-cis 5-equatorial isomer. This difference is about twice the expected pseudo-*A* value (0.80−0.97 kcal/mol) for methyl at the C5 position of a 1,3-dioxane (ref 31). Steric interactions between the equatorial C4 lithium atom and the adjacent axial C5 methyl group may account for the difference.

(35) Buckmelter, A. J.; Powers, J. P.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **1998**, *120*, 5589−90.

calculations, the C2 and C4 substitutents were replaced by methyl groups. In each case, the chair conformation with an equatorial 2-substitutent was favored over the next lowest conformation by at least 4 kcal/mol.[37] The very large pseudo-*A* value at the C2 position of a 1,3-dioxane presumably is responsible for this pronounced conformational bias. Under the conditions of the reductive lithiation only a single ring conformation will be significantly populated, and the contribution of other conformers can be safely ignored.

Discussion

High axial selectivities for reductive lithiations of 4-(phenylthio)-1,3-dioxanes were observed for all cases, and this outcome is consistent with previous observations.[5] Presumably the reaction proceeds by stepwise reduction of the phenylthio ethers to PhSLi and a modestly pyramidal axial 4-dioxyl radical. The axial radical is predicted to be much more stable than the equatorial radical.[8,38] Rapid reductive lithiation of the axial radical gives the axial alkyllithium. Reductive lithiation of 4-(phenylthio)-1,3-dioxanes reliably generates axial alkyllithium reagents with high stereoselectivity.

The equilibration of 4-lithio-1,3-dioxanes is much more substrate dependent. The thermodynamic equilibrium strongly favors the equatorial alkyllithium reagent with the unsubstituted and equatorial (5-methylalkyl)lithiums **26a** and **26b**. The axial (5-methylalkyl)lithium **24c** and the (5,5-dimethylalkyl)lithium **24d** do not equilibrate effectively, but the problem is slow equilibration rather than an unfavorable equilibrium constant. Tables 3 and 4 show that the equatorial/axial ratios continue to improve with longer equilibration times. In the case of the axial (5-methylalkyl)lithium reagent, the axial and equatorial alkyllithium reagents were prepared from the corresponding stannanes and equilibrated under identical conditions. The axial alkyllithium **24c** gave a mixture of equatorial and axial products, showing that the equilibration was taking place (Table 5). In contrast, the equatorial alkyllithium reagent **26c** did not isomerize under the equilibration conditions. We conclude that the equatorial alkyllithium reagent is essentially at equilibrium. Thus, the equilibrium favors the equatorial alkyllithium by several kilocalories per mole for compounds **26a**, **26b**, and **26c**, and we assume that the same is true of the (5,5-dimethylalkyl)lithium **26d**.

Both unsubstituted and equatorial (5-methylalkyl)-lithium reagents equilibrate effectively, but the axial (5-methyl- and (5,5-dimethylalkyl)lithium reagents do not. As discussed above, the problem is one of kinetics rather than thermodynamics. The more hindered alkyllithium reagents also tend to be more basic,[19] and competing protonation by THF effectively limits the utility of the equilibration reaction. This general trend is born out by the data in Table 2, where increasing steric hindrance leads to more protonated product and less coupled product under the equilibration conditions. The rate of equilibration is clearly slower for the hindered lithium reagents **24c** and **24d** than for the relatively unhindered alkyllithium reagent **24a** (Table 2). An associative mechanism is consistent with this trend, and would be analogous to that demonstrated for the epimerization of Grignard reagents[39] and a cyclohexyllithium.[40] If a more efficient equilibration procedure were developed, it could overcome this difficulty and make all of these alkyllithium equilibrations practical. We are investigating this possibility.

Conclusions

The 4-(phenylthio)-1,3-dioxanes were prepared by three different methods, with the DIBAL-H reduction and in situ acetylation being the most general. Reductive lithiation gave excellent selectivity for the axial alkyllithium reagent in all cases. Copper and zinc additives extended the range of electrophiles that could be alkylated with these configurationally defined anions. The equilibration of 4-lithio-1,3-dioxanes to the equatorial alkyllithium reagent works very well for unhindered acetals, but is not effective in hindered systems. Steric hindrance reduces the rate of equilibration and increases the rate of protonation by solvent. Configurationally defined α-alkoxylithium reagents have great potential in organic synthesis, and these studies help to define the scope and limitations of the reductive lithiation and equilibration reactions.

Experimental Section[41]

Preparation of 4-(Phenylthio)-1,3-dioxanes by Reductive Acetylation and Exchange. (2*R*,3*S*)-3-Hydroxy-2-methylnonanoic acid (19). The reaction of boron enolate of (*R*)-3-(1-oxopropyl)-4-(phenylmethyl)-2-oxazolidinone (10.6 g, 45.5 mmol, 1.0 equiv), generated by using dibutylboron triflate (1 M in CH_2Cl_2, 53.2 mmol, 1.17 equiv) and triethylamine (6.1 g, 60.1 mmol, 1.3 equiv) in dry CH_2Cl_2 (100 mL), with heptanal (5.8 g, 50.5 mmol, 1.1 equiv) was performed according to the procedure described by Evans[42] to get a viscous oil (17.0 g). The crude product was purified by flash chromatography (SiO_2, gradient 10−20−25% ethyl acetate/hexanes) to yield a colorless viscous oil (12.8 g, 81.0%, 36.8 mmol). This compound (5.34 g, 15.36 mmol, 1.00 equiv) was hydrolyzed according to the procedure of Evans using lithium hydroperoxide, generated from lithium hydroxide (0.59 g, 24.6 mmol, 1.60 equiv) and 30% hydrogen peroxide (6.30 mL, 61.6 mmol, 4.00 equiv), to yield **19** as a colorless viscous oil (2.89 g, 100%, 15.4 mmol): $[\alpha]^{24}_D = -11.3°$ (*c* 0.98, $CHCl_3$); IR (neat) 3400, 2930, 1709, 1462, 1208 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.30−6.80 (br, m, 2 H), 3.96−3.90 (m, 1 H), 2.60−2.52 (m, 1 H), 1.50−1.22 (m, 10 H), 1.17 (d, $J = 7.2$ Hz, 3 H), 0.86 (t, $J = 6.5$ Hz, 3 H); ^{13}C NMR (50 MHz, $CDCl_3$, DEPT) δ *C* 180.9; *C*H 71.9, 44.2; *C*H_2 33.7, 31.8, 29.2, 25.9, 22.6; *C*H_3, 14.0, 10.4. Anal. Calcd for $C_{10}H_{20}O_3$: C, 63.80; H, 10.71. Found: C, 63.88; H, 10.62.

A Standard Procedure for Noyori Acetalization/Ketalization of β-Hydroxy Acids. Hydroxy acid (2.0 mmol) was dissolved in dry CH_2Cl_2 (10 mL), to it was added Et_3N (552 mg, 0.61 mL, 4.4 mmol, 2.2 equiv), and the mixture was cooled

(36) Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440−67.

(37) Rotamers around the C4−S and S−Ph bonds lead to a group of structures with similar steric energies for each ring conformation. Rotations around these bonds should have little effect on the chemistry and were ignored in the analysis.

(38) (a) Malatesta, V.; McKelvey, R. D.; Babcock, B. W.; Ingold, K. U. *J. Org. Chem.* **1979**, *44*, 1872−3. (b) Gregory, A. R.; Malatesta, V. *J. Org. Chem.* **1980**, *45*, 122−5.

(39) (a) Whitesides, G. M.; Roberts, J. D. *J. Am. Chem. Soc.* **1965**, *87*, 4878−88. (b) Fraenkel, G.; Cottrell, C. E.; Dix, D. T. *J. Am. Chem. Soc.* **1971**, *93*, 1704−8.

(40) Reich, H. J.; Medina, M. A.; Bowe, M. D. *J. Am. Chem. Soc.* **1992**, *114*, 11003−4.

(41) The general experimental is included in the Supporting Information.

(42) Gage, J. R.; Evans, D. A. *Organic Syntheses*; Wiley: New York, 1993; Coll. Vol. VIII, pp 339−343.

in an ice bath. TMSCl (652 mg, 0.76 mL, 6.0 mmol, 3.0 equiv) was then added to it, and the mixture was stirred under N_2 atmosphere for 20 h at room temperature. The red-colored reaction mixture was cooled in an ice bath, to it was added dry pentane (10 mL) to precipitate $Et_3N{\cdot}HCl$, and then the suspension was filtered to remove the precipitate. Solvents were evaporated under N_2 atmosphere using a regular short path distillation apparatus. The resulting red residue was distilled bulb to bulb to afford a colorless viscous semisolid which was immediately transferred to a dry flask using dry CH_2Cl_2 (15 mL) and then cooled under N_2 atmosphere to −78 °C. Freshly distilled aldehyde or ketone (2.0 equiv) was syringed in followed by 2,6-di-*tert*-butylpyridine (15 μL, 0.1 mmol, 0.05 equiv) and TMSOTf (35 μL, 0.2 mmol, 0.1 equiv). After the specified time of stirring at −78 °C, the reaction mixture was quenched by adding a mixture of MeOH and Et_3N (1:1, 0.3 mL). Removal of volatile solvents gave a pale yellow oil which was purified by chromatography.

(2*S*,5*R*,6*S*)-2,5-Dimethyl-6-hexyl-1,3-dioxan-4-one (20). Using the general procedure described above for acetalization, hydroxy acid **19** (376 mg, 2.0 mmol) was reacted with acetaldehyde (0.22 mL, 4.0 mmol, 2.0 equiv) (3 h of stirring at −78 °C) to obtain a pale yellow oil. The crude product was purified by chromatography (SiO_2, gradient 10−20% Et_2O/pentane) to afford a colorless oil (351 mg, 1.64 mmol, 81.8%): $[\alpha]^{24}_D = 5.94°$ (*c* 1.25, $CHCl_3$); IR (neat) 2929, 1748, 1248, 1070, 948 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.46 (q, J = 5.1 Hz, 1 H), 3.91−3.87 (m, 1 H), 2.64 (dq, J = 7.5, 4.2 Hz, 1 H), 1.72−1.63 (m, 1 H), 1.58 (d, J = 7.8 Hz, 3 H), 1.54−1.37 (m, 9 H), 1.32 (d, J = 7.2 Hz, 3 H), 0.98 (t, J = 6.6 Hz, 3 H); ^{13}C NMR (50 MHz, $CDCl_3$, DEPT) δ *C* 172.5; *C*H 100.2, 77.0, 39.0; *C*H_2 31.7, 31.1, 29.1; 25.2, 22.6; *C*H_3 21.2, 14.0, 11.9. MS (HRCI−NH_3) calcd for $C_{12}H_{22}O_3$ (M + H) 215.1647, found 215.1643.

A Standard Procedure for a One-Pot DIBAL-H Reduction and Acetate Formation from Lactones.[14] The lactone (1.0 mmol) was dissolved in dry CH_2Cl_2 (5 mL), the solution was cooled to −78 °C, and DIBAL-H (1 M in cyclohexane, 1.1 mL, 1.1 mmol, 1.1 equiv) was added dropwise. After being stirred for 3 h, the reaction mixture was treated with pyridine (237 mg, 0.24 mL, 3.0 mmol, 3.0 equiv), and then DMAP (134 mg, 1.1 mmol, 1.1 equiv) was cannulated in the reaction mixture as a solution in dry CH_2Cl_2 (2 mL). Finally, Ac_2O (408 mg, 0.38 mL, 4.0 mmol, 4.0 equiv) was added, and the reaction mixture was allowed to warm slowly to room temperature. The resulting red-orange reaction mixture was quenched after 14 h with saturated NH_4Cl, and allowed to stir for 30 min. After extraction with CH_2Cl_2 (4×), the combined CH_2Cl_2 extracts were washed with 1 N $NaHSO_4$ (2×), saturated $NaHCO_3$ (3×), and brine. After drying (anhydrous Na_2SO_4) and evaporation of CH_2Cl_2, the residue obtained was purified by flash chromatography.

(2*S*,4*R*,5*R*,6*S*)-4-Acetoxy-2,5-dimethyl-6-hexyl-1,3-dioxane (15). Application of the one-pot reduction and acetate formation procedure to lactone **20** (214 mg, 1.0 mmol) gave a yellow oil which was purified by chromatography (SiO_2, 5% EtOAc/hexanes) to afford **15** as a colorless oil (233 mg, 0.83 mmol, 90.3%): $[\alpha]^{24}_D = -17.45°$ (*c* 0.975, $CHCl_3$); IR (neat) 2931, 1762, 1226, 1112, 1056 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.88 (d, J = 2.5 Hz, 1 H), 4.85 (q, J = 5 Hz, 1 H), 3.66 (ddd, J = 7.5, 5.0, 2.0 Hz, 1 H), 2.13 (s, 3 H), 1.77−1.21 (m, 11 H), 1.38 (d, J = 5.5 Hz, 3 H), 0.98 (d, J = 6.5 Hz, 3 H), 0.88 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (50 MHz, $CDCl_3$, DEPT) δ *C* 169.1; *C*H 97.6, 95.8, 78.4, 35.1; *C*H_2 31.9, 31.76, 29.2, 25.3, 22.6; *C*H_3 21.1, 20.6, 14.1, 5.0. Anal. Calcd for $C_{14}H_{26}O_4$: C, 65.09; H, 10.14. Found: C, 65.14; H, 10.22.

Standard Procedure for the Preparation of 4-(Phenylthio)-1,3-dioxanes from 4-Acetoxy-1,3-dioxanes. The acetate (0.50 mmol) was dissolved in dry CH_2Cl_2 (5 mL), and to it was added thiophenol (110 mg, 0.10 mL, 1.0 mmol, 2.0 equiv). After being cooled to −78 °C, the reaction mixture was treated with $BF_3{\cdot}Et_2O$ (213 mg, 0.19 mL, 1.50 mmol, 3.0 equiv). The colorless reaction mixture was stirred for 1 h at −78 °C and then quenched at that temperature by adding 1 N NaOH (5 mL). The reaction mixture was warmed to room temperature and extracted with CH_2Cl_2 (3×). The combined CH_2Cl_2 extracts were washed with 1 N NaOH (3×) and brine and dried over anhydrous Na_2SO_4. The residue obtained after evaporation was purified by flash chromatography.

(2*S*,4*S*,5*R*,6*S*)-2,5-Dimethyl-6-hexyl-4-(phenylthio)-1,3-dioxane (17). According to the general procedure for the preparation of phenylthioacetals described above, acetate **15** (129 mg, 0.50 mmol) gave a pale yellow oil which was purified by chromatography (SiO_2, 5% EtOAc/hexanes) and gave a colorless oil (154 mg, 0.5 mmol, 100%): $[\alpha]^{24}_D = -216°$ (*c* 1.33, $CHCl_3$); IR (neat) 2934, 1584, 1147, 1106, 937 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.44 (d, J = 7.0 Hz, 2 H), 7.30−7.20 (m, 3 H), 5.43 (q, J = 5.0 Hz, 1 H), 5.38 (s, 1 H), 4.00 (ddd, J = 7.7 Hz, 5.5, 2.2 Hz, 1 H), 1.85 (qd, J = 7.0, 2.5 Hz, 1 H), 1.60−1.22 (m, 10 H), 1.33 (d, J = 5.0 Hz, 3 H), 1.17 (d, J = 7.0 Hz, 3 H), 0.89 (t, J = 6.8 Hz, 3 H); ^{13}C NMR (50 MHz, $CDCl_3$, DEPT) δ *C* 135.5; *C*H 130.9, 129.0, 126.9, 92.3, 90.2, 75.3, 36.8; *C*H_2 32.5, 31.8, 29.3, 25.3, 22.7; *C*H_3 20.7, 14.1, 12.8. Anal. Calcd for $C_{18}H_{28}O_2S$: C, 70.09; H, 9.15. Found: C, 70.01; H, 8.99.

(2*S*,4*R*,5*S*,6*S*)- and (2*S*,4*S*,5*S*,6*S*)-2,5-Dimethyl-6-hexyl-4-(phenylthio)-1,3-dioxane (18). Acetate **15** (3.00 g, 11.6 mmol) was converted to the thiophenyl ether using standard conditions described above, and the product was isolated as a colorless oil (3.42 g, 11.1 mmol, 96%) after chromatographic purification (SiO_2, 20% CH_2Cl_2/hexanes to 5% EtOAc/hexanes). ^1H NMR and GC analysis indicated it to be a 3:1 mixture of C4 anomers: IR (mixture of isomers, neat) 2929, 1409, 1139, 1015, 940 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, major isomer) δ 7.47−7.45 (m, 2 H), 7.34−7.22 (m, 3 H), 5.60 (q, J = 5.2 Hz, 1 H), 5.49 (d, J = 4.9 Hz, 1 H), 3.61 (ddd, J = 10.4, 8.1, 2.6 Hz, 1 H), 2.26−2.18 (m, 1 H), 1.65−1.23 (m, 10 H), 1.32 (d, J = 5.2 Hz, 3 H), 0.95 (d, J = 7.3 Hz, 3 H), 0.89 (t, J = 7.0 Hz, 3 H); characteristic ^1H NMR peaks for the minor isomer δ 4.76 (q, J = 4.9 Hz, 1 H), 4.61 (d, J = 10.2 Hz, 1 H), 3.27−3.22 (m, 1 H), 1.39 (d, J = 5.2 Hz, 3 H), 0.98 (d, J = 6.7 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT, major isomer) δ *C* 135.4; *C*H 132.0, 128.9, 126.8, 91.7, 90.5, 77.7, 39.0; *C*H_2 32.7, 31.9, 29.3, 24.6, 22.7; *C*H_3 20.6, 14.1, 13.9. Anal. Calcd for $C_{18}H_{28}O_2S$; C, 70.09; H, 9.15. Found: C, 69.89; H, 8.95.

(2*S*,4*R*,5*R*,6*S*)- and (2*S*,4*S*,5*R*,6*S*)-6-Hexyl-5-methyl-2-phenyl-4-(phenylthio)-1,3-dioxane (21). The corresponding acetate precursor was prepared in three steps from **19** in 74% overall yield in the manner described in Scheme 4. This acetate (2.33 g, 7.27 mmol) was converted to thiophenyl ether **21** using the standard conditions described above, and the product was isolated as a pale yellow oil (2.43 g, 6.56 mmol, 90%) after chromatographic purification (SiO_2, 15% CH_2Cl_2/hexanes to 3% EtOAc/hexanes). ^1H NMR analysis indicated it to be a 2:1 mixture of C4 anomers: IR (mixture of isomers, neat) 2930, 2856, 1455, 1115, 987 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, major isomer) δ 7.56−7.46 (m, 4 H), 7.39−7.23 (6 H), 6.40 (s, 1 H), 5.56 (s, 1 H), 4.26 (ddd, J = 7.9, 5.3, 2.4 Hz, 1 H), 1.95 (dddd, J = 7.0, 7.0, 7.0, 2.1 Hz, 1 H), 1.75−1.64 (m, 1 H), 1.53−1.40 (m, 2 H), 1.39−1.27 (m, 7 H), 1.28 (d, J = 7.0 Hz, 3 H), 0.92 (t, J = 6.7 Hz, 3 H); characteristic ^1H NMR peaks for minor isomer δ 5.59 (s, 1 H), 5.30 (d, J = 2.1 Hz, 1 H), 3.87 (ddd, J = 7.9, 5.6, 2.2 Hz, 1 H), 1.20 (d, J = 6.7 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT, major isomer) δ *C* 138.5, 135.2; *C*H 132.6, 131.1, 129.0, 128.3, 126.3, 126.2, 94.4, 90.5, 75.9, 37.0; *C*H_2 32.4, 31.8, 29.3, 25.3, 22.6; *C*H_3 14.1, 12.9. Anal. Calcd for $C_{23}H_{30}O_2S$; C, 74.55; H, 8.16. Found: C, 74.60; H, 7.93.

(4*R,6*S**)-4-(Phenylthio)-2,2,6-trimethyl-1,3-dioxane (22).** The corresponding acetate precursor (94 mg, 0.50 mmol) was converted to thiophenyl ether **22** using the standard conditions described above, and the product was isolated as a colorless oil (110 mg, 0.46 mmol, 92%) after chromatographic purification (SiO_2, 50% CH_2Cl_2/hexanes to 10% EtOAc/hexanes): IR (neat) 2990, 1168, 959, 691 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$)) δ 7.49−7.47 (m, 2 H), 7.31−7.24 (m, 3 H), 5.26 (dd, J = 12.1, 2.6 Hz, 1 H), 4.05 (ddddd, J = 11.6, 5.9, 5.9, 5.9, 2.5 Hz, 1 H), 1.81 (dt, J = 13.0, 2.6 Hz, 1 H), 1.56−1.48 (m, 1 H), 1.50 (s, 3 H), 1.49 (s, 3 H), 1.18 (d, J = 5.8 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ *C* 134.2, 100.1; *C*H 131.2, 128.8, 127.1, 77.5, 65.6; *C*H_2 38.2; *C*H_3 30.2, 21.9, 19.8. Anal. Calcd for $C_{13}H_{18}O_2S$; C, 65.51; H, 7.61. Found: C, 65.77; H, 7.39.

Reduction and Alkylation of a 4-(Phenythio)-1,3-dioxane. A Standard Procedure for Kinetic Reductive Coupling of Phenylthioacetals Using LiDBB. A solution of LiDBB in dry THF (ca. 0.2 M) was prepared according to the procedure described by Cohen.[43] The phenylthioacetal (1 mmol) was dissolved in dry THF (4 mL), and to it was added a crystal of 1,10-phenanthroline. The solution was cooled under Ar to −78 °C, and then *n*-BuLi (2.0 M solution in hexanes) was added dropwise until a permanent red coloration just appeared (typically about 50−100 μL was enough to quench any moisture in the reaction). The LiDBB solution (4.0 mmol, 4.0 equiv) was added dropwise to the reaction mixture. Initially, an orange-red color appeared, and addition was continued until a permanent dark green color persisted. For kinetic coupling experiments, after 5 min the green reaction mixture was treated with electrophile (6 mmol, 6 equiv) and then allowed to stir at −78 °C for 1 h. The reaction mixture was quenched with 10% NH_4OH/saturated NH_4Cl (1:1) (Me_2SO_4 as electrophile) or with saturated NH_4Cl solution (for acetone or tributyltin chloride as electrophiles). The reaction mixture was extracted with CH_2Cl_2 (3×), and the combined organic layers were washed with brine (1×), dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The crude product was purified by chromatography (SiO_2). Initially, 20% CH_2Cl_2/hexanes was used as eluant to remove thiophenol and di-*tert*-butylbiphenyl, followed by the appropriate solvent system to elute the product.

(2*R,4*S**,6*S**)-6-Hexyl-4-methyl-2-(1-methylethyl)-1,3-dioxane (25a):** IR (neat) 2930, 2857, 1459, 1151, 1015 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.43 (d, J = 5.6 Hz, 1H), 4.25 (quintet, J = 6.8 Hz, 1H), 3.75−3.63 (m, 1H), 1.82−1.58 (m, 2H), 1.55−1.15 (m, 11H), 1.29 (d, J = 6.8 Hz, 3H), 0.90−0.80 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) *C*H 98.0, 71.2, 67.6, 32.7; *C*H_2 36.1, 35.2, 31.7, 29.1, 24.9, 22.4; *C*H_3 17.1, 17.0, 13.9. Anal. Calcd for $C_{14}H_{28}O_2$: C, 73.63; H, 12.36. Found C, 73.54; H, 12.26.

(2*R*,4*S*,5*R*,6*S*)-2,4,5-Trimethyl-6-hexyl-1,3-dioxane (25b). Treatment of **23b** (200 mg, 0.648 mmol) with LiDBB under kinetic conditions followed by reaction with Me_2SO_4 (492 mg, 370 μL, 3.90 mmol, 6.0 equiv) and chromatography (3% *tert*-butylmethyl ether/hexanes) gave a mixture of protonated and desired products (136 mg). On the basis of GC analysis of the mixture, the total yield of **25b** was estimated to be 76.5% (106 mg, 0.494 mmol). Careful rechromatography of the mixture gave some pure fractions of **25b**, a pale yellow oil: $[\alpha]^{24}_D$ = 73.2° (*c* 0.505, $CHCl_3$); IR (neat) 2927, 1407, 1144, 1139 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.98 (q, J = 4.9 Hz, 1 H), 4.07−4.02 (m, 1 H), 3.46−3.42 (m, 1 H), 1.98−1.90 (m, 1 H), 1.56−1.22 (m, 10 H), 1.24 (d, J = 5.2 Hz, 3 H), 1.20 (d, J = 7.0, 3 H), 0.85 (t, J = 6.9 Hz, 3 H), 0.68 (d, J = 7.0 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ *C*H 91.1, 76.2, 72.6, 36.7; *C*H_2 32.9, 31.9, 29.4, 24.9, 22.6; *C*H_3 21.4, 14.1, 12.9, 12.4. Anal. Calcd for $C_{13}H_{26}O_2$: C, 72.85; H, 12.23. Found: C, 73.00; H, 12.19.

(2*R*,4*S*,5*S*,6*S*)-2,4,5-Trimethyl-6-hexyl-1,3-dioxane (25c): $[\alpha]^{24}_D$ = − 17.0° (*c* 1.06, $CHCl_3$); IR (neat) 2932, 2858, 1409, 1154, 1112 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.95 (q, J = 5.1 Hz, 1 H), 3.91 (q, J = 7.0 Hz, 1 H), 3.85−3.82 (m, 1 H), 1.56−1.48 (m, 1 H), 1.34 (d, J = 6.9 Hz, 3 H), 1.32−1.17 (m, 10 H), 1.24 (d, J = 5.2 Hz, 3 H), 1.08 (d, J = 5.1 Hz, 3 H), 0.85 (t, J = 6.9 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$, DEPT) δ *C*H, 91.7; *C*H, 75.3; *C*H, 73.8; *C*H, 35.0; *C*H_2 32.6; *C*H_2 31.8; *C*H_2 29.3; *C*H_2 25.4; *C*H_2 22.6; *C*H_3 21.4; *C*H_3 17.1; *C*H_3 14.1; *C*H_3 13.0; Anal. Calcd for $C_{13}H_{26}O_2$: C, 72.85; H, 12.23. Found: C, 73.00; H, 12.41.

(2*R,4*S**,6*S**)-2,4,5,5-Tetramethyl-6-hexyl-1,3-dioxane (25d).** Treatment of **23d** (200 mg, 0.620 mmol) with LiDBB under kinetic conditions followed by reaction with Me_2SO_4 (492 mg, 370 μL, 3.90 mmol, 6.0 equiv) and chromatography (4% *tert*-butylmethyl ether/hexanes) gave a mixture of protonated and desired products (131 mg). On the basis of GC analysis of the mixture, the total yield was estimated to be 83.1% (118 mg, 0.517 mmol). Careful rechromatography of the mixture gave some pure fractions of **25d**, a pale yellow oil: IR (neat) 2958, 2929, 1407, 1136 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.98 (q, J = 5.2 Hz, 1 H), 3.64 (q, J = 6.9 Hz, 1 H), 3.53−3.51 (m, 1 H), 1.58−1.58 (m, 1 H), 1.38−1.14 (m, 9 H), 1.26 (s, 3 H), 1.25 (d, J = 7.2 Hz, 3 H), 1.10 (s, 3 H), 0.86 (t, J = 6.9 Hz, 3 H), 0.67 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ *C* 34.9; *C*H 91.7, 78.8, 78.7; *C*H_2 31.9, 29.4, 29.1, 26.7, 22.7; *C*H_3 22.0, 21.7, 21.3, 14.1, 13.5. Anal. Calcd for $C_{14}H_{28}O_2$: C, 73.63; H, 12.36. Found: C, 73.54; H, 12.25.

Reduction, Equilibration, and Alkylation of a 4-(Phenylthio)-1,3-dioxane. A Standard Procedure for Thermodynamic Reductive Coupling of Phenylthioacetals Using LiDBB. The procedure was identical to kinetic coupling, except after 5 min at −78 °C the reaction mixture was warmed to −20 °C in a cryobath. After being stirred for 30 min at −20 °C, the green reaction mixture was recooled to −78 °C and then stirred for 5 min before being quenched with the electrophile.

(2*R,4*R**,6*S**)-6-Hexyl-4-methyl-2-(1-methylethyl)-1,3-dioxane (27a):** IR (neat) 2931, 2855, 1165, 1121, 1031 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.15 (d, J = 5.8 Hz, 1 H), 3.74−3.56 (m, 1 H), 3.55−3.42 (m, 1 H), 1.85−1.68 (m, 1 H), 1.65−1.20 (m, 12 H), 1.19 (d, J = 6.2 Hz, 3 H), 0.91 (d, J = 6.8 Hz, 6 H), 0.87 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) *C*H 105.4, 76.2, 72.3, 32.8; *C*H_2 39.1, 36.0, 31.8, 29.3, 25.1, 22.6; *C*H_3 21.7, 17.6, 17.3, 14.1. Anal. Calcd for $C_{14}H_{28}O_2$: C, 73.63; H, 12.36. Found: C, 73.66; H, 12.19.

(2*R*,4*R*,5*R*,6*S*)-2,4,5-Trimethyl-6-hexyl-1,3-dioxane (27b): $[\alpha]^{24}_D$ = 24.6° (*c* = 0.9, $CHCl_3$); IR (neat) 2931, 2857, 1150, 1133 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.68 (q, J = 5.1 Hz, 1 H), 3.29 (dddd, J = 9.6, 6.2, 6.2, 6.2 Hz, 1 H), 3.16−3.12 (m, 1 H), 1.62−1.55 (m, 1 H), 1.52−1.45 (m, 1 H), 1.42−1.34 (m, 1 H), 1.29 (d, J = 5.2 Hz, 3 H), 1.29−1.22 (m, 8 H), 1.20 (d, J = 6.1 Hz, 3 H), 0.86−0.84 (app t, 3 H), 0.73 (d, J = 6.4 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ *C*H 98.2, 81.7, 77.9, 40.3; *C*H_2 32.8, 31.9, 29.4, 25.1, 22.6; *C*H_3 21.2, 19.4, 14.1, 12.4. Anal. Calcd for $C_{13}H_{26}O_2$; C, 72.85; H, 12.23. Found: C, 73.00; H, 12.36.

(2*S*,4*S*,5*R*,6*S*)-2,5-Dimethyl-4-(tributylstannyl)-6-hexyl-1,3-dioxane (28) Prepared from phenylthioacetal **23c** in 88% yield according to the kinetic coupling procedure using tributyltin chloride as the electrophile: $[\alpha]^{24}_D$ = − 41.9° (*c* 0.63, $CHCl_3$); IR (neat) 2927, 1460, 1378, 1112 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.53 (q, J = 5.2 Hz, 1 H), 4.41 (t, J = 12.3 Hz, 1 H), 3.70−3.67 (m, 1 H), 1.54−1.47 (m, 8 H), 1.35−1.24 (m, 18 H), 1.15 (d, J = 6.8 Hz, 3 H), 0.93 (d, J = 7.5 Hz, 3 H), 0.91−0.87 (m, 15 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 98.8, 81.8, 78.6, 36.1, 33.1, 31.8, 29.3, 29.1, 27.4, 25.3, 22.6, 21.2, 14.0, 14.0, 13.6, 10.2; MS (HRCI) calcd for $C_{24}H_{50}O_2Sn$ (M − Bu) 433.2128, found 433.2130.

(2*S*,4*R*,5*R*,6*S*)-2,5-Dimethyl-4-(tributylstannyl)-6-hexyl-1,3-dioxane (32). A solution of **31** (52 mg, 0.08 mmol) in CH_2Cl_2 (2 mL) was cooled to −78 °C, and $BF_3{\cdot}OEt_2$ (13 μL, 0.105 mmol) was added. The reaction was stirred at −78 °C for 5 h, and was then quenched with 3 mL of saturated $NaHCO_3$, being allowed to warm to room temperature. The mixture was extracted with CH_2Cl_2 (2×), and dried over Na_2SO_4. Filtration, concentration, and MPLC separation (SiO_2, 5% *t*-BuOMe/hexanes) gave the product (29 mg, 74%) as a colorless oil: $[\alpha]^{24}_D$ = + 3.80° (*c* 0.69, $CHCl_3$) IR (neat) 2928, 1459, 1406, 1378, 1113, 967 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 4.59 (dd, J = 9.9, 4.8 Hz, 1 H), 4.27−4.23 (app t, 1 H), 3.66−3.65 (m, 1 H), 1.53−1.47 (m, 8 H), 1.37−1.28 (m, 15 H), 1.24 (d, J = 5.2 Hz, 3 H), 1.06 (d, J = 7.2 Hz, 3 H), 0.93−0.84 (m, 18 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 101.8, 81.7, 80.3, 36.0, 33.4, 31.8, 29.3, 29.1, 27.3, 25.2, 22.6, 21.3, 14.1, 13.7, 11.9, 9.2; MS (HRCI−NH_3) calcd for $C_{24}H_{50}O_2Sn$ (M + H) 491.2911, found 491.2916.

Transmetalation and Equilibration Using Alkylstannanes. Standard Procedure for Kinetic Tin−Lithium Transmetalations. The tributylstannyl compound **28** or **32** was dissolved in toluene, and any residual water was removed by azeotrope on a rotary evaporator. This sequence was repeated twice to ensure the compound was thoroughly dry before continuing. The flask was equipped with a stirbar, fitted

(43) Mudryk, B.; Cohen, T. *Org. Synth.* **1993**, *72*, 173−179.

with a septum, and placed under argon. Dry THF (typically 1−3 mL) was added, the solution was cooled to −78 °C, and a solution of *n*-BuLi (ca. 2.0 M solution in hexanes, 3 equiv) was added at once to the mixture. After 5 min, Me_2SO_4 (5−10 equiv) was added at once, and the flask was packed in a dry ice bath and allowed to warm to room temperature overnight. Saturated NH_4Cl (5 mL) and water (5 mL) were added, and the mixture was extracted with Et_2O (3×). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. Chromatography (SiO_2, 5% *t*-BuOMe/hexanes) afforded the corresponding methylated product as a colorless oil.

Preparation of 4-(Phenylthio)-1,3-dioxanes by the Acetal Exchange Reaction. (2*S,4*S**,6*S**)-6-Hexyl-2-(1-methylethyl)-4-(phenylthio)-1,3-dioxane (33).** Racemic *β*-hydroxy aldehyde **8** (2.05 g, 13.0 mmol), DMAP (158 mg, 1.29 mmol), and freshly distilled isobutyraldehyde (18.0 mL, 198.2 mmol) were dissolved in THF (75 mL), and DBU (1.0 mL, 6.69 mmol) was added neat. The reaction was stirred for 14 h, at which point NEt_3 (3.6 mL, 25.8 mmol) and Ac_2O (2.0 mL, 21.2 mmol) were added sequentially. After 1 h, the reaction was quenched by the slow addition of saturated $NaHCO_3$ (10 mL). Ether (500 mL) was added, the layers were separated, and the organic layer was washed with 1 N $NaHSO_4$ (2×) and brine (1×) and dried ($MgSO_4$). The crude product was filtered, concentrated, and Kugelrohr distilled (110 °C, 0.3 mmHg) to yield a colorless oil (3.65 g). This oil was dissolved in CH_2Cl_2 (50 mL), and thiophenol (2.0 mL, 19.5 mmol) was added. The mixture was cooled to −78 °C, and $BF_3{\cdot}OEt_2$ was added (4.0 mL, 32.5 mmol). After 1 h at −78 °C, the reaction was quenched with MeOH (5 mL), 1 N NaOH (10 mL) was added, and the mixture was warmed to room temperature. After addition of Et_2O, the layers were separated, and the organic layer was washed with 1 N NaOH (2×) and brine (1×). The crude product was dried (Na_2SO_4), filtered, concentrated, and passed through a short plug of silica gel (eluting with 5% *tert*-butylmethyl ether/hexanes). The crude product was concentrated to a yellow oil and distilled under reduced pressure (140−160 °C, 0.3 mmHg) to yield **33** (3.64 g, 11.3 mmol, 87%). Major isomer (4,6-anti): IR (mixture, neat) 2958, 2929, 1474, 1113, 738 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.52−7.45 (m, 2 H), 7.31−7.20 (m, 3 H), 5.73 (d, J = 5.5 Hz, 1 H), 5.03 (d, J = 6.0 Hz, 1 H), 3.92−3.83 (m, 1 H), 2.07 (ddd, J = 13.7, 11.8, 6.0 Hz, 1 H), 1.85−1.76 (m, 2 H), 1.64−1.22 (m, 10 H), 0.92 (d, J = 6.8 Hz, 3 H), 0.89 (t, J = 7.0 Hz, 3 H), 0.86 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) *C* 135.1; *C*H 130.9, 128.6, 126.6, 98.0, 83.4, 72.5, 32.3; *C*H_2 36.2, 35.7, 31.7, 29.0, 24.7, 22.4; *C*H_3 17.2, 17.0, 13.9. Anal. Calcd for $C_{19}H_{30}O_2S$: C, 70.76; H, 9.38. Found: C, 71.03; H, 9.28. Minor isomer (4,6-syn): ^1H NMR (500 MHz, $CDCl_3$, characteristic peaks) δ 4.96 (dd, J = 11.8, 2.5 Hz, 1 H), 4.24 (d, J = 5.8 Hz, 1 H), 3.60−3.55 (m, 1 H).

(2*R,4*S**,6*R**)-6-Hexyl-4-(2-propenyl)-2-(1-methylethyl)-1,3-dioxane (34).** A solution of LiDBB in dry THF (ca. 0.2 M) was prepared according to the procedure described by Cohen.[43] The phenylthioacetal **33** (161 mg, 0.50 mmol) was first titrated with *n*-BuLi and then treated with LiDBB until the deep green color persisted. After 5 min, $CuBr{\cdot}Me_2S$ (122 mg, 0.59 mmol) was added as a solid at −78 °C, and the mixture was stirred for 20 min. Allyl bromide (0.22 mL, 2.50 mmol) was then added neat, and the reaction was allowed to warm to room temperature over 7 h, when it was quenched with saturated NH_4Cl, and worked up as above. After initial crude chromatography (SiO_2, eluting with 20% CH_2Cl_2/hexanes and then 5% EtOAc/hexanes), further purification by MPLC (2% EtOAc/hexanes) yielded a pale yellow oil (88 mg, 69%): IR (neat) 2929, 2857, 1470, 1118, 995 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.80 (dddd, J = 17.1, 10.2, 7.0, 7.0 Hz, 1 H), 5.11−5.06 (m, 2 H), 4.43 (d, J = 5.8 Hz, 1 H), 4.14−4.09 (m, 1 H), 3.74−3.70 (m, 1 H), 2.72−2.67 (m, 1 H), 2.31 (ddd, J = 14.2, 7.1, 7.1 Hz, 1 H), 1.79−1.69 (m, 2 H), 1.59−1.51 (m, 1 H), 1.41−1.36 (m, 3 H), 1.35−1.24 (m, 7 H), 0.93−0.87 (m, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.0, 116.9, 98.7, 71.8, 71.5, 36.2, 35.5, 33.5, 32.9, 31.8, 29.2, 25.0, 22.6, 17.3, 17.3, 14.1. Anal. Calcd for $C_{16}H_{30}O_2$: C, 75.54; H, 11.89. Found: C, 75.42; H, 11.70.

(2*R,4*R**,6*R**)-6-Hexyl-4-(2-propenyl)-2-(1-methylethyl)-1,3-dioxane (35).** A solution of LiDBB in dry THF (ca. 0.2 M) was prepared according to the procedure described by Cohen.[43] The phenylthioacetal **33** (221 mg, 0.69 mmol) was first titrated with *n*-BuLi and then treated with LiDBB until the deep green color persisted. After 5 min, the solution was warmed to −20 °C for 30 min, and then recooled to −78 °C. After 5 min, $CuBr{\cdot}SMe_2$ (169 mg, 0.82 mmol) was added as a solid at −78 °C, and the solution was stirred for 20 min. Allyl bromide (0.18 mL, 2.1 mmol) was then added neat, and the reaction was allowed to warm to room temperature over 7 h, when it was quenched with saturated NH_4Cl, and worked up as above. After initial crude chromatography (SiO_2, eluting with 20% CH_2Cl_2/hexanes and then 5% EtOAc/hexanes), further purification by MPLC (2% EtOAc/hexanes) yielded a pale yellow oil (65 mg, 38%): IR (neat) 2930, 2857, 1472, 1120, 1032 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.84 (dddd, J = 17.0, 10.0, 7.0, 7.0 Hz, 1 H), 5.10−5.03 (m, 2 H), 4.15 (d, J = 5.9 Hz, 1 H), 3.58 (dddd, J = 11.0, 6.5, 6.5, 2.3 Hz, 1 H), 3.52−3.48 (m, 1 H), 2.38−2.33 (m, 1 H), 2.22−2.16 (m, 1 H), 1.79 (dddd, J = 13.1, 6.6, 6.6, 6.6 Hz, 1 H), 1.58−1.53 (m, 1 H), 1.49 (dt, J = 13.0, 2.4 Hz, 1 H), 1.43−1.38 (m, 2 H), 1.32−1.27 (m, 8 H), 0.93 (d, J = 6.8 Hz, 6 H), 0.88 (t, J = 6.9 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 134.4, 116.8, 105.5, 76.3, 75.8, 40.4, 36.8, 36.0, 32.9, 31.8, 29.2, 25.1, 22.6, 17.5, 17.4, 14.1. Anal. Calcd for $C_{16}H_{30}O_2$: C, 75.54; H, 11.89. Found: C, 75.39; H, 11.78.

Cyclohexenone Adduct 37. The phenylthioacetal **33** (302 mg, 0.94 mmol) was dried by titration with *n*-BuLi and then lithiated with the LiDBB solution as described above. After 5 min, $CuBr{\cdot}Me_2S$ (231 mg, 1.12 mmol) was added as a solid at −78 °C and the reaction stirred for 1 h, after which TMSCl (0.36 mL, 2.82 mmol) was added. After 5 min, a precooled solution of TMSCl (0.36 mL, 2.82 mmol) and cyclohexenone (0.27 mL, 2.82 mmol) in THF (2 mL) was cannulated into the reaction mixture, the flask was packed in dry ice, and the mixture was stirred for 14 h at −78 °C. The reaction was quenched by the addition of 5% NaOH (5 mL) and 40% *n*-Bu_4-OH (0.2 mL), and warmed to room temperature. The product was filtered through Celite, extracted 3× with Et_2O, washed with brine, and dried over $MgSO_4$. Chromatography (SiO_2), eluting first with 20% CH_2Cl_2/hexanes to remove nonpolar impurities, followed by 5% EtOAc/hexanes afforded the product (228 mg, 78%), from which an analytically pure sample could be recrystallized from acetone/hexanes: mp = 62−65 °C; IR (KBr) 2957, 2921,1705, 1129, 1118, 1019 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.34 (d, J = 5.9 Hz, 1 H), 3.72 (dd, J = 10.1, 5.5 Hz, 1 H), 3.63−3.58 (m, 1 H), 2.51−2.39 (m, 2 H), 2.36−2.27 (m, 2 H), 2.17−2.10 (m, 2 H), 1.94 (t, J = 12.8 Hz, 1 H), 1.78−1.61 (m, 3 H), 1.54−1.48 (m, 2 H), 1.44−1.34 (m, 3 H), 1.33−1.27 (m, 7 H), 0.93 (d, J = 4.6 Hz, 3 H), 0.92 (d, J = 4.6 Hz, 3 H), 0.88 (t, J = 6.9 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.0, 99.5, 75.7, 71.9, 44.9, 41.5, 37.9, 36.2, 33.1, 31.8, 31.1, 29.2, 27.6, 25.0, 24.9, 22.6, 17.3, 17.3, 14.1. Anal. Calcd for $C_{19}H_{34}O_3$: C, 73.50; H, 11.04. Found: C, 73.61; H, 10.95.

Crotonaldehyde Adduct 39. The phenylthioacetal **33** (302 mg, 0.94 mmol) was dried by titration with *n*-BuLi and then lithiated with the LiDBB solution as described above. After 5 min, a precooled solution of $CuCN{\cdot}2LiCl$ (126 mg, 0.72 mmol) in THF (2 mL) was cannulated into the reaction at −78 °C, and the reaction was stirred for 1 h, after which TMSCl (0.23 mL, 1.8 mmol) was added. After 5 min, a precooled solution of TMSCl (0.23 mL, 1.8 mmol) and crotonaldehyde (0.15 mL, 1.8 mmol) in THF (2 mL) was cannulated into the reaction mixture, the flask was packed in dry ice, and the mixture was allowed to slowly warm to room temperature overnight. The reaction was quenched by the addition of 5% NaOH (5 mL) and 40% *n*-Bu_4OH (0.2 mL), and warmed to room temperature. The product was filtered through Celite, extracted 3× with Et_2O, washed with brine, and dried over $MgSO_4$. Chromatography (SiO_2), eluting first with 20% CH_2Cl_2/hexanes to remove nonpolar impurities, followed by 5% EtOAc/hexanes afforded a colorless oil (145 mg, 0.51 mmol, 85%): IR (neat) 2929, 2718, 1727, 1461, 1380, 1133, 1118 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.79 (s, 1 H), 4.38 (d, J = 6.0 Hz, 1 H), 3.72−3.67 (m, 1 H), 3.62 (ddd, J = 10.2, 5.9, 1.9 Hz, 1 H), 2.78−2.72 (m, 1 H), 2.40

(dd, J = 17.0, 4.1 Hz, 1 H), 2.23 (ddd, J = 17.0, 8.3, 2.2 Hz, 1 H), 1.76−1.67 (m, 2 H), 1.55−1.51 (m, 1 H), 1.47 (dt, J = 13.7, 2.4 Hz, 1 H), 1.40−1.35 (m, 2 H), 1.34−1.27 (m, 7 H), 1.04 (d, J = 6.6 Hz, 3 H), 0.93 (d, J = 6.8 Hz, 3 H), 0.92 (d, J = 6.8 Hz, 3 H), 0.89−0.86 (app t, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.5, 99.5, 75.4, 71.9, 48.2, 36.2, 33.1, 31.8, 31.5, 29.2, 27.4, 25.0, 22.6, 17.4, 17.3, 16.8, 14.1. Anal. Calcd for $C_{17}H_{32}O_3$: C, 71.79; H, 11.34. Found: C, 71.62; H, 11.15.

(*E*)-4-Phenyl-2-butenone Adduct 40. The phenylthioacetal **33** (302 mg, 0.94 mmol) was dried by titration with *n*-BuLi and then lithiated with the LiDBB solution as described above. After 5 min, a precooled solution of CuCN·2LiCl (133 mg, 0.76 mmol) in THF (2 mL) was cannulated into the reaction at −78 °C, and the reaction was stirred for 1 h, after which TMSCl (0.23 mL, 1.92 mmol) was added. After 5 min, a precooled solution of TMSCl (0.23 mL, 1.92 mmol) and benzylidene acetone (281 mg, 1.92 mmol) in THF (2 mL) was cannulated into the reaction mixture, the flask was packed in dry ice, and the mixture was allowed to slowly warm to room temperature overnight. The reaction was quenched by the addition of 5% NaOH (5 mL) and 40% *n*-Bu_4OH (0.2 mL), and warmed to room temperature. The product was filtered through Celite, extracted 3× with EtOAc, and dried over $MgSO_4$. Chromatography (SiO_2), eluting first with 20% CH_2Cl_2/hexanes to remove nonpolar impurities, followed by 10% EtOAc/hexanes afforded a yellow oil (127 mg, 55%): IR (neat) 2926, 2857, 1717, 1359, 1129, 1000 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 (t, J = 7.5 Hz, 2 H), 7.21 (d, J = 7.1 Hz, 2 H), 7.17 (t, J = 7.2 Hz, 1 H), 4.28 (d, J = 6.4 Hz, 1 H), 4.16 (ddd, J = 10.3, 5.9, 2.0 Hz, 1 H), 3.86−3.79 (m, 2 H), 2.77 (dd, J = 16.6, 8.2 Hz, 1 H), 2.64 (dd, J = 16.6, 4.8 Hz, 1 H), 1.98 (s, 3 H), 1.77 (ddd, J = 13.6, 10.9, 5.9 Hz, 1 H), 1.58−1.36 (m, 5 H), 1.33−1.29 (m, 7 H), 0.90−0.87 (app t, 3 H), 0.68 (t, J = 6.8 Hz, 3 H), 0.38 (t, J = 6.8 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.9, 141.5, 128.5, 128.3, 126.5, 99.6, 74.0, 71.8, 48.3, 41.0, 36.2, 32.8, 32.0, 31.8, 30.9, 29.2, 25.1, 22.6, 17.2, 16.5, 14.1. Anal. Calcd for $C_{23}H_{36}O_3$: C, 76.62; H, 10.06. Found: C, 76.52; H, 10.10.

(*E*)-Alkene 41. A solution of LiDBB in dry THF (ca. 0.2 M) was prepared according to the procedure described by Cohen.[43] Phenylthioacetal **33** (195 mg, 0.60 mmol) was dissolved in dry THF (2 mL), and to it was added a crystal of 1,10-phenanthroline. The solution was cooled under Ar to −78 °C, and then *n*-BuLi (2.0 M solution in hexanes) was added dropwise until a permanent red coloration just appeared (typically about 50−100 μL was enough to quench any moisture present). The LiDBB solution was added dropwise to the reaction mixture until the deep green color persisted (indicating excess LiDBB). In a separate flask, a homogeneous CuI−TMEDA solution in THF was made by sequential addition of CuI (123 mg, 0.64 mmol), THF (4 mL), and TMEDA (0.11 mL, 0.71 mmol). After 5 min, the solution of CuI−TMEDA was cooled to −78 °C and cannulated into the reaction mixture. After 20 min, TMSCl (0.19 mL, 1.5 mmol) was added, followed by addition of ethyl propiolate (0.08 mL, 0.75 mmol) after 5 min. The reaction was allowed to stir at −78 °C for 3 h, then was quenched with saturated NH_4Cl, and allowed to warm to room temperature. Et_2O (15 mL) and H_2O (10 mL) were added, the reaction mixture was extracted with Et_2O (×3). The combined organic layers were washed sequentially with 1 N HCl, saturated $NaHCO_3$, and brine (×1), and dried over anhydrous $MgSO_4$. The crude product was purified by chromatography (SiO_2), eluting first with 20% CH_2Cl_2/hexanes as eluant to remove nonpolar impurities, followed by 5% EtOAc/hexane. MPLC using 5% EtOAc/hexane afforded **41** (88 mg, 47%) as a colorless oil: IR (neat) 2930, 1723, 1653, 1268, 1174, 1139 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.02 (dd, J = 16.1, 3.5 Hz, 1 H), 5.99 (dd, J = 16.1, 2.4 Hz, 1 H), 4.78−4.77 (m, 1 H), 4.46 (d, J = 5.7 Hz, 1 H), 4.23 (q, J = 7.1 Hz, 2 H), 3.60−3.55 (m, 1 H), 1.93 (ddd, J = 13.4, 11.8, 6.6 Hz, 1 H), 1.79−1.75 (m, 1 H), 1.64−1.60 (m, 1 H), 1.56−1.53 (m, 1 H), 1.40−1.38 (m, 1 H), 1.31 (t, J = 7.1 Hz, 3 H), 1.29−1.24 (m, 8 H), 0.95 (d, J = 6.8 Hz, 3 H), 0.93 (d, J = 6.8 Hz, 3 H), 0.89−0.86 (m, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.2; 148.0, 122.8, 100.3, 72.7, 71.1, 60.6, 36.0, 34.1, 33.0, 31.8, 29.2, 24.9, 22.6, 17.2, 17.1, 14.3, 14.1. Anal. Calcd for $C_{18}H_{32}O_4$: C, 69.19; H, 10.32. Found: C, 69.38; H, 10.16.

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Supporting Information Available: Calculated geometries and energies for the compounds in Figures 1 and 2 and preparation of compounds **30** and **31**, general experimental details, NOE data for **28**, **32**, **25c**, **27c**, **39**, and **40**, and the X-ray structure of **37**. This material is available free of charge via the Internet at http://pubs.acs.org.

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