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Selectivity Guidelines and a Reductive Elimination-Based Model for Predicting the Stereochemical Course of Conjugate Addition Reactions of Organocuprates to γ-Alkoxy-α,β-enoates

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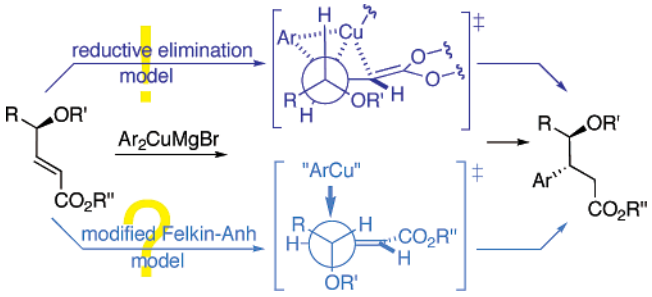
Received November 18, 2005



Current models used to predict the stereochemical outcome of organocopper conjugate addition processes focus on the nucleophilic addition step as stereochemistry-determining. Recent kinetic, NMR, kinetic isotope effect, and theoretical density functional studies strongly support the proposal that stereochemical preferences in these processes are dictated by the reductive elimination step, transforming Cu^{III} to Cu^{I} intermediates. A new model that considers various steric and stereoelectronic factors involved in the transition state of the reductive elimination step is proposed and then used to interpret the results of systematic studies of arylcuprate conjugate addition reactions with cis and trans γ-alkoxy-α,β-enoates. The results give rise to the following selectivity guidelines for this process. To achieve high anti-addition diastereoselectivities the use of trans esters with a bulky nonalkoxy substituent at the γ-position is recommended. While stereoelectronics disfavor syn-addition, a judicious choice of properly sized γ-substituents may lead to the predominant formation of syn-products, especially with cis enoates. However, high syn-selelectivities may be achieved by using γ-amino-α,β-enoates.

Introduction

Conjugate addition reactions of organocopper reagents to α,β-unsaturated carbonyl compounds represent important methods for carbon−carbon bond construction.[1] Control of stereoselectivity in these reactions has attracted considerable attention from both theoretical and synthetic viewpoints.[2] Diastereoselective addition processes with cyclic enones and enoates are highly predictable and have proven to be particularly useful. In contrast, stereochemical outcomes of reactions of conformationally flexible acyclic substrates are much less predictable and these processes often produce mixtures of epimeric products. To make matters worse, the acyclic diastereomers generated in these reactions are rarely well-resolved chromatographically.

Despite being plagued by these problems, reactions of α,β-enoates containing γ-stereocenters have found significant utility in synthesis. Most prominent in this respect are reactions of organocuprates with trans γ-alkoxy-α,β-enoates, which commonly yield products possessing an anti-stereochemical relationship between the γ- and the newly formed β-stereocenters. Although the magnitude of anti-selectivity varies from moderate to high, it is consistently observed in reactions of alkyl-, alkenyl-, and arylcuprates.[3,4] The uniformity of this stereochemical outcome has prompted various investigators to propose transition state models that can be used to predict the stereoselectivity of new transformations.

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10.1021/jo052383v CCC: $33.50
Published on Web 03/02/2006

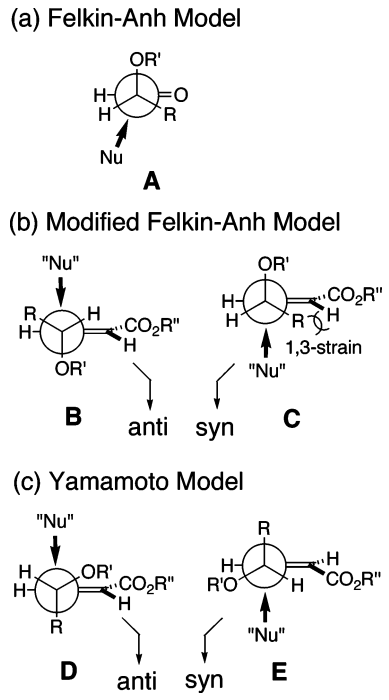

FIGURE 1. Modified Felkin−Anh and Yamamoto interpretations of the stereochemical outcome of organocuprate conjugate addition to γ-alkoxy-α,β-enoates.

The most direct interpretation of anti-selectivity employs the "modified Felkin−Anh" model, in which the carbonyl group in the aldehyde of the original model (Figure 1a, **A**)[5] is replaced by the enoate C−C π-bond (Figure 1b).[6] Originally discussed by Roush more than 20 years ago,[6a,b] this model suggests that nucleophilic attack by an organocuprate takes place from the face opposite to a γ-alkoxy substituent via the preferred reactive conformation **B** rather than **C** owing to allylic 1,3-strain that is present in **C**. Yamamoto and co-workers have systematically studied the dependence of the stereoselectivity on organocopper reagent type and enoate double bond geometry. This effort led to the discovery of a diastereoselectivity reversal from anti to syn as the enoate geometry is changed from trans to cis.[7a,b] A stereochemical model, involving a transition state in which an R group is oriented anti to the approaching nucleophile and an alkoxy group is located at an "inside" position (Figure 1c, **D**), was proposed. These investigators argued that this conformation is stabilized by mixing of the σ-orbital of an electron-rich C−R bond with the developing σ*-orbital of an electron-deficient incipient Nu−C bond, a proposal analogous to one serving as the basis for the Cieplak electronic model.[8] While experimental[9] and theoretical[10] support for the "inside" OR′ preference in ground state enoates exists, the structure of the reactive conformer in the conjugate addition process is not necessarily similar to the ground-state one. Despite having this weakness, this model explains the syn-selectivity observed in reactions with cis enoates, since allylic 1,3-strain would force an OR′ group into an "outside" position as shown in the reactive conformer **E**.

Importantly, a chelation model, which is often used successfully to predict the stereochemical outcome of organometallic addition reactions with α-alkoxy carbonyl compounds, is of less significance due to the lower chelation ability of organocopper reagents relative to organolithium and organomagnesium counterparts. Yamamoto and co-workers have shown that diastereoselectivity trends in organocuprate additions of γ-OTBS and γ-OBn enoates are similar. Because the TBSO group is considered nonchelating, this observation supports the view that chelation is negligible in these reactions.[7b]

As part of a synthetic program aimed at developing practical pathways for the synthesis of medicinally promising Amaryllidaceae constituents (Figure 2), we have extensively utilized conjugate addition reactions of functionalized aromatic copper reagents with various γ-alkoxy-α,β-enoates.[3r,6j] The relative cis orientation of an aromatic group and an adjacent oxygen (marked with asterisks below) is highly conserved in this series of natural products. This corresponds to an anti-stereochemical relationship of these groups in an open-chain precursor.

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(4) Reactions of allylcopper reagents seem to be an exception to the "anti-addition" rule, see: Nicolaou, K. C.; Pavia, M. R.; Seitz, S. P. *J. Am. Chem. Soc.* **1981**, *103*, 1224−1226.

(5) For demonstration of the importance of σ*-orbital energies in determining the "large" group in the Felkin model, see: Lodge, E. P.; Heathcock, C. H. *J. Am. Chem. Soc.* **1987**, *109*, 3353−3361.

(6) For selected discussions of the modified Felkin−Anh model, see: (a) Roush, W. R.; Lesur, B. M. *Tetrahedron Lett.* **1983**, *24*, 2231−2234. (b) Roush, W. R.; Michaelides, M. R.; Tai, D. F.; Lesur, B. M.; Chong, W. K. M.; Harris, D. J. *J. Am. Chem. Soc.* **1989**, *111*, 2984−2995. (c) Bernardi, A.; Cardani, S.; Poli, G.; Scolastico, C. *J. Org. Chem.* **1986**, *51*, 5041−5043. (d) Bernardi, A.; Cardani, S.; Pilati, T.; Poli, G.; Scolastico, C.; Villa, R. *J. Org. Chem.* **1988**, *53*, 1600−1607. (e) Cardani, S.; Poli, G.; Scolastico, C.; Villa, R. *Tetrahedron* **1988**, *44*, 5929−5938. (f) Hanessian, S.; Sumi, K. *Synthesis* **1991**, 1083−1089. (g) Nilsson, K.; Ullenius, C. *Tetrahedron* **1994**, *50*, 13173−13180. (h) Raczko, J. *Tetrahedron*: *Asymmetry* **1997**, *8*, 3821−3828. (i) Mengel, A.; Reiser, O. *Chem. Rev.* **1999**, *99*, 1191−1223. (j) Manpadi, M.; Kornienko, A. *Tetrahedron Lett.* **2005**, *46*, 4433−4437. See also refs 7a,b,g.

(7) For selected discussions of the Yamamoto model, see: (a) Yamamoto, Y.; Nishii, S.; Ibuka, T. *J. Chem. Soc., Chem. Commun.* **1987**, 464−466. (b) Yamamoto, Y.; Chounan, Y.; Nishii, S.; Ibuka, T.; Kitahara, H. *J. Am. Chem. Soc.* **1992**, *114*, 7652−7660. (c) Dominguez, E.; Carretero, J. C. *Tetrahedron Lett.* **1993**, *34*, 5803−5806. (d) Funaki, I.; Bell, R. P. L.; Thijs, L.; Zwanenburg, B. *Tetrahedron* **1996**, *52*, 12253−12274. (e) Hanessian, S.; Wang, W.; Gai, Y.; Olivier, E. *J. Am. Chem. Soc.* **1997**, *119*, 10034−10041. (f) Amigoni, S.; Schulz, J.; Martin, L.; LeFloch, Y. *Tetrahedron*: *Asymmetry* **1997**, *8*, 1515−1518. (g) Chounan, Y.; Ono, Y.; Nishii, S.; Kitahara, H.; Ito, S.; Yamamoto, Y. *Tetrahedron* **2000**, *56*, 2821−2831. See also refs 6f,g,h,i.

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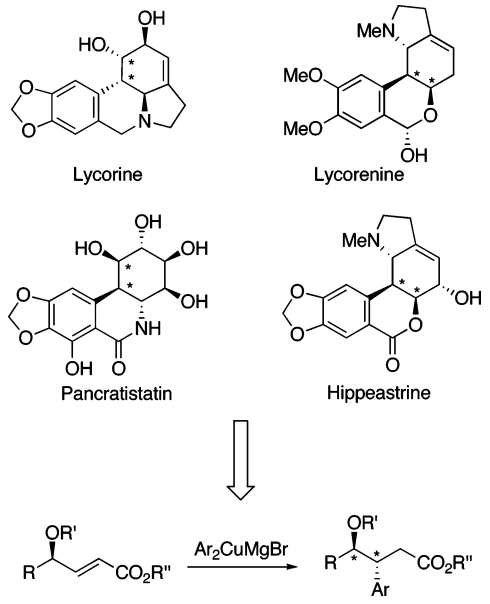

FIGURE 2. Anti-selective arylcuprate conjugate addition to γ-alkoxy-α,β-enoates as a solution to the stereochemical challenges presented by selected Amaryllidaceae constituents.

The practicality and scalability of the synthetic sequences employed in our efforts rely to a large extent on the requirement that the arylcuprate conjugate addition reactions take place with anti-diastereoselectivities exclusively. Although we have been successful with the empirical optimization of reaction conditions needed for the exclusive formation of anti-products, we have also searched for a unified, theoretically based stereochemical model to guide these efforts. While both the modified Felkin−Anh and Yamamoto models have the virtue of simplicity, it now appears that they are fundamentally flawed in view of the recent experimental and theoretical mechanistic investigations of the organocuprate conjugate addition process.[11] Below, the details of a systematic investigation of arylcuprate reactions with γ-alkoxy-α,β-enoates are given. In addition, a new stereochemical model, which is consistent with the results of both the current effort and that previously reported by other investigators as well as the current mechanistic understanding of this process, is proposed.

Results

In the pursuit of practical synthetic approaches to Amaryllidaceae constituents, we recently conducted a study of arylcuprate conjugate addition reactions of a series of γ,δ,ϵ-trialkoxyenoates, derived from various carbohydrate precursors (Figure 3).[12] In each one of these processes, a single anti-addition product was formed regardless of the identity of the alkoxy groups (OBn or OMOM) or their relative stereochemical relationship. These observations imply that even in complex settings 1,2-asymmetric induction by a γ-stereocenter is the predominant stereochemistry-determining factor in the transition states of the addition processes.

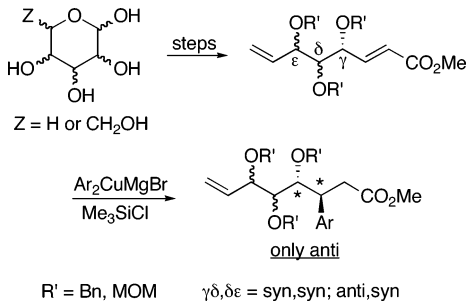

FIGURE 3. Highly anti-selective arylcuprate conjugate addition reactions of carbohydrate-derived γ,δ,ϵ-trialkoxy-α,β-enoates.

To elucidate the sufficiency of a single γ-alkoxy stereocenter to attain exclusive anti-selectivities as well as other structural features that would be necessary for such a highly diastereoselective process, we synthesized enoates **1**−**7** (Figure 4) varying the identity of the γ-alkoxy group OR′ (**1** vs **2**), the steric bulk of the group R (**2** vs **3** vs **4** and **5** vs **6** vs **7**), and the double bond geometry (**2** vs **5**, **3** vs **6**, and **4** vs **7**). While the synthesis of enoates **4** and **7** followed previously reported procedures starting from lactaldehyde,[13] compounds **1**, **2**, **3**, **5**, and **6** were prepared through sequences utilizing various known intermediates derived from D-mannitol.[14] Underlying these approaches is the known (*E*,*Z*)-selectivity dependence on the solvent (CH_2Cl_2 vs MeOH) in reactions of α-alkoxyaldehydes with stabilized Wittig reagents.[15]

We further investigated the reactions of **1**−**7** with a series of arylcuprates, derived from various multisubstituted aromatic Grignard reagents (**a**−**f**, Table 1). With enoates **1** and **2** as substrates, only single (by ^{1}H NMR analysis of crude and purified product mixtures) diastereomeric addition products were formed in all reactions. Chemical correlation of the phenyl adducts **12a** and **13a** with the known lactones **19** and **20**[16] confirmed the anti-stereochemical outcome of the cuprate reactions (Figure 5). The results strongly argue in favor of the adequacy of a single γ-alkoxy stereocenter for governing exclusive (within the NMR detection limit) anti-selectivities and bode well for future synthetic applications of this methodology, especially in cases where scale-up is anticipated. Combined with the similar results obtained in experiments with γ,δ,ϵ-trialkoxy-enoates these findings lead to the tempting speculation that the chemical nature of the R group (but not its size) has little influence on reaction stereoselectivity.

Further, reactions of the trans enoates showed a progressive erosion of anti-selectivity as the size of the R decreased (**2** → **3** → **4**). In contrast, the reactions of the cis enoates, while being moderately anti-selective (enoates **6** and **7**), did not display consistent selectivity dependence on the R group. The chemical correlation of the epimeric phenyl adduct mixtures **14a** and **15a** with the known trans and cis pairs of lactones **19**, **20**[16] and **21**, **22**[17] led to the assignment of stereochemistry for the major and minor diastereomers (Figure 6).

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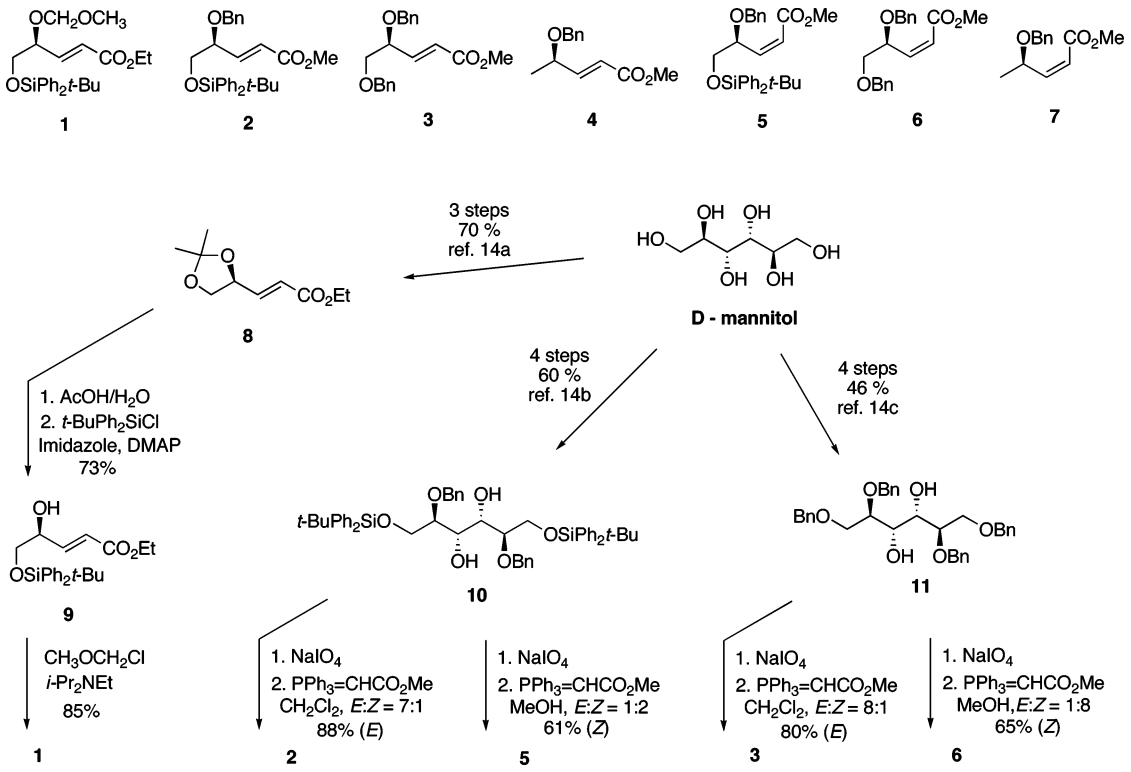
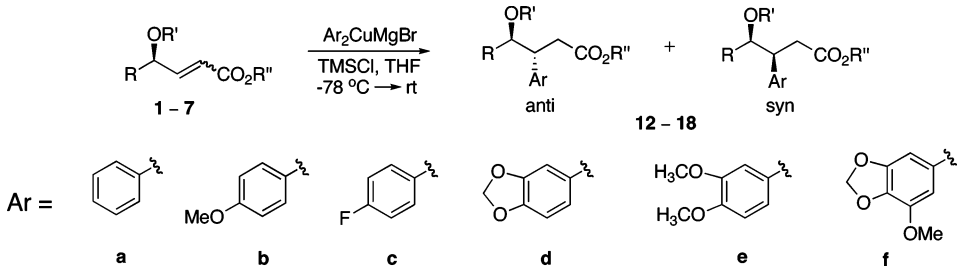


FIGURE 4. Preparation of trans and cis α,β-enoates with a single γ-alkoxy stereocenter.

TABLE 1. Stereoselectivities of Reactions of Arylcuprates with Trans and Cis α,β-Enoates with a Single γ-Alkoxy Stereocenter



trans enoates				cis enoates			
enoate	adduct	% yield	anti:syn	enoate	adduct	% yield	anti:syn
1	**12a**	80	>50:1	5	**16a**	87	1.6:1
1	**12b**	78	>50:1	5	**16d**	69	1:1.3
1	**12c**	79	>50:1	5	**16f**	53	1:1.3
1	**12d**	75	>50:1	6	**17a**	72	2.8:1
1	**12e**	76	>50:1	6	**17d**	68	2.7:1
1	**12f**	75	>50:1	6	**17f**	63	2.9:1
2	**13a**	88	>50:1	7	**18a**	65	3.4:1
2	**13d**	93	>50:1	7	**18d**	56	1.9:1
2	**13f**	82	>50:1	7	**18f**	54	2.2:1
3	**14a**	94	14.6:1				
3	**14d**	76	11.3:1				
3	**14f**	88	9.9:1				
4	**15a**	89	5.4:1				
4	**15d**	80	6.1:1				
4	**15f**	82	5.9:1				

Discussion

In principle, the observations made in studies with trans enoates can be adequately interpreted on the basis of the modified Felkin−Anh model (Figure 1b). According to this model, the stereochemistry of the addition process should not depend on the identity of the alkoxy substituent, which is oriented anti to the incoming nucleophile. In agreement with this prediction, no difference was seen between reactions of the γ-OMOM and γ-OBn enoates **1** and **2**. Moreover, others have reported high anti-addition selectivities in reactions with γ-OMe,[6a,b,f] γ-OBOM,[3j,m,n,q,s] γ-O-CR_2-δ-O (part of a ketal with a vicinal oxygen),[3a,b,k,p,6g] γ-OMTM,[6f] and γ-OMPM[3f] enoates.

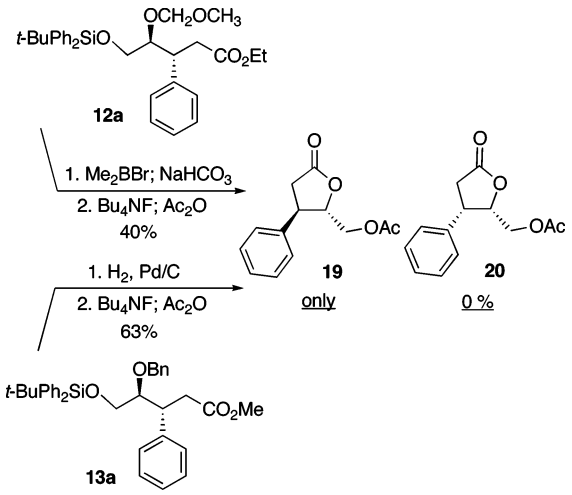


FIGURE 5. Confirmation of anti-stereochemistry for the phenyl addition products **12a** and **13a**.

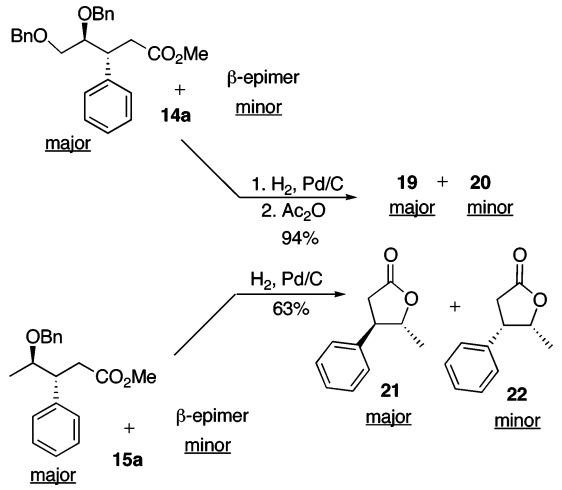


FIGURE 6. Confirmation of stereochemistry for the major and minor phenyl addition products **14a** and **15a**.

The Felkin−Anh model also suggests that large γ-R groups further destabilize the transition state conformer **C** leading to syn-products. The results of experiments with enoates **2**, **3**, and **4** match this expectation. Interestingly, application of the Yamamoto model for organocuprate conjugate additions leads to an opposite prediction: specifically that the stereochemical outcome of these processes should be strongly dependent on the identity of the alkoxy group and that a change in the size of the anti oriented R group should result in only a small perturbation.

Importantly, the low stereochemical selectivities observed for conjugate addition reactions of cis enoates cannot be explained by using either of these models or even by invoking a more complex four-conformer equilibrium process that mixes both models. For example, the modified Felkin−Anh interpretation predicts improved anti-selectivities, since 1,3-strain, the main factor causing energetic difference between conformers **B** and **C**, significantly increases in transition states for reactions of the cis enoates. In contrast, a preponderance of syn-products would be expected on the basis of the Yamamoto model due to allylic strain-promoted destabilization of the conformer **D**.

It is clear that synthetic applications of organocuprate conjugate additions to enoates have outpaced the mechanistic

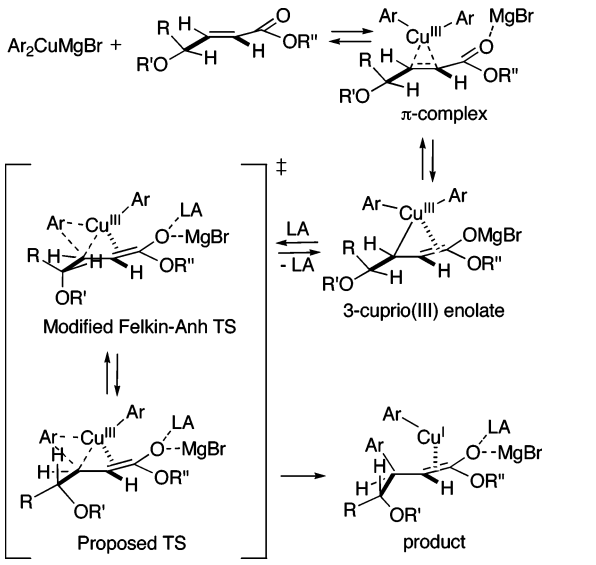


FIGURE 7. Summary of experimental and theoretical mechanistic studies of the organocopper conjugate addition reaction as adapted for the case of γ-alkoxy-α,β-enoates.

understanding of these reactions. As a result, the recent, insightful experimental and theoretical investigations of the mechanism of organocopper reactions[11] had not been included in developing models for predicting the stereochemical course of these processes. The fundamental assumption made in developing the modified Felkin-Ahn and Yamamoto models is that diastereofacial selection takes place during the first step involving either copper−olefin π-complex formation or simple nucleophilic addition of the cuprate.[6f,7b] Yet, detailed studies by several research groups[18] clearly indicate that the carbon−carbon bond forming reductive elimination step, converting Cu^{III} to Cu^{I} intermediates, is both rate- and stereochemistry-determining. Recent theoretical studies by Nakamura and co-workers[19] have provided a more detailed mechanistic description that has been adapted in developing a new model (Figure 7) for predicting the stereochemical course of organocuprate γ-alkoxy-α,β-enoate conjugate addition reactions.

In the route for organocuprate conjugate additions, π-complexation of a cuprate reagent with the enoate double bond is followed by reversible formation of the β-cuprio(III) enolate,

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(19) (a) Nakamura, E.; Mori, S.; Morokuma, K. *J. Am. Chem. Soc.* **1997**, *119*, 4900−4910. (b) Mori, S.; Nakamura, E. *Chem. Eur. J.* **1999**, *5*, 1534−1543. (c) Nakamura, E.; Yamanaka M. *J. Am. Chem. Soc.* **1999**, *121*, 8941−8942. (d) Reference 11. (e) Yamanaka, M.; Inagaki, A.; Nakamura, E. *J. Comput. Chem.* **2003**, *24*, 1401−1409. (f) Nakanishi, W.; Yamanaka, M.; Nakamura, E. *J. Am. Chem. Soc.* **2005**, *127*, 1446−1453. (g) Yoshikai, N.; Yamashita, T.; Nakamura, E. *Angew. Chem., Int. Ed.* **2005**, *44*, 4721−4723.

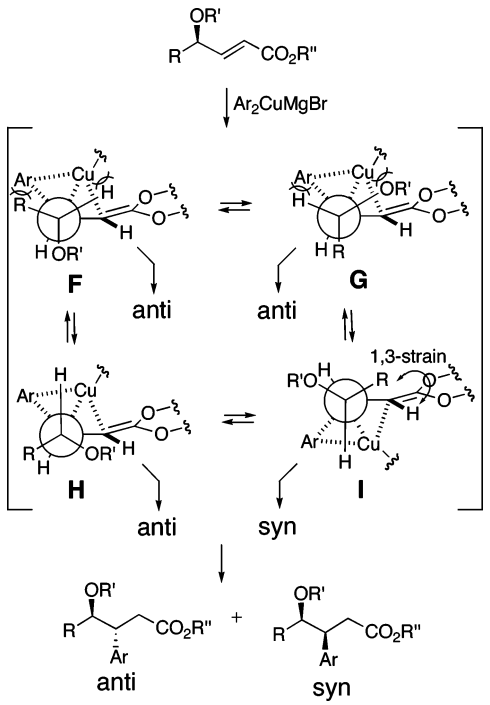

FIGURE 8. Inadequacy of the Felkin−Anh and Yamamoto models (**F** and **G**) and the proposed reductive elimination-based transition state conformations (**H** and **I**).

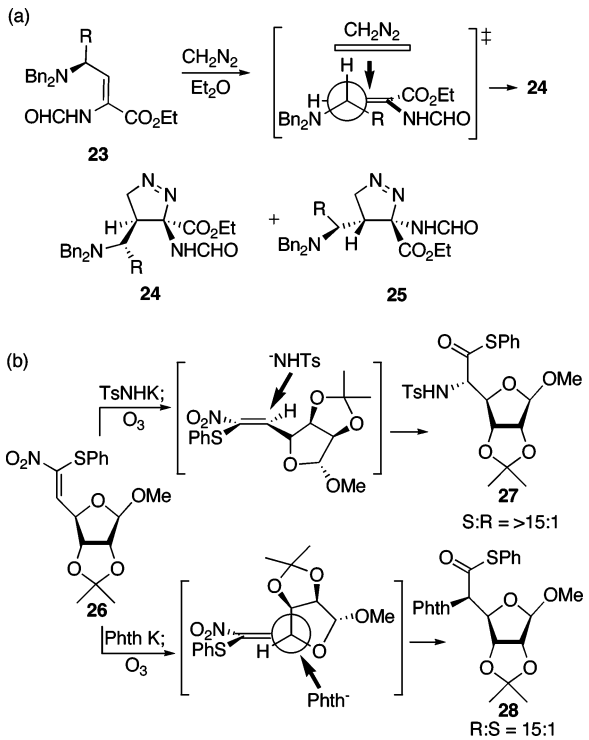

FIGURE 9. The "flat" approach model proposed by Reetz and co-workers[21c] and the aerofoil long-range steric congestion invoked by Barrett and co-workers.[21a]

in which the high oxidation state of copper is stabilized by the donation from the electron-rich enolate double bond. A correlation of the results of density functional studies with those arising from experimental ^{13}C NMR[19b] and kinetic isotope effect investigations[18i] demonstrates that β-cuprio(III) enolates are direct precursors of addition products with enals and enones, formed through rate- and stereochemistry-determining reductive elimination.[20] With less reactive esters a Lewis acidic or electrophilic additive, such as BF_3 or Me_3SiCl, is required to reduce the electron-rich enolate double bond character, thus destabilizing the Cu^{III} intermediate and promoting reductive elimination to generate Cu^{I} species. *Clearly, a model aimed at understanding and predicting the stereochemical course of organocopper conjugate addition processes should center on the reductive elimination step in this general pathway*. Both the modified Felkin−Anh and Yamamoto models are inconsistent with this new mechanistic information. Furthermore, processes involving these models in the first mechanistic step evolve into highly energetic reductive elimination transition state conformations that are highly destabilized by eclipsing interactions (Figure 8, **F** and **G**).

We propose a mechanistically more relevant approach to evaluating the stereochemistry of organocuprate enoate conjugate additions. The "Reductive Elimination" model focuses on competitive transition states (**H** and **I**) for the C−C bond formation step. In these transition states, the γ-H atom is oriented toward the cuprate cluster, thus minimizing steric strain associated with interactions of the large R and OR′ substituents with the nearly planar copper complex. Reactive conformation **H**, leading to the anti-product, is energetically more favorable than **I** from both stereoelectronic and steric perspectives. In the reductive elimination transition state the C_β−Ar bond is forming, while the C_β−Cu bond is being broken. Both of these processes are facilitated in conformer **H** by the relative positioning of R and OR′, which allows favorable mixing of the σ-orbital of the forming C_β−Ar bond with the low-lying σ^*-orbital of the C_γ−OR′ bond. In addition, donation from the electron-rich C_γ−R bond into the σ^* C_β−Cu orbital weakens the C_β−Cu bond and assists departure of copper. Importantly, both of these interactions increase during the course of reductive elimination due to the increasingly better overlap of the component orbitals: the dihedral angles Ar−C_β−C_γ−H and Cu−C_β−C_γ−H become larger as the Ar−Cu bond elongates. Furthermore, as the size of the group R increases, conformer **I** becomes increasingly disfavored due to allylic 1,3-strain. The results of the current study (Table 1) fully comply with this new stereochemical model.

Similar transition state models have been proposed by other investigators for reactions involving "flat" or "aerofoil" nucleophiles.[21] An instructive example comes from a study by Reetz and co-workers of the stereochemistry of the cycloaddition reactions of ester **23** with diazomethane (Figure 9a).[21c] The authors noted that the "flat" nature of the approaching π-system results in a consensus transition state conformation, in which the hydrogen atom points toward the incoming reagent and the bulky NBn_2 group occupies an "outside" position, leading to the major cycloaddition product **24**. As the size of the R group increased the ratio of the diastereomeric products **24**:**25** decreases, a consequence presumably of allylic 1,3-strain in the transition state to **24**. Barrett and co-workers reported an

(20) The first evidence for this pathway and its role in the stereochemistry of organocopper addition reactions was disclosed by Corey and Boaz: Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1984**, *26*, 6015−6018.

(21) (a) Barrett, A. G. M.; Weipert, P. D.; Dhanak, D.; Husa, R. K.; Lebold, S. A. *J. Am. Chem. Soc.* **1991**, *113*, 9820−9824. (b) Burgess, L. E.; Meyers, A. I. *J. Am. Chem. Soc.* **1991**, *113*, 9858−9859. (c) Reetz, M. T.; Kayser, F.; Harms, K. *Tetrahedron Lett.* **1992**, *33*, 3453−3456.

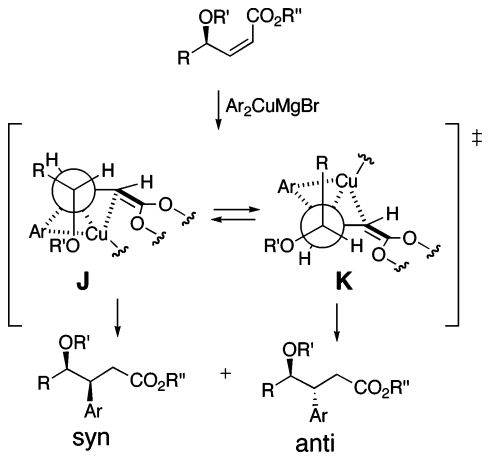

FIGURE 10. Possible additional transition states that may result from reactions of cis enoates.

interesting divergent stereochemical outcome in Michael addition reactions of nucleophiles to nitroolefin **26** (Figure 9b). "Small" nucleophiles (NaOMe, NaOBn, TsNHK) led to highly selective formation of S-configured products **27**, while reactions with "aerofoil" shaped nucleophiles, such as phthalimide K or succinamide K, give mainly R-adducts **28**.[21a] Barrett noted that the modified Felkin−Anh transition state, leading to the S-configured phthalimide adduct, suffers from a steric interaction between the phthalimide carbonyl and the C-3 oxygen substituent. This steric congestion would be minimized in the transition state leading to **28** even though it is not favored stereoelectronically.

The "Reductive Elimination" model accounts for the significant decrease in anti-selectivity observed in conjugate addition reactions of cis enoates **5**−**7**. The severe 1,3-strain that arises when cis double bond geometry is present leads to rotation about the $C_\beta-C_\gamma$ to produce an energetic minimum (Figure 10). Reactive conformations **J** and **K** may become more competitive and, conceivably, the absence of a clearly defined transition state preference leads to small selectivity values. Although Yamamoto and co-workers reported selectivity reversal from anti to syn when the enoate geometry is changed from trans to cis, their results show that anti-selectivities in reactions with trans enoates are high, while syn-stereochemical preference with cis enoates was at best marginal (on the order of 2:1 to 3:1).[7a,b]

The "Reductive Elimination" model can also be used to understand the significant decrease in reaction yields and an increase in reaction times from 6 h at −30 °C for trans enoates **1**−**4** to 24−48 h at 25 °C for cis enoates **5**−**7** found in this study. Other investigators have reported similar observations, including the complete failure of cis enoates to undergo conjugate additions compared to facile reactions of their trans counterparts.[2b,7a,b] In this connection it is noteworthy that several research groups have reported that identical stereoselectivitites accompany reactions of trans and cis enoates.[2b,3f,t,6a,b,g] While cis → trans enoate isomerization in organocuprate reactions is a logical interpretation, an electron transfer mechanism for this process has been substantially refuted.[11] The density functional investigation by Nakamura and co-workers suggests that the 3-cuprio(III) enolate may be viewed as a copper(III) species with the enolate double bond serving as a ligand.[19a] In addition, the early experiments by Corey and Boaz indicate that this species may undergo silylation with Me_3SiCl changing the stereochemical course of the addition process.[20] This conclusion

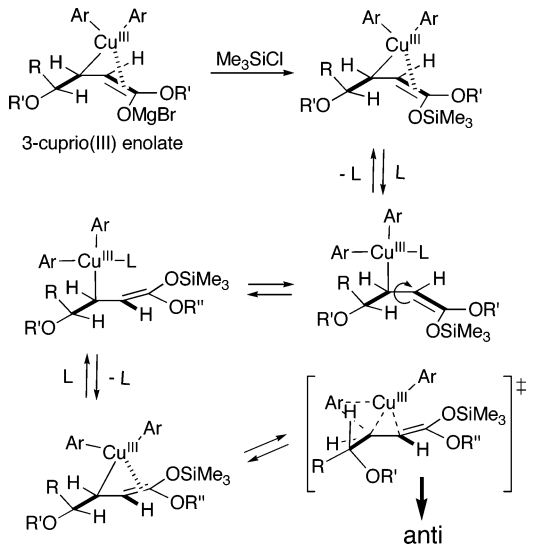

FIGURE 11. Alternative mechanism for cis → trans isomerization of γ-akoxy-α,β-enoates with the assistance of Me_3SiCl.

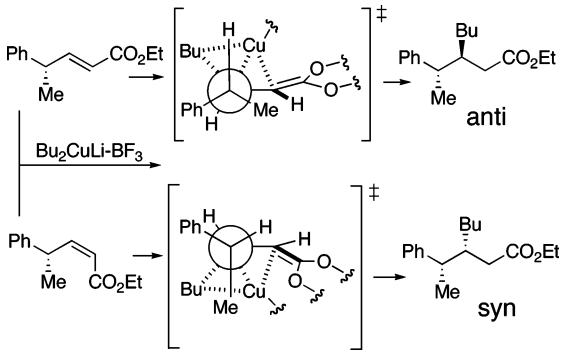

FIGURE 12. Stereochemistry reversal as the enoate double bond geometry is changed from trans to cis observed by Yamamoto and co-workers.[7g]

is further supported by the results of kinetic isotope studies (with ^{17}O replacement at the carbonyl oxygen) by Frantz and Singleton[18k] which show that silylation with Me_3SiCl could be rate-limiting. Thus, it is not inconceivable that the slow reactivity of cis enoates enables silylation of the 3-cuprio(III) enolate to take place, a process that weakens the donor ability of the enolate double bond (Figure 11). Ligand exchange (with HMPA or THF) may allow rotation about the $C_\alpha-C_\beta$ bond leading to a 3-cuprio(III) enolate that would be derived directly from the trans enoate starting material. It is not unlikely that the marginal excesses of anti-addition products formed in reactions of enoates **5**−**7** are a consequence of competing double bond isomerization of the reactants. It should be noted that Yamamoto and co-workers performed their addition reactions in the presence of BF_3 as an activating agent compared with Me_3SiCl used in our experiments.

The "Reductive Elimination" model can be effectively applied to predicting the stereochemistry of conjugate addition reactions of other types of γ-stereocenter-containing enoates. If an alkoxy substituent is not present at the γ-position, the stereochemical outcome will depend on the relative sizes of the two non-hydrogen substituents. For example, ethyl *E*-4-phenyl-2-pentenoate (Figure 12) is known to react with $Bu_2CuLi{\cdot}BF_3$ to yield mainly the anti-product (anti:syn = 7:3).[7g] When the *Z*-enoate is reacted with the copper reagent, stereochemistry reversal (anti:

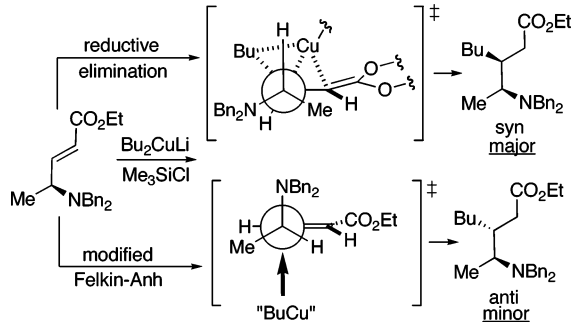

FIGURE 13. Correct prediction of the stereochemical outcome of reactions of γ-amino-α,β-enoates with the reductive elimination model and prediction of the opposite result with the modified Felkin−Anh interpretation.[22a]

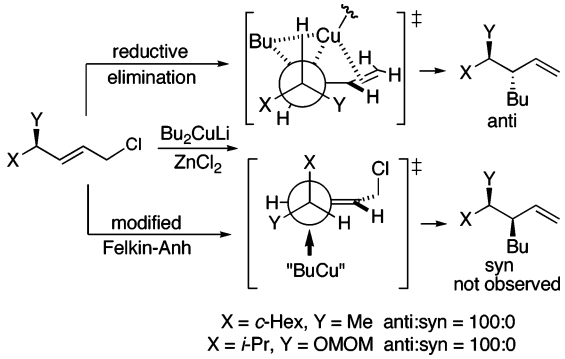

FIGURE 14. Application of the reductive elimination model and the modified Felkin−Anh interpretation to S_N2' processes indicating their mechanistic kinship to conjugate addition reactions.[26]

syn = 3:7) is observed. It is possible that in the *Z*-enoate case the 1,3-strain is minimized in a transition state conformation in which the smaller Me group is close to the copper complex (bottom transition state in Figure 12). This would result in preferential formation of the syn-product. Thus, in reactions of trans enoates that lack γ-substituents capable of exerting strong stereoelectronic effects, a transition state conformation that places the smaller of the two non-hydrogen groups into the 1,3-strain position would lead to an accurate prediction of the stereochemical outcome. Similar selelectivity patterns have also been reported by Yamada and co-workers in their systematic studies with enoates and enones containing a methyl group and a large steroidal substituent at the γ-position.[2b]

Reactions of trans γ-amino-α,β-enoates with organocopper reagents generally take place with syn-stereoselectivities.[22] While these processes have been extensively employed in synthesis, no logical reason for why their stereochemistry is opposite to that observed with γ-akoxy-α,β-enoates has been offered. Interestingly, application of the new model to reactions of the trans γ-amino-α,β-enoate substrates nicely explains this stereochemical divergence. Accordingly, a lower energy reductive elimination transition state conformation that has the bulky amino group[23] in the "outside" position (Figure 13) would result in formation of the observed syn-products.[22a] Importantly, when the other non-hydrogen subsituent is large, this transition state would be of exceptionally high energy and, as a result, the enoate would be unreactive toward conjugate addition.[6f] It is noteworthy that the application of the Felkin−Anh model is equally successful with α-amino-aldehydes as it is with α-alkoxy-aldehydes. Yet, the modified Felkin−Anh hypothesis predicts anti-selelectivity for γ-amino-α,β-enoates, which is not what is observed experimentally.

A last point worth making stems from the proposal that if the transition state model works well for predicting two synthetically distinct organocopper-promoted processes then there is a high probability that the two processes follow similar mechanistic pathways. The case in point is the S_N2' reaction of allylic substrates with organocopper reagents where little is known about the mechanism. Experimental studies by Bäckvall and co-workers[24] and density functional investigation by Nakamura and co-workers[25] suggest that these reactions proceed through the intermediacy of π-allylcopper(III) intermediates. Furthermore, the conclusion of theoretical study is that C−C bond formation occurs not from σ-allylcopper(III) species, as had been thought previously, but rather via enyl[σ+π]-type transition states that are mechanistically similar to those involved in the enoate conjugate addition process. Since the selectivities of reactions of γ-substituted allylic halides follow a pattern[26,6i] that is similar to that for enoate conjugate additions, we believe that the reductive elimination step is rate- and stereochemistry-determining for organocuprate S_N2' reactions as well (Figure 14). Importantly, the application of the modified Felkin−Anh model to these processes leads to the expectation that syn-stereochemistry would predominate, a prediction that opposes the experimental observations. We believe that this stereochemical analogy provides an important clue about the mechanism of S_N2' reactions of organocuprates with allylic substrates, which matches the conclusions drawn from theoretical studies.[25]

Conclusions

The reductive elimination-based stereochemical model described above explains the high anti-selectivities observed in organocopper conjugate addition reactions with trans γ-alkoxy-α,β-enoates. Both steric and stereoelectronic factors favor the transition state conformer that leads to the anti-adduct. However, it is possible to direct preferential formation of syn-products by judiciously choosing properly sized γ-substituents, especially in cis enoate reactants. In this event, steric factors outweigh stereoelectronic control. Analysis of previous observations demonstrates that the proposed model is fully consistent with the stereochemical outcomes of conjugate additions of other γ-stereocenter-containing enoates, such as those containing

(22) For selected examples, see: (a) Reetz, M. T.; Rohrig, D. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 1706−1709. (b) Jako, I.; Uiber, P.; Mann, A.; Taddei, M.; Wermuth, C. G. *Tetrahedron Lett.* **1990**, *31*, 1011−1014. (c) Reference 6f. (d) Hanessian, S.; Wang, W.; Gai, Y. *Tetrahedron Lett.* **1996**, *37*, 7477−7480. (e) Hanessian, S.; Demont, E.; van Otterlo, W. A. L. *Tetrahedron Lett.* **2000**, *41*, 4999−5003. (f) Liang, X.; Andersch, J.; Bols, M. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2136−2157. (g) Flamant-Robin, C.; Wang, Q.; Sasaki, N. A. *Tetrahedron Lett.* **2001**, *42*, 8483−8484. (h) Flamant-Robin, C.; Wang, Q.; Chiaroni, A.; Sasaki, N. A. *Tetrahedron* **2002**, *58*, 10475−10484. (i) Kumar, S.; Flamant-Robin, C.; Wang, Q.; Chiaroni, A.; Sasaki, A. *J. Org. Chem.* **2005**, *70*, 5946−5953.

(23) Amino groups are considerably more bulky than ethers, presumably due to the fact that the ether alkyl group can turn so as to point away from the steric congestion site. For example, various reported "*A* values" for −OMe and $-NMe_2$ groups are 2.13−3.14 and 6.4−10.0 kJ/mol, respectively. See in: Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; Wiley-Interscience: New York, 1994.

(24) Karlstrom, A.; Sofia, E.; Bäckvall, J.-E. *Chem. Eur. J.* **2001**, *7*, 1981−1989.

(25) Yamanaka, M.; Kato, S.; Nakamura, E. *J. Am. Chem. Soc.* **2004**, *126*, 6287−6293.

(26) Arai, M.; Kawasuji, T.; Nakamura, E. *J. Org. Chem.* **1993**, *58*, 5121−5129.

γ-C,C,H and γ-C,H,N substituents. Significantly, the model can be used to design highly diastereoselective conjugate addition processes. For example, by using trans γ-alkoxy-α,β-enoates containing a larger γ-R group high anti-selective transformation should take place. In contrast, trans γ-amino-α,β-enoates with smaller γ-R groups should be employed if syn-selective processes are desired. Also, the proposed stereochemical/mechanistic analogy with organocopper-mediated S_N2' processes is expected to facilitate mechanistic investigations of this important synthetic method. Further work is underway to study the proposed transition states computationally and to validate the results of the theoretical analysis by designing more narrowly targeted experimental systems.

Experimental Section

A. Preparation of Enoates: Ethyl (2*E*,4*S*)-5-(*tert*-Butyldiphenylsilanyloxy)-4-hydroxy-2-pentenoate (9). Compound **8**[14a] (4.8 g, 24 mmol) was stirred in a mixture of water and acetic acid (100 mL, 1:3) for 20 h at room temperature. The mixture was evaporated under reduced pressure and the traces of acetic acid were removed by coevaporating with toluene (5 × 10 mL). The oily residue was dissolved in DMF (26 mL) and cooled to 0 °C. To the mixture were added DMAP (0.3 g, 2.4 mmol), imidazole (1.94 g, 24.8 mmol), and *tert*-butyl(chloro)diphenylsilane (7.8 g, 28.4 mmol). The resulting mixture was stirred overnight at room temperature. The reaction mixture was quenched with water (20 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and evaporated under reduced pressure. The residual oil was presorbed on silica gel and purified by column chromatography (5−20% EtOAc/hexanes) to afford enoate **9** (7.0 g, 73%) as a colorless oil. R_f 0.59 (20% EtOAc/hexanes); $[\alpha]^{22}_D$ −16.4 (*c* 0.17, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.39−7.65 (m, 10H), 6.83 (dd, *J* = 15.7, 4.1 Hz, 1H), 6.11 (dd, *J* = 15.7, 1.9, Hz, 1H), 4.41 (m, 1H), 4.18 (q, *J* = 7.2 Hz, 2H), 3.75 (dd, *J* = 10.2, 4.0 Hz, 1H), 3.54 (dd, *J* = 10.2, 7.2, Hz, 1H), 2.73 (d, *J* = 4.1 Hz, 1H), 1.27 (t, *J* = 7.2 Hz, 3H), 1.06 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 166.3, 145.8, 135.6, 132.8, 130.1, 127.9, 127.8, 122.0, 71.5, 67.0, 60.5, 26.9, 19.3, 14.3; HRMS *m*/*z* (ESI) calcd for $C_{23}H_{30}O_4SiNa$ (M + Na)$^+$ 421.1805, found 421.1805.

Ethyl (2*E*,4*S*)-5-(*tert*-Butyldiphenylsilanyloxy)-4-methoxymethoxy-2-pentenoate (1). To a solution of **9** (1.36 g, 3.42 mmol) in CH_2Cl_2 (80 mL) at 0 °C was added *i*-Pr_2NEt (4.3 g, 33.3 mmol) followed by the dropwise addition of chloro(methoxy)methane (1.34 g, 16.6 mmol). The resulting solution was stirred for 20 h while it was allowed to warm to room temperature. The reaction mixture was quenched with saturated NH_4Cl (30 mL). The aqueous phase was extracted with ether (3 × 50 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and evaporated to afford dark yellow oil. The crude material was presorbed on silica gel and purified by column chromatography (5−20% EtOAc/hexanes) to afford enoate **1** (1.2 g, 85%) as a colorless oil. R_f 0.64 (20% EtOAc/hexanes); $[\alpha]^{21}_D$ 12.3 (*c* 1.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.38−7.69 (m, 10H), 6.85 (dd, *J* = 15.7, 5.5 Hz, 1H), 6.06 (dd, *J* = 15.7, 1.4 Hz, 1H), 4.72 (d, *J* = 6.6 Hz, 1H), 4.65 (d, *J* = 6.6 Hz, 1H), 4.32 (m, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 3.71 (dd, *J* = 10.5, 6.6 Hz, 1H), 3.63 (dd, *J* = 10.7, 5.2 Hz, 1H), 3.35 (s, 3H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.05 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 166.2, 145.2, 135.7, 133.2, 129.9, 127.8, 122.9, 95.3, 76.0, 66.1, 60.5, 55.7, 26.8, 19.3, 14.3; HRMS *m*/*z* (ESI) calcd for $C_{25}H_{34}O_5SiNa$ (M + Na)$^+$ 465.2067, found 465.2063.

Methyl (2*E*,4*S*)-4-Benzyloxy-5-(*tert*-butyldiphenylsilanyloxy)-2-pentenoate (2). To a solution of diol **10**[14b] (3.15 g, 3.7 mmol) in dry methanol (150 mL) at 0 °C was added $NaIO_4$ (0.96 g, 4.5 mmol). The resulting suspension was vigorously stirred for 24 h at room temperature. The precipitate was filtered and solution was concentrated under reduced pressure. The residue was dissolved in ether (50 mL) and the formed precipitate was filtered. The ether fraction was evaporated under reduced pressure to give viscous oil. The residue was dissolved in dry CH_2Cl_2 (100 mL). To this solution at −78 °C was added methyl (triphenylphosphoranylidene)acetate (2.6 g, 8.0 mmol) in one portion. The resulting mixture was stirred for 28 h while it was allowed to warm to room temperature. Water (100 mL) was added to the reaction mixture, the two layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and evaporated under reduced pressure. The crude olefin (*E*:*Z* = 7:1) was presorbed on silica gel and purified by column chromatography (2−5% EtOAc/hexanes) to afford enoate **2** (3.08 g, 88%) as a colorless oil. R_f 0.4 (12% EtOAc/hexanes); $[\alpha]^{21}_D$ 16.4 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.76−7.65 (m, 5H), 7.47−7.30 (m, 10H), 6.93 (dd, *J* = 15.7, 5.8 Hz, 1H), 6.12 (dd, *J* = 15.7, 1.4 Hz, 1H), 4.64 (d, *J* = 11.8 Hz, 1H), 4.51 (d, *J* = 11.8 Hz, 1H), 4.14 (q, *J* = 5.0 Hz, 1H), 3.82 (dd, *J* = 10.7, 6.3 Hz, 1H), 3.76 (s, 3H), 3.71 (dd, *J* = 10.7, 5.0 Hz, 1H), 1.07 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 166.6, 145.9, 138.1, 135.7, 134.9, 133.2, 129.9, 129.7, 128.5, 127.8, 127.7, 122.7, 78.9, 71.7, 66.1, 51.7, 26.9, 19.3; HRMS *m*/*z* (ESI) calcd for $C_{29}H_{34}O_4SiNa$ (M + Na)$^+$ 497.2118, found 497.2123.

Methyl (2*E*,4*S*)-4,5-Dibenzyloxy-2-pentenoate (3). To a solution of diol **11**[14c] (2.01 g, 3.7 mmol) in dry methanol (150 mL) at 0 °C was added $NaIO_4$ (0.94 g, 4.4 mmol). The resulting suspension was vigorously stirred for 24 h at room temperature. The precipitate was filtered and the solution was concentrated under reduced pressure. The residue was dissolved in ether (50 mL) and the formed precipitate was filtered. The ether fraction was evaporated under reduced pressure to give viscous oil. The residue was dissolved in dry CH_2Cl_2 (100 mL). To this solution at −78 °C was added methyl (triphenylphosphoranylidene)acetate (2.7 g, 8.1 mmol) in one portion. The resulting mixture was stirred for 10 h while it was allowed to warm to room temperature. Water (100 mL) was added, the two layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and evaporated under reduced pressure. The crude olefin (*E*:*Z* = 8:1) was presorbed on silica gel and purified by column chromatography (5−10% EtOAc/hexanes) to afford enoate **3** (1.92 g, 80%) as a colorless oil. R_f 0.3 (35% EtOAc/hexanes); $[\alpha]^{28}_D$ 22.6 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.45−7.20 (m, 10H), 6.94 (dd, *J* = 15.7, 5.5 Hz, 1H), 6.16 (dd, *J* = 16.0, 1.4 Hz, 1H), 4.68 (d, *J* = 12.1 Hz, 1H), 4.58 (s, 2H), 4.54 (d, *J* = 12.1 Hz, 1H), 4.25 (q, *J* = 5.0 Hz, 1H), 3.77 (s, 3H), 3.61 (t, *J* = 6.3 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 166.6, 145.6, 138.0, 137.9, 128.5, 127.9, 127.8, 127.7, 122.8, 73.6, 72.2, 71.7, 51.8; HRMS *m*/*z* (ESI) calcd for $C_{20}H_{22}O_4Na$ (M + Na)$^+$ 349.1410, found 349.1419.

Methyl (2*Z*,4*S*)-4-Benzyloxy-5-(*tert*-butyldiphenylsilanyloxy)-2-pentenoate (5). To a solution of diol **10**[14b] (3.15 g, 3.7 mmol) in dry methanol (150 mL) at 0 °C was added $NaIO_4$ (0.96 g, 4.5 mmol). The resulting suspension was vigorously stirred for 24 h at room temperature. The precipitate was filtered and solution was concentrated under reduced pressure. The residue was dissolved in ether (50 mL) and the formed precipitate was filtered. The ether fraction was evaporated under reduced pressure to give viscous oil. The residue was dissolved in dry methanol (100 mL). To this solution at 0 °C was added methyl (triphenylphosphoranylidene)-acetate (2.6 g, 8 mmol) in one portion. The resulting mixture was stirred for 10 h while it was allowed to warm to room temperature. The solvent was evaporated under reduced pressure. The residue was dissolved in CH_2Cl_2 (100 mL), washed with water (3 × 50 mL) and brine, dried ($MgSO_4$), and evaporated under reduced pressure. The crude olefin (*E*:*Z* = 1:2) was presorbed on silica gel and purified by column chromatography (2−5% EtOAc/hexanes) to afford enoate **5** (2.08 g, 61%) as a colorless oil. R_f 0.47 (12% EtOAc/hexanes); $[\alpha]^{21}_D$ 16.4 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.73−7.68 (m, 5H), 7.45−7.28 (m, 10H), 6.25 (dd, *J* = 11.8, 8.5 Hz, 1H), 5.95 (dd, *J* = 11.8, 1.1 Hz, 1H), 5.32−5.25 (m, 1H),

4.63 (d, J = 11.8 Hz, 1H), 4.57 (d, J = 11.8 Hz, 1H), 3.85 (dd, J = 10.5, 5.8 Hz, 1H), 3.8 (dd, J = 10.5, 4.4 Hz, 1H), 3.69(s, 3H), 1.06 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 166.2, 148.1, 138.7, 135.8, 135.7, 133.6, 133.5, 129.7, 128.4, 127.8, 127.7, 127.6, 122.1, 76.2, 71.7, 66.2, 51.4, 26.9, 19.4; HRMS *m*/*z* (ESI) calcd for $C_{29}H_{34}O_4SiNa$ $(M + Na)^+$ 497.2118, found 497.2127.

Methyl (2*Z*,4*S*)-4,5-Dibenzyloxy-2-pentenoate (6).[2727] To a solution of diol **11**[14c] (2.01 g, 3.7 mmol) in dry methanol (150 mL) at 0 °C was added $NaIO_4$ (0.94 g, 4.4 mmol). The resulting suspension was vigorously stirred for 24 h at room temperature. The precipitate was filtered and solution was concentrated under reduced pressure. The residue was dissolved in ether (50 mL) and the formed precipitate was filtered. The ether fraction was evaporated under reduced pressure to give viscous oil. The residue was dissolved in dry methanol (100 mL). To this solution at 0 °C was added methyl (triphenylphosphoranylidene)acetate (2.7 g, 8.1 mmol) in one portion. The resulting mixture was stirred for 10 h while it was allowed to warm to room temperature. The solvent was evaporated under reduced pressure. The residue was dissolved in CH_2Cl_2 (100 mL), washed with water (3 × 50 mL) and brine, dried ($MgSO_4$), and evaporated under reduced pressure. The crude olefin (*E*:Z = 1:8) was presorbed on silica gel and purified by column chromatography (5−10% EtOAc/hexanes) to afford enoate **6** (1.56 g, 65%) as a colorless oil.

B. Arylcuprate Reactions: General Procedure for Arylcuprate Addition. A few drops of a required aryl bromide were added to crushed Mg turnings (0.17 g, 7.03 mmol) in THF (10 mL) under nitrogen atmosphere. Once the reaction started the solution warmed and slightly darkened. The rest of the aryl bromide (7.03 mmol total) was added dropwise to allow a gentle reaction. The reaction mixture was allowed to cool to room temperature and then cannulated to a slurry of CuI (0.67 g, 3.52 mmol) in THF (10 mL) at −78 °C. The mixture was stirred at −78 °C for 40 min (in the synthesis of **12e** the mixture was stirred at 0 °C for 2 h, as no trans-metalation occurred at −78 °C). Me_3SiCl (0.38 g, 7.03 mmol) and a corresponding enoate (0.703 mmol in 10 mL of THF) were added sequentially dropwise at −78 °C. The yellow-brown suspension was stirred overnight while slowly being warmed up to room temperature. At this time reactions of trans enoates **1**, **2**, **3**, and **4** were finished. In the addition reactions of cis enoates **5**, **6**, and **7** the reaction mixtures were stirred for an additional 24−48 h until the starting material disappeared. The reaction mixture was quenched with a mixture of concentrated NH_4OH and saturated NH_4Cl (1:9, 30 mL) and extracted with ether (3 × 30 mL). The combined organic layers were washed with brine, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was absorbed on silica gel and purified by column chromatography (5−30% EtOAc/hexanes) to yield corresponding addition product as an oil.

Compound 12a: 80%, R_f 0.58 (20% EtOAc/hexanes); $[\alpha]^{21}_D$ −43.9 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.19−7.60 (m, 15H), 4.68 (d, J = 6.9 Hz, 1H), 4.51 (d, J = 6.9 Hz, 1H), 3.97 (q, J = 7.2 Hz, 2H), 3.75 (m, 1H), 3.46 (m, 3H), 3.27 (s, 3H), 2.97 (dd, J = 15.6, 5.2 Hz, 1H), 2.64 (dd, J = 15.6, 10.2 Hz, 1H), 1.08 (t, J = 7.2 Hz, 3H), 1.03 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 172.8, 141.3, 135.5, 133.2, 129.8, 128.5, 127.8, 126.9, 96.4, 81.0, 63.9, 60.0, 56.0, 43.1, 37.2, 26.8, 19.2, 14.0; HRMS *m*/*z* (ESI) calcd for $C_{31}H_{40}O_5SiNa$ $(M + Na)^+$ 543.2537, found 543.2530.

Compound 12b: 78%, R_f 0.45 (20% EtOAc/hexanes); $[\alpha]^{21}_D$ −45.7 (*c* 0.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 6.76−7.60 (m, 14H), 4.52 (d, J = 6.9 Hz, 1H), 4.69 (d, J = 6.9 Hz, 1H), 3.98 (q, J = 7.0 Hz, 2H), 3.77 (s, 3H), 3.75 (m, 1H), 3.42 (m, 3H), 3.29 (s, 3H), 2.96 (dd, J = 15.4, 5.2 Hz, 1H), 2.59 (dd, J = 15.4, 10.5 Hz, 1H), 1.07 (t, J = 7.0 Hz, 3H), 1.03 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 172.7, 158.4, 135.7, 135.6, 133.4, 133.2, 129.7, 129.3, 127.7, 116.1, 114.8, 113.8, 96.4, 81.1, 63.7, 60.2, 56.1, 55.3, 42.6, 37.4, 26.9, 19.3, 14.2; HRMS *m*/*z* (ESI) calcd for $C_{32}H_{42}O_6SiNa$ $(M + Na^+)$ 573.2642, found 573.2630.

Compound 12c: 79%, R_f 0.48 (20% EtOAc/hexanes); $[\alpha]^{21}_D$ −37.8 (*c* 0.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.63−6.92 (m, 14H), 4.67 (d, J = 6.9 Hz, 1H), 4.50 (d, J = 6.9 Hz, 1H), 3.99 (q, J = 7.1 Hz, 2H), 3.71 (m, 1H), 3.52 (m, 3H), 3.27 (s, 3H), 2.97 (dd, J = 15.7, 4.9 Hz, 1H), 2.60 (dd, J = 15.7, 10.5 Hz, 1H), 1.07 (t, J = 7.1 Hz, 3H), 1.03 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 172.4, 136.9, 135.7, 135.5, 133.3, 133.1, 129.9, 129.8, 127.7, 115.4, 115.1, 96.4, 80.8, 63.6, 60.3, 56.1, 42.6, 37.1, 31.0, 26.9, 19.2, 14.2; HRMS *m*/*z* (ESI) calcd for $C_{31}H_{39}FO_5SiNa$ $(M + Na)^+$ 561.2443, found 561.2422.

Compound 12d: 75%, R_f 0.46 (20% EtOAc/hexanes); $[\alpha]^{21}_D$ −35.6 (*c* 0.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.59−7.30 (m, 10H), 6.66 (m, 3H), 5.91 (s, 2H), 4.70 (d, J = 6.9 Hz, 1H), 4.53 (d, J = 6.9 Hz, 1H), 4.0 (q, J = 7.2 Hz, 2H), 3.69 (m, 1H), 3.51 (m, 3H), 2.94 (dd, J = 15.4, 4.95 Hz, 1H), 2.56 (dd, J = 15.4, 10.2, Hz, 1H), 1.12 (t, J = 7.2 Hz, 3H), 1.03 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 172.5, 147.8, 146.3, 135.6, 133.7, 129.7, 127.7, 121.8, 108.3, 108.0, 100.9, 96.5, 81.7, 64.0, 60.3, 56.0, 35.8, 34.7, 31.7, 26.9, 25.3, 22.7, 14.2; HRMS *m*/*z* (ESI) calcd for $C_{32}H_{40}O_7SiNa$ $(M + Na)^+$ 587.2435, found 587.2421.

Compound 12e: 76%, R_f 0.38 (20% EtOAc/hexanes); $[\alpha]^{21}_D$ −26.8 (*c* 0.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.63−7.28 (m, 10H), 6.73 (m, 3H), 4.69 (d, J = 6.9 Hz, 1H), 4.52 (d, J = 6.9 Hz, 1H), 3.99 (q, J = 7.7 Hz, 2H), 3.85 (s, 3H), 3.78 (s, 3H), 3.73 (m, 1H), 3.52 (m, 3H), 3.30 (s, 3H), 2.97 (dd, J = 15.4, 4.9 Hz, 1H), 2.61 (dd, J = 15.4, 10.5 Hz, 1H), 1.11 (t, J = 7.7 Hz, 3H), 1.03 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 172.7, 148.7, 147.7, 135.6, 133.7, 133.4, 133.1, 129.8, 27.7, 120.3, 111.5, 111.0, 96.4, 81.0, 63.7, 60.2, 56.1, 55.9, 43.0, 37.6, 26.9, 19.3, 14.2; HRMS *m*/*z* (ESI) calcd for $C_{33}H_{44}O_7SiNa$ $(M + Na)^+$ 603.2748, found 603.2764.

Compound 12f: 75%, R_f 0.56 (40% EtOAc/hexanes); $[\alpha]^{21}_D$ −27.2 (*c* 0.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.61−7.30 (m, 10H), 6.38 (m, 2H), 5.92 (s, 2H), 4.69 (d, J = 6.7 Hz, 1H), 4.52 (d, J = 6.7 Hz, 1H), 4.02 (q, J = 6.9 Hz, 2H), 3.79 (s, 3H), 3.68 (m, 1H), 3.50 (m, 3H), 3.29 (s, 3H), 2.94 (dd, J = 15.4, 4.9 Hz, 1H), 2.56 (dd, J = 15.4, 10.2 Hz, 1H), 1.13 (t, J = 6.9 Hz, 3H), 1.04 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 172.5, 148.7, 143.3, 135.8, 135.7, 135.5, 133.9, 133.3, 133.1, 129.7, 127.7, 107.7, 102.1, 101.4, 96.4, 80.9, 63.7, 60.3, 56.4, 56.1, 43.4, 37.4, 26.8, 19.2, 14.2; HRMS *m*/*z* (ESI) calcd for $C_{33}H_{42}O_8SiNa$ $(M + Na)^+$ 617.2541, found 617.2551.

Compound 13a: 88%, R_f 0.35 (15% EtOAc/hexanes); $[\alpha]^{25}_D$ −49.2 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.66−7.57 (m, 5H), 7.47−7.22 (m, 15H), 4.72 (d, J = 11.6 Hz, 1H), 4.44 (d, J = 11.6 Hz, 1H), 3.73−3.52 (m, 4H), 3.49 (s, 3H), 3.02 (dd, J = 16.0, 4.9 Hz, 1H), 2.71 (dd, J = 16.0, 8.8 Hz, 1H), 1.09 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 173.2, 141.7, 138.6, 135.7, 135.6, 135.4, 134.9, 133.5, 133.3, 129.7, 128.6, 128.4, 127.9, 127.8, 127.6, 126.9, 83.4, 72.7, 63.5, 51.5, 43.6, 37.4, 26.9, 19.3; HRMS *m*/*z* (ESI) calcd for $C_{35}H_{40}O_4SiNa$ $(M + Na)^+$ 575.2588, found 575.2598.

Compound 13d: 93%, R_f 0.4 (15% EtOAc/hexanes); $[\alpha]^{26}_D$ −49.4 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.61−7.55 (m, 5H), 7.42−7.26 (m, 10H), 6.67 (d, J = 8.0 Hz, 3H), 5.92 (s, 2H), 4.67 (d, J = 11.6 Hz, 1H), 4.39 (d, J = 11.6 Hz, 1H), 3.67−3.43 (m, 4H), 3.48 (s, 3H), 2.92 (dd, J = 16.0, 4.9 Hz, 1H), 2.60 (dd, J = 16.0, 9.4 Hz, 1H), 1.04 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 173.0, 147.6, 146.3, 138.5, 135.7, 135.6, 135.4, 133.4, 133.2, 129.7, 128.3, 127.8, 127.7, 127.5, 121.5, 108.5, 108.2, 100.9, 83.4, 72.7, 63.6, 51.4, 43.3, 37.5, 26.9, 19.2; HRMS *m*/*z* (ESI) calcd for $C_{36}H_{40}O_6SiNa$ $(M + Na)^+$ 619.2486, found 619.2495.

Compound 13f: 82%, R_f 0.6 (30% EtOAc/hexanes); $[\alpha]^{25}_D$ −47.9 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.62−7.56 (m, 5H), 7.43−7.26 (m, 10H), 6.39 (s, 2H), 5.95 (s, 2H), 4.68 (d, J = 11.6 Hz, 1H), 4.39 (d, J = 11.6 Hz, 1H), 3.77 (s, 3H), 3.74−3.44 (m, 4H), 3.50 (s, 3H), 2.92 (dd, J = 16.0, 4.9 Hz, 1H), 2.60 (dd, J = 16.0, 9.4 Hz, 1H), 1.05 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 173.0, 148.8, 143.4, 138.5, 136.3, 135.7, 135.6, 134.0, 133.5, 133.1, 129.7, 128.5, 128.3, 127.8, 127.7, 127.7, 127.6, 107.8, 101.9, 101.4, 83.4, 72.6, 63.5,

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56.5, 51.5, 43.6, 37.3, 26.9, 19.3; HRMS *m*/*z* (ESI) calcd for $C_{37}H_{42}O_7SiNa$ $(M + Na)^+$ 649.2592, found 649.2569.

Epimeric mixture 14a:[28] 94% (anti:syn = 14.6:1), R_f 0.45 (30% EtOAc/hexanes); selected ^1H NMR ($CDCl_3$) data for the *anti*-isomer δ 7.55−7.15 (m, 15H), 4.80 (d, J = 11.6 Hz, 1H), 4.55 (d, J = 11.6 Hz, 1H), 4.44 (s, 2H), 3.81−3.73 (m, 1H), 3.58−3.47 (m, 1H), 3.50 (s, 3H), 3.36 (dd, J = 10.5, 5.2 Hz, 1H), 3.04 (dd, J = 16.0, 5.8 Hz, 1H), 2.64 (dd, J = 16.0, 9.1 Hz, 1H); HRMS *m*/*z* (ESI) calcd for $C_{26}H_{28}O_4Na$ $(M + Na)^+$ 427.1879, found 427.1891.

C. Stereochemistry Confirmation: (4*R*,5*S*)-5-Acetoxymethyl-4-phenyl-4,5-dihydro-2(3*H*)-furanone (19).[16] **Method 1:** To a solution of **12a** (136 mg, 0.26 mmol) in CH_2Cl_2 (15 mL) was added Me_2BBr (0.8 mL of 1.6 M solution in CH_2Cl_2) at −78 °C. The resulting mixture was stirred for 3 h at −78 °C. THF (3 mL) and saturated aqueous $NaHCO_3$ (1.5 mL) was added to reaction mixture at −78 °C and the temperature was raised to room temperature. Ether (50 mL) was added to the mixture. The two layers were separated and the organic layer was washed with saturated NH_4Cl and brine, dried with Na_2SO_4, and evaporated. The crude residue was presorbed on silica gel and purified by column chromatography (10−20% EtOAc/hexane) to give pure intermediate 5-*tert*-butyldiphenylsilyloxymethyl lactone **29** (65 mg, 63%) as a colorless oil. R_f 0.4 (12% EtOAc/hexanes); $[\alpha]^{21}_D$ 23.8 (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.25−7.66 (m, 15H), 4.51 (m, 1H), 3.94 (dd, J = 2.8, 11.6 Hz, 1H), 3.73 (m, 2H), 3.09 (dd, J = 9.4, 17.8 Hz, 1H), 2.69 (dd, J = 8.0, 17.8 Hz, 1H), 1.06 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 176.2, 140.7, 135.7, 135.6, 130.0, 129.2, 127.9, 127.7, 127.0, 86.8, 63.7, 42.4, 37.4, 26.9, 19.3; HRMS *m*/*z* (ESI) calcd for $C_{27}H_{30}O_3SiNa$ $(M + Na^+)$ 453.1856, found 453.1851.

To a solution of the lactone **29** (25 mg, 0.058 mmol) in THF (1 mL) at 0 °C was added TBAF (0.29 mL of 1 M solution in THF, 0.29 mmol). The resulting mixture was stirred for 1 h at 0 °C and then aqueous saturated NH_4Cl (1 mL) was added. The aqueous phase was extracted with ether (3 × 5 mL). The combined organic layers were dried with Na_2SO_4 and evaporated to give pure intermediate 5-hydroxymethyl lactone **30** (10.8 mg, 96%). R_f 0.4 (35% EtOAc/hexanes); $[\alpha]^{22}_D$ 28.3 (*c* 0.68, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.39−7.16 (m, 5H), 4.56−4.51 (m, 1H), 4.10−3.85 (m, 1H), 3.81−3.56 (m, 2H), 3.03 (dd, J = 18.0, 9.1 Hz, 1H), 2.78 (dd, J = 18.0, 9.6 Hz, 1H), 2.44 (t, J = 6.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 176.0, 139.2, 129.3, 127.9, 127.3, 87.0, 62.0, 42.1, 37.3; HRMS *m*/*z* (ESI) calcd for $C_{11}H_{12}O_3Na$ $(M + Na)^+$ 215.0678, found 215.0679.

Lactone **30** (15 mg, 0.078 mmol) was dried by coevaporating with toluene (5 × 1 mL) and dissolved in anhydrous pyridine (1 mL). To this solution at 0 °C was added acetic anhydride (80 mg, 0.78 mmol). The resulting mixture was allowed to warm to room temperature and the reaction mixture was stirred for 5 h. The mixture was extracted with ether (3 × 5 mL). The combined organic layers were washed with water (5 mL), dried ($MgSO_4$), and evaporated. The residue was presorbed on silica gel and purified by column chromatography (5−10% EtOAc/hexanes) to afford lactone **19**[16] (12 mg, 66%).

Method 2: To a stirred solution of phenyl addition product **13a** (54.6 mg, 0.1 mmol) in a mixture of dioxane−water (1:1, 5 mL) was added 10% Pd/C (5 mg, 0.004 mmol). The suspension was stirred for 3 days under H_2 atmosphere at atmospheric pressure. The catalyst was filtered off with a Celite pad and solution was concentrated under reduced pressure. The residue was dissolved in ether (30 mL), washed with water (3 × 20 mL) and brine, dried ($MgSO_4$), and evaporated under reduced pressure. The crude residue was presorbed on silica gel and purified by column chromatography (10−20% EtOAc/hexane) to give pure lactone **29** (35 mg, 67%), which was treated as in method 1 to provide **19**.

Method 3: To a stirred solution of the epimeric mixture **14a** (14:1, 0.48 g, 1.2 mmol) in dioxane−water (1:1, 25 mL) was added 10% Pd/C (25 mg, 0.02 mmol). The suspension was stirred for 3 days under H_2 atmosphere at atmospheric pressure. The catalyst was filtered off with a Celite pad and solution was concentrated under reduced pressure. The residue was dissolved in ether (50 mL), washed with water (3 × 20 mL) and brine, dried ($MgSO_4$), and evaporated under reduced pressure to give trans lactone **30** (0.24 g, 90%) with traces of the corresponding cis lactone. This mixture was further treated as in method 1 to obtain **19** with only traces of **20**.

(4*R*,5*R*)-5-Methyl-4-phenyl-4,5-dihydro-2(3*H*)-furanone (21) and (4*S*,5*R*)-5-Methyl-4-phenyl-4,5-dihydro-2(3*H*)-furanone (22).[17] To a stirred solution of the epimeric mixture (6:1) of **15a** (0.4 g, 1.2 mmol) in dioxane−water (1:1, 25 mL) was added 10% Pd/C (25 mg, 0.02 mmol). The suspension was stirred for 3 days under H_2 atmosphere at atmospheric pressure. The catalyst was filtered off with a Celite pad and solution was concentrated under reduced pressure. The residue was dissolved in ether (50 mL), washed with water (3 × 20 mL) and brine, dried ($MgSO_4$), and evaporated under reduced pressure to give lactones **21**[17] (0.174 g, 76%) and **22**[16] (0.029 g, 13%).

Acknowledgment. We thank Professor Patrick S. Mariano for his advice and help with the preparation of the manuscript. This work is supported by the National Institutes of Health (CA-99957 and RR-16480) under the AREA and BRIN/INBRE programs.

Supporting Information Available: Description of the general methods, copies of ^1H and ^{13}C NMR of all new compounds, complete characterization data, and copies of ^1H NMR showing the epimeric ratios of cuprate addition product mixtures **14a**, **14d**, **14f**, **15a**, **15d**, **15f**, **16a**, **16d**, **16f**, **17a**, **17d**, **17f**, **18a**, **18d**, and **18f**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO052383V

(28) Characterization data of all epimeric mixtures obtained in this work can be found in the Supporting Information.