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Overriding Felkin Control: A General Method for Highly Diastereoselective Chelation-Controlled Additions to α-Silyloxy Aldehydes

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Abstract: According to the Felkin−Anh and Cram-chelation models, nucleophilic additions to α-silyloxy aldehydes proceed through a nonchelation pathway due to the steric and electronic properties of the silyl group, giving rise to Felkin addition products. Herein we describe a general method to promote chelation-control in additions to α-silyloxy aldehydes. Dialkylzincs, functionalized dialkylzincs, and (*E*)-disubstituted, (*E*)-trisubstituted, and (*Z*)-disubstituted vinylzinc reagents add to silyl-protected α-hydroxy aldehydes with high selectivity for chelation-controlled products (dr of 10:1 to >20:1) in the presence of alkylzinc halides or triflates, RZnX. With the high functional group tolerance of organozinc reagents, the mild Lewis acidity of RZnX, and the excellent diastereoselectivities favoring the chelation-controlled products, this method will be useful in the synthesis of natural products. A mechanism involving chelation is supported by (1) NMR studies of a model substrate, (2) a dramatic increase in reaction rate in the presence of an alkylzinc halide, and (3) higher diastereoselectivity with larger alkyl substituents on the α-carbon of the aldehyde. This method provides access to chelation-controlled addition products with high diastereoselectivity previously unavailable using achiral organometallic reagents.

1. Introduction

A fundamental strategy in complex molecule synthesis is to utilize substrate stereochemistry to control the introduction of new stereogenic centers.[1−4] Within this conceptual framework, the Felkin−Anh and Cram-chelation models for predicting stereochemical outcomes in additions to chiral aldehydes and ketones are among the most powerful and widely employed (Figure 1).[5−15] According to these models, stereoinduction with protected α- and β-hydroxy aldehydes and ketones is protecting group dependent.[16] Small protecting groups such as benzyl and methyl favor carbonyl addition via chelation control (Cram-chelate model).[7,17] In contrast, sterically encumbering silyl protecting groups disfavor chelation, instead promoting a nonchelation pathway leading to Felkin addition products with moderate to excellent diastereoselectivity.[5,7,18] Exceptions to this paradigm are scarce[19−25] and are detailed in later sections. The

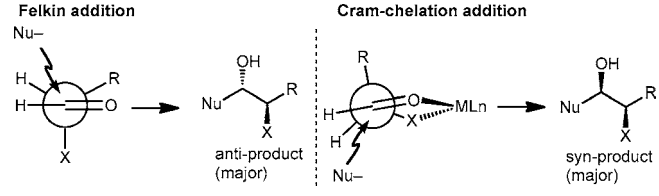

Figure 1. Felkin−Ahn and Cram-chelation models.

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importance of these principles has resulted in their coverage in many organic textbooks.[26−29]

The ability to predict stereochemical outcomes of carbonyl addition reactions based on protecting groups has proven very useful in natural product synthesis. Compounds containing *syn*-vicinal diols may be synthesized from α-hydroxyl aldehydes or ketones bearing small, coordinating protecting groups such as Me, MOM, Bn, or PMB. In contrast, *anti*-vicinal diol motifs can be generated with good to excellent diastereoselectivity when an α-silyloxy aldehyde or ketone is employed, resulting from Felkin addition. Despite the well-documented utility of this paradigm, it is not without drawbacks. Namely, the protecting group strategy is dictated by the relative stereochemistry of the diol-containing motif. Thus, rather than employing the most suitable protecting group for the global synthetic approach, the protecing group is chosen to achieve the desired diastereoselectivity in the carbonyl addition step.[16]

In cases where the most advantageous protecting group for the global synthesis does not provide the requisite stereochemistry in the addition to enantioenriched protected α- and *β*-silyloxy aldehydes and ketones, chemists have relied on chiral reagents and catalysts or a deprotection/reprotection strategy. Substrate stereocontrol can be overridden by use of enantioenriched stoichiometric auxiliaries, optically active stoichiometric additives,[5,30−38] or chiral catalysts.[39−43] Successful examples using stoichiometric Lewis acids are illustrated in Scheme 1A−C. Although these techniques led to the desired stereoisomer with moderate to high diastereoselectivity, they are not ideal. They employ large amounts of enantioenriched additives (A−C), which must be prepared and ultimately separated from the product. The chiral catalyst approach (D) gave excellent diastereoselectivity in both the matched and mismatched cases, although yields were low to moderate (24−68%).[39] These examples highlight a long-standing problem in organic synthesis: there are no general methods for highly diastereoselective chelation-controlled or anti-Felkin addition of organometallic reagents to α-silyloxy aldehydes.

A more refined approach employing α-silyloxy aldehydes would be to override the expected Felkin control by using *achiral* reagents to enable the synthesis of chelation-controlled addition products. If successful, chemists could then prepare either the Felkin or chelation-controlled diastereomer from chiral α-silyloxy aldehydes by proper choice of organometallic reagents.[25] Herein, we present a general method to achieve such highly diastereoselective chelation-controlled additions to α-silyloxy aldehydes with a variety of functionalized organozinc reagents, including dialkylzincs and in situ generated (*E*)-di-, (*E*)-tri-, and (Z)-disubstituted vinylzinc species.

2. Background

Inspiration for this study stemmed from our research into the additions of various vinylzinc reagents to enantioenriched α-silyloxy aldehydes. We recently developed a protocol for the synthesis of (*Z*)-allylic alcohols beginning with 1-bromo-1-alkynes (Scheme 2).[44] Hydroboration of 1-bromo-1-alkynes with dicyclohexylborane followed by addition of a nucleophile,[45−51] in this case a hydride delivered from *t*-BuLi,[48] to the coordinatively unsaturated boron initiates a rearrangement that results in generation of a (*Z*)-vinylborane intermediate. Srebnik[52] and Oppolzer[53] had reported that vinylboranes undergo boron to zinc vinyl exchange (i.e., transmetalation) in the presence of dialkylzinc reagents.[54] Thus, treatment of the resulting (*Z*)-vinylborane with dialkylzinc reagents generated (*Z*)-vinylzinc intermediates. The greater nucleophilicity of vinylzinc organometallics over their vinylborane counterparts enabled additions to aldehydes to proceed smoothly to generate (*Z*)-allylic alcohols.[44,55] When enantioenriched α-silyloxy aldehydes were employed, low diastereoselectivity (dr 4:1) favoring chelation-controlled addition was observed. Surprisingly, however, addition of the (*Z*)-vinylzinc reagent to TBS-protected α-hydroxy propanal in the presence of 2 equiv of $BF_3 \cdot OEt_2$, a monodentate Lewis acid, resulted in formation of the anti-Felkin or Cram-chelation addition product with 8:1 dr (Scheme 2).[44] We observed a similar enhancement in the diastereoselectivity in the addition of heterobimetallic vinylzinc reagents[56,57] to trialkylsilyl-protected α-hydroxy propanals in the presence of $BF_3 \cdot OEt_2$.[56] It is noteworthy that monodentate Lewis acids such as BF_3 are expected to *increase* the ratio of Felkin to anti-Felkin products.[7] The role of the $BF_3 \cdot OEt_2$ and the origin of the diastereoselec-

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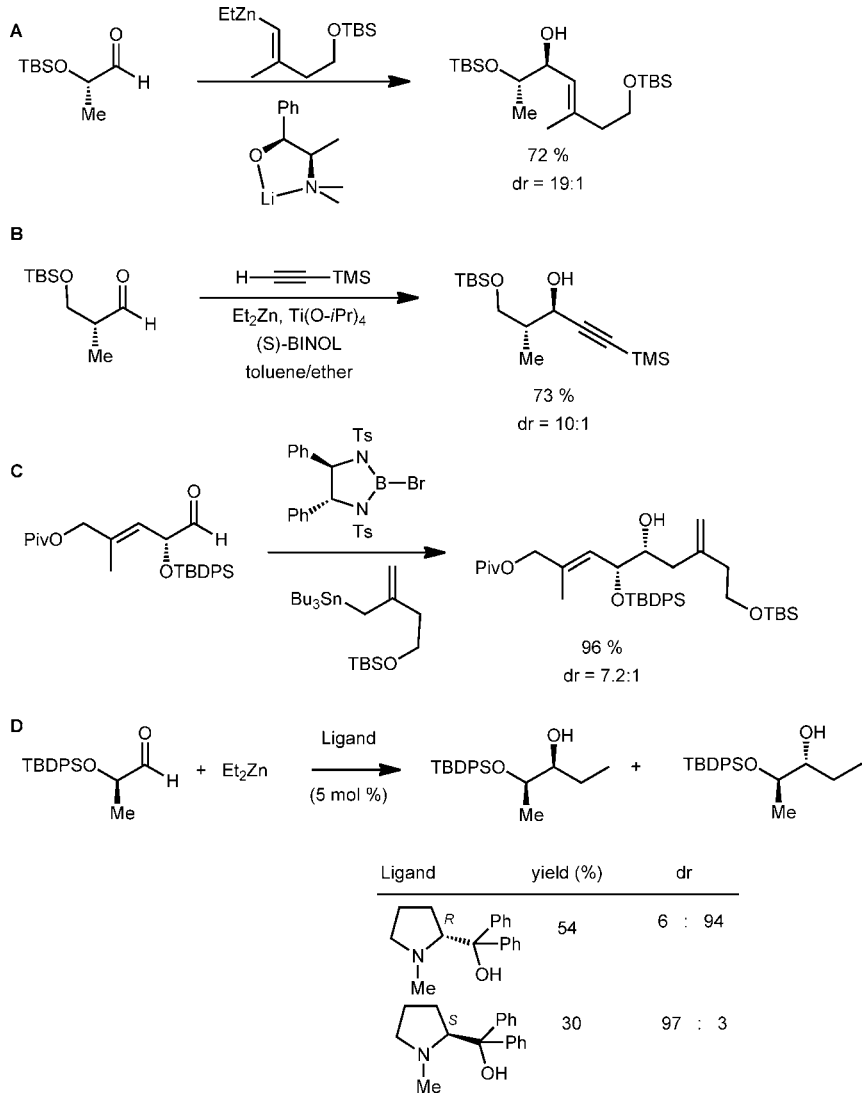
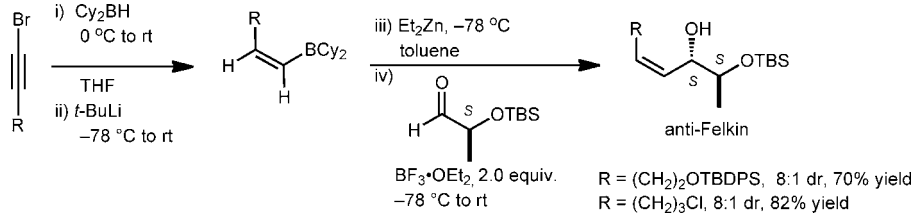
Scheme 1. Overriding Substrate Control with Enantioenriched Stoichiometric Additives (A−C) and Catalysts (D)



Scheme 2. One-Pot Synthesis of (*Z*)-Disubstituted Allylic Alcohols in the Presence of $BF_3 \cdot OEt_2$ with Unexpected Anti-Felkin Stereoselectivity

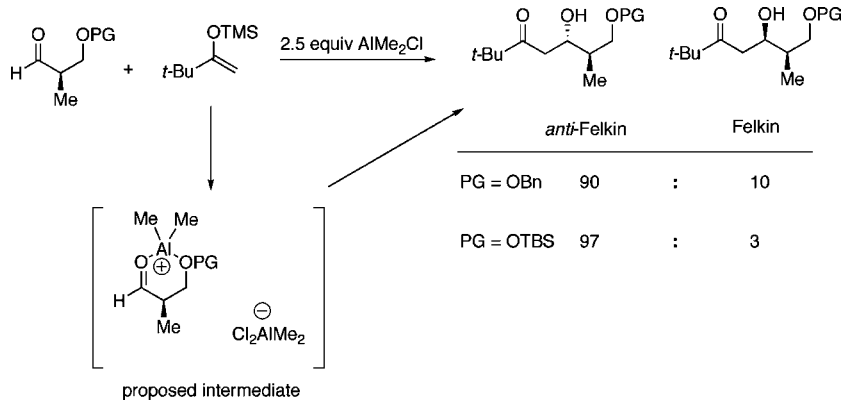


tivity in these reactions were unprecedented and remained unclear until the results outlined below were obtained.

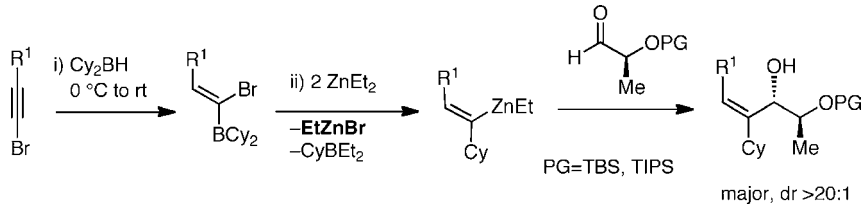
Given the Lewis acidity of BF_3 and low diastereoselectivity in its absence, we hypothesized that it was responsible for the observed stereoselectivity. In a series of elegant studies,[23−25] Evans and co-workers demonstrated that $ClAlMe_2$ and Cl_2AlMe, which are monodentate Lewis acids like BF_3, engage in chelation-controlled addition reactions with enantioenriched β-silyloxy aldehydes. For example, the Mukayama aldol reaction is proposed to proceed by the mechanism outlined in Scheme 3.[23] The key feature of this proposal is the abstraction of an aluminum halide by a second equiv of Lewis acidic aluminum reagent to afford a cationic aluminum species capable of chelating chiral β-silyloxy aldehydes and forming the chelation controlled product with excellent diastereoselectivity. Although unprecedented, we speculated that a similar mechanism might be responsible for the stereocontrol in our additions in the presence of $BF_3 \cdot OEt_2$.[56]

Greater insight into our unexpected stereoselectivities in Scheme 2 was obtained when (*Z*)-trisubstituted vinylzinc reagents were added to TBS or TIPS protected α-hydroxy propanals.[50,51] (*Z*)-Trisubstituted vinylzinc intermediates were generated from 1-bromo-1-alkenylboranes. Instead of addition of a hydride source (*t*-BuLi), a dialkylzinc reagent was added to first promote the rearrangement and then to effect the transmetalation to generate the (*Z*)-trisubstituted vinylzinc intermediates.[50] Addition of α-silyloxy aldehydes to the resultant vinylzinc solution led to chelation-controlled addition products

Scheme 3. Evans' Proposal for Chelation Control with Aluminum Lewis Acids in the Diastereoselective Mukayama Aldol Reaction (PG = Protecting Group)



Scheme 4. One-Pot Generation of (*Z*)-Trisubstituted Allylic Alcohols with High Diastereoselectivity

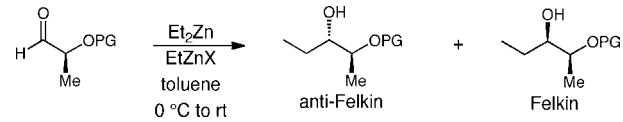


with very high diastereoselectvity (dr >20:1).[51] Importantly, no $BF_3 \cdot OEt_2$ was employed in this process. If the BF_3 was not responsible for the observed anti-Felkin addition pathway in Scheme 4, was it possible that the EtZnBr byproduct was activating the α-silyloxy aldehydes by chelation? A priori, it seemed unlikely that a mild Lewis acid such as EtZnBr would chelate sterically encumbered α-silyloxy aldehydes. Based on these results, we hypothesized that the diastereoselectivity in Scheme 2 might be due to alkyl abstraction from ZnR_2 by BF_3, to form a cationic zinc Lewis acid[58] or that EtZnF is generated. Both of these species have at least two open coordination sites and would be capable of chelating a bidentate substrate. As outlined below, we set out to determine if EtZnCl and EtZnBr were responsible for the high diastereoselectivity in additions of organozinc reagents to α-silyloxy aldehydes.

3. Results and Discussion

3.1. Addition of Dialkylzinc Reagents to Silyl Protected α-Hydroxy Aldehydes. Our initial experiments involved the use of commercially available diethylzinc with the TBS or TES-protected (*S*)-α-hydroxy propanal. We first determined the diastereoselectivity of the addition of diethylzinc to the aldehyde substrates. As illustrated in Table 1 (entries 1 and 10) diethylzinc reacts sluggishly with α-silyloxy aldehydes in the absence of a Lewis acid with no selectivity, providing a 1:1 ratio of the Felkin to the chelation-controlled products. The reactions were then performed in the presence of 0.1−1.5 equiv EtZnX (X = Cl, Br). Lewis acidic RZnX (R = Et, Me, *n*-Bu) were easily prepared by conproportionation of ZnX_2 and ZnR_2 in toluene at 70 °C for 3 d followed by filtration and removal of the volatiles (Scheme 5).[59,60] These materials could be used directly or stored under a nitrogen atmosphere for months.

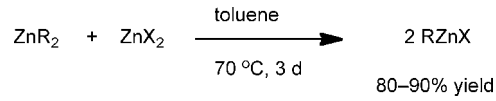
Table 1. Diastereoselective Ethyl Additions to Silyl-Protected α-Hydroxy Propanal



entry	PG	EtZnX	mol %[a]	yield (%)	dr[b]
1	TBS	EtZnCl	0	77	1:1
2			150	90	28:1[c]
3			100	93	31:1[c]
4			50	94	14:1
5			25	91	6.7:1
6	TBS	EtZnBr	150	92	22:1
7			100	94	20:1
8			25	89	13:1
9			10	81	6:1
10	TES	EtZnCl	0	69	1:1
11			150	77	>20:1
12			100	85	>20:1
13			50	72	15.4:1
14	TIPS	EtZnCl	0	60	1:2
15			150	80	>20:1[d]

[a] Mol % EtZnX relative to aldehyde. [b] dr (Cram-chelation:Felkin) determined by ^{1}H NMR of crude products. [c] dr (Cram-chelation:Felkin) determined by GC analysis of TMS-protected derivative. [d] Reaction conducted at −50 °C.

Scheme 5. Synthesis of RZnX via Conproportionation



Performing the addition of diethylzinc to TBS or TES-protected (*S*)-α-hydroxy propanal in toluene in the presence of 1.0−1.5 equiv EtZnCl or EtZnBr provided addition product of very high diastereoselectivity favoring the chelation-controlled products (entries 2, 3, 6, 7, 11, and 12). The relative configurations were ascertained by ^{1}H NMR analysis using the modified

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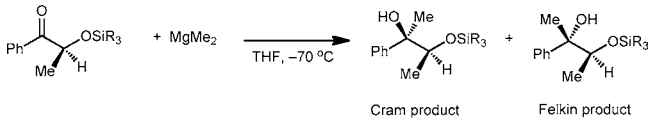
Table 2. Selected Results for the Addition of $MgMe_2$ to α-Hydroxy Propiophenones by Eliel and Coworkers.[20]



entry	SiR_3	relative rate	dr[a]
1	$SiMe_3$	~100	99:1
2	$SiEt_3$	8	96:4
3	Si(*t*-Bu)Me_2	2.5	88:12
4	Si(*t*-Bu)Ph_2	0.8	63:37
5	Si(*i*-Pr)$_3$	0.5	42:58

[a] dr = Cram-chelation:Felkin.

Mosher method.[61,62] Substoichiometric EtZnX also afforded chelation-controlled products, albeit with diminished diastereoselectivity (entries 4, 5, 8, 9, and 13). Ethyl addition to the extremely bulky TIPS-protected aldehyde in the absence of additional Lewis acid favored the expected Felkin addition product (dr = 2:1). Conducting the reaction in the presence of 1.5 equiv EtZnCl at −50 °C resulted in formation of the chelation-controlled addition product with excellent diastereoselectivity (dr > 20:1, entry 14 vs 15). It is noteworthy that at −50 °C no product was formed upon addition of Et_2Zn to the TBS-protected α-hydroxy propanal after 8 h, whereas the identical reaction employing 1.5 equiv EtZnCl reached 65% conversion in 16 min. A considerable increase in addition rate would be expected if the reaction proceeded via a chelated intermediate.[19,20]

The significant increase in the rate of reaction in the presence of EtZnX can be compared with prior investigations by Eliel and Frye.[19−21] Using dimethylmagnesium in THF at −70 °C, the methylation of silyl protected 3-hydroxy-2-butanone was performed. With smaller protecting groups, such as TMS, very high diastereoselectivities were observed favoring the chelation-controlled product (Table 2, entry 1, dr = 99:1). As the size of the protecting group was increased, the dr steadily diminished.[20] Ultimately, with the TIPS protecting group, the Felkin addition product predominated (entry 5, 58:42) and the reaction was proposed to occur by monodentate activation of the ketone carbonyl. These authors observed a rate acceleration with the TMS protected substrate, which was around 2 orders of magnitude faster than the TIPS derivative and a model ketone devoid of the α-silyloxy group (propiophenone). Although the results in this mechanistic study are conceptually related to chemistry reported herein, the scope was limited to $MgMe_2$ and protected chiral α-hydroxy propiophenones. Reetz also observed chelation-controlled addition to TBS-protected 2-hydroxy-3-pentanone with $MeTiCl_3$ with dr's as high as 85:15.[22]

We next explored the substrate scope of the addition with respect to the other dialkylzinc reagents. Due to the rapid alkyl exchange between alkylzinc species, it was necessary that the R groups on ZnR_2 and RZnX be identical to avoid a mixture of products.[63] Additions of Me_2Zn and (n-Bu)$_2$Zn in the presence of MeZnCl and *n*-BuZnCl, respectively, exhibited diastereoselectivities ≥18:1 favoring the chelation-controlled products (Table 3, entries 1 and 2). Functionalized dialkylzinc reagents, prepared by the method of Knochel,[64−66] were likewise used in additions to TBS-protected α-hydroxy propanal. In these cases, the Lewis acid employed was generated by reaction of 2.7 equiv of the dialkylzinc reagent with 1.5 equiv triflic acid. The resulting mixture then contained 1.5 equiv of RZn(OTf)[67] and 1.2 equiv of the functionalized dialkylzinc reagent, ZnR_2. Reaction of this mixture with TBS-protected α-hydroxy propanal provided the chelation-controlled addition products with high diastereoselectivities. The yields, however, were diminished due to partial reduction of the aldehyde substrate. Reduction most likely occurred via a β-hydrogen transfer mechanism.[68−70] At this time, we have not successfully inhibited the reduction pathway.

Having demonstrated the ability to control diastereoselectivity with silyl protected α-hydroxy propanals, we examined alkyl additions to related aldehydes (Table 3, entries 5−8). If the additions occur via chelated intermediates, larger alkyl and aryl substituents on the α-carbon should increase the chelation-controlled diastereoselectivity by more effectively blocking the Felkin addition pathway. As representative substrates, the methyl in the TBS protected α-hydroxy propanal substrate was substituted with *i*-Pr and Ph. As shown in Table 3, high diastereoselectivities were again obtained with the chelation-controlled product dominating (entries 5−8). As seen in entries 3 vs 6, larger substituents on the α-carbon do in fact lead to higher diastereoselectivity. Although the phenyl-substituted aldehyde in entry 8 contains an acidic α-hydrogen, addition to the aldehyde occurred more rapidly than deprotonation. The high diastereoselectivities observed in the additions to three different aldehydes indicate that the methods introduced herein should be applicable to a host of related substrates.

3.2. Additions Involving (*E*)-Di- and Trisubstituted Vinylzinc Reagents. Allylic alcohols are important intermediates in organic synthesis and are common structural motifs in natural products.[71,72] It can be difficult, however, to simultaneously control both the double bond geometry and the formation of the stereocenter in the vinylation of chiral aldehydes. We therefore applied our approach, as described in the previous sections, to additions with vinylzinc reagents. In this context, Oppolzer's procedure[52,53,73,74] was used to generate (*E*)-vinylzinc intermediates. Thus alkyne hydroboration with Et_2BH and B to Zn transmetalation with Et_2Zn in dichloromethane was followed by addition of TBS- or TES-protected (*S*)-α-hydroxy propanal at 0 °C. In the absence of additional Lewis acid, Felkin addition narrowly predominated (1.5:1 dr, Table 4, entry 1).

(61) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092–4096.
(62) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1968**, *90*, 3732–3738.
(63) Blake, A. J.; Shannon, J.; Stephens, J. C.; Woodward, S. *Chem.—Eur. J.* **2007**, *13*, 2462–2472.
(64) Rozema, M. J.; Sidduri, A.; Knochel, P. *J. Org. Chem.* **1992**, *57*, 1956–1958.
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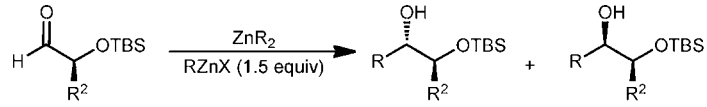
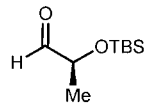
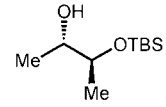
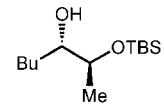
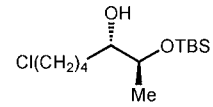
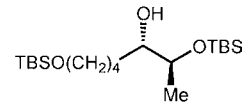
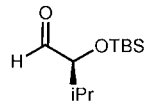
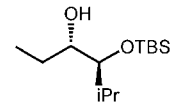
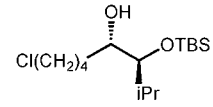
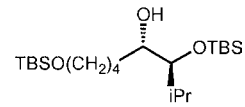
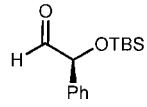
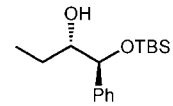
(66) Knochel, P.; Jones, P. *Organozinc Reagents*; Oxford University Press: Oxford, U.K., 1999.
(67) Oppolzer, W.; Schroder, F.; Kahl, S. *Helv. Chim. Acta* **1997**, *80*, 2047–2057.
(68) Fennie, M. W.; DiMauro, E. F.; O'Brien, E. M.; Annamalai, V.; Kozlowski, M. C. *Tetrahedron* **2005**, *61*, 6249–6265.
(69) DiMauro, E. F.; Kozlowski, M. C. *Org. Lett.* **2002**, *4*, 3781–3784.
(70) DiMauro, E. F.; Kozlowski, M. C. *J. Am. Chem. Soc.* **2002**, *124*, 12668–12669.
(71) Katsuki, T.; Martin, V. S. *Org. React.* **1996**, 1.
(72) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307–1370.
(73) Oppolzer, W.; Radinov, R. N.; Brabander, J. D. *Tetrahedron Lett.* **1995**, *36*, 2607–2610.
(74) Oppolzer, W.; Radinov, R. N.; El-Sayed, E. *J. Org. Chem.* **2001**, *66*, 4766–4770.

Table 3. Determination of the Scope with Respect to Dialkylzinc Reagents and Aldehyde



entry	chiral aldehyde	ZnR_2	yield (%)	dr	major product
1		$ZnMe_2$	91	18:1	
2		$ZnBu_2$	87	>20:1	
3		$Zn((CH_2)_4Cl)_2$	50	16:1	
4		$Zn((CH_2)_4OTBS)_2$	47	20:1	
5		$ZnEt_2$	82	>20:1	
6		$Zn((CH_2)_4Cl)_2$	52	20:1	
7		$Zn((CH_2)_4OTBS)_2$	58	>20:1	
8		$ZnEt_2$	93	>20:1	

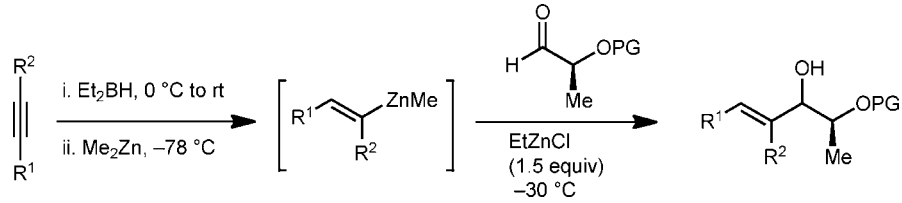
After screening various addition temperatures, we found that −30 °C provided a balance between EtZnCl solubility in dichloromethane and suppression of the background addition (Table 4, entry 1). As shown in Table 4, terminal alkynes were successfully utilized to afford (*E*)-disubstituted allylic alcohols with dr's of 10:1 to >20:1, favoring the chelation-controlled addition products (entries 2−6). Use of an enyne afforded the *syn*-dienyl alcohol with >20:1 dr and 70% yield (entry 7). Finally, the internal alkyne 4,4-dimethyl-2-pentyne enabled the synthesis of (*E*)-trisubstituted allylic alcohols with >20:1 dr using the TBS or TES protecting groups in ≥85% yield (entries 8 and 9).

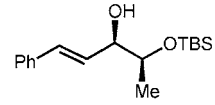
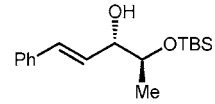
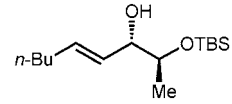
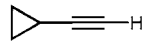
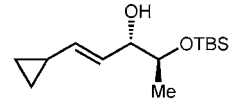
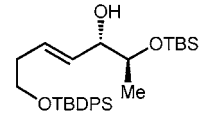
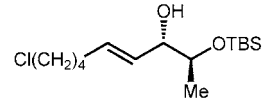
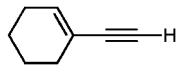
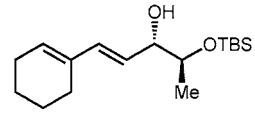
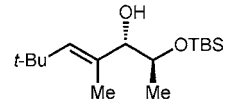
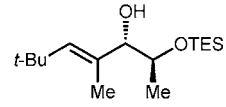
For any method to be synthetically useful, scalability must be demonstrated. When phenyl acetylene was employed on a 5 mmol scale, the allylic alcohol was obtained in 82% yield (dr >20:1, entry 2). In each entry in Table 4 only a single double bond isomer was observed by ^{1}H NMR spectroscopy.

3.3. Diastereoselective Additions of (*Z*)-Disubstituted Vinylzinc Reagents to Silyl Protected α-Hydroxy Aldehydes. As outlined in Scheme 2, we developed a method for the diastereoselective addition of (*Z*)-vinylzinc reagents to aldehydes.[44] An asymmetric version of this reaction was recently introduced.[51,55] In the addition to TBS protected α-hydroxy propanal (Scheme 2), the dr was 4:1 in the absence of added Lewis acid and increased to 8:1 in the presence of $BF_3 \cdot OEt_2$. Both reactions favored the chelation-controlled addition products.

For the present study, we investigated the impact of EtZnCl on the diastereoselective (*Z*)-vinylation of TBS protected α-hydroxy aldehydes with the goal of increasing the diastereoselectivity of the addition and circumventing the use of the harsh Lewis acid BF_3. In our initial reports on the (*Z*)-vinylation of aldehydes, the reactions were conducted in THF or TBME to stabilize the polar intermediates.[44] These solvents are not compatible with the Lewis acids RZnX, because they effectively

Table 4. Diastereoselective Generation of (*E*)-Di- and Trisubstituted Allylic Alcohols and Dienyols



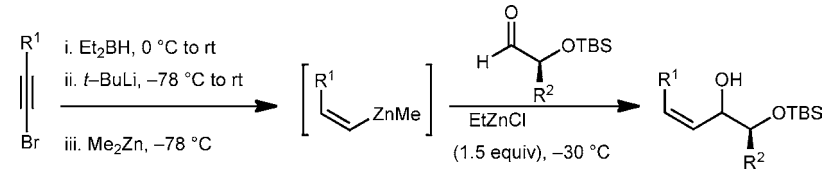
entry	PG	alkyne	yield (%)	dr[a]	major product[b]
1	TBS	Ph—≡—H	20	1:1.5[c]	
2		Ph—≡—H	82	>20:1	
3		*n*-Bu—≡—H	54	17:1	
4			82	11:1	
5		TBDPSO(CH$_2$)$_2$—≡—H	72	>20:1	
6		Cl(CH$_2$)$_4$—≡—H	92	10:1	
7			70	>20:1	
8		*t*-Bu—≡—Me	85	>20:1	
9	TES	*t*-Bu—≡—Me	93	>20:1	

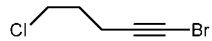
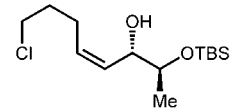
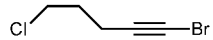
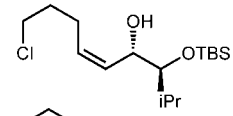
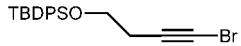
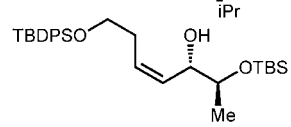
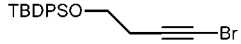
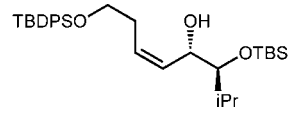
[a] dr determined by ^{1}H NMR of the crude product and refers to the ratio of Cram-chelation:Felkin addition products. [b] Absolute configurations of alcohols were determined by modified Mosher ester analysis. [c] The yield and dr correspond to the reaction without EtZnCl.

compete with the aldehyde substrate for the open coordination sites on RZnX and nullify its impact on the diastereoselective addition. Thus, the hydroboration 1-bromo-1-alkynes and addition of *tert*-butyllithium were conducted in THF solvent. The volatiles were then removed under reduced pressure, toluene was added, and the volatiles again evacuated to ensure that as much THF as possible was removed. Fresh toluene was then added followed by transmetalation, addition of EtZnCl (1.5 equiv) and the TBS protected aldehyde at −30 °C. After 12 h, the reactions were quenched and the ^{1}H NMR of the crude material acquired to determine the dr. In the case of the TBS protected α-hydroxy propanal, dr's were ≥14:1 favoring chelation-controlled addition products and the yields ranged from 72−90% (entries 1 and 3).

It is noteworthy that both the dr's and yields were higher in the (*Z*)-vinylations with EtZnCl (Table 5) than in the BF_3 promoted reaction (Scheme 2). Use of the isopropyl-substituted aldehyde resulted in higher diastereoselectivity than the propanal derivative (compare entries 2 and 4). Although the greater diastereoselectivity with the isopropyl-substituted aldehyde, with respect to the methyl analog, is not proof of chelation control,

Table 5. Diastereoselective (*Z*)-Vinylation of α-Silyloxy Aldehydes in the Presence of EtZnCl



entry	alkyne	R^2	yield (%)	dr	major product
1		Me	72	20:1	
2		*i*Pr	90	>20:1	
3		Me	78	14:1	
4		*i*Pr	80	>20:1	

it is consistent with it. The question of substrate chelation with EtZnCl is further explored in the next section.

3.4. NMR Binding Studies with EtZnCl and a Substrate Model. Chelation-controlled additions to silyloxy aldehydes or ketones are uncommon,[57,19−25] and we are not aware of any examples of chelation with the very bulky TIPS group. The possibility of chelation of protected α-hydroxy aldehydes and ketones to Lewis acids has been examined by NMR spectroscopy[6,8,75−78] and X-ray crystallography.[79] Ketones are usually preferred for these studies over aldehydes due to their greater stability in the presence of Lewis acids. With strong Lewis acids like $MeTiCl_3$ and substrates with benzyl protecting groups, Reetz observed tight κ^2-binding of the substrate to form a five membered chelate.[75] In this case, significant shifts were observed in the ^{13}C NMR spectra of the carbonyl and α-*C*H-OPG moiety (Table 6, entry 1). When the substrate contained a bulky silyl protecting group, however, binding was less favorable for steric and electronic reasons. In these cases chelation may not be observed at all, as ascertained by smaller chemical shift changes (Δ′s, defined as the change in chemical shift) of the C*H* bearing the silyloxy group. As a model for the observed reactivity of silyl protected α-hydroxy propiophenones with $MgMe_2$, Eliel and Frye[20,21] examined the NMR shifts of a series of ketones in the presence of the stronger Lewis acid $MgBr_2$ in CD_2Cl_2. They observed larger shifts in the α-C*H*-OSi than the α′-C*H*'s in the ^1H NMR spectra when chelation was predominant and similar shifts when η^1-coordination of the carbonyl oxygen was dominant (Table 6, entries 2 vs 3).[20] The decreasing binding strength can also be seen in comparison of the α-C*H*-OSi shifts as the protecting group is varied (entries 4−6). The observations in entries 2 vs 3 and 5 vs 6 are consistent with the relative rates of carbonyl additions of $MgMe_2$ to these aldehydes presented in Table 2.

To indirectly probe the possibility of chelation of silyloxy aldehydes to EtZnX, we employed TBS-protected 3-hydroxy butanone as a substrate analogue, because it is more stable in the presence of EtZnCl than the aldehyde substrates. The NMR spectrum of TBS-protected 3-hydroxy butanone was recorded in CD_2Cl_2 before and after combination with one equiv of EtZnCl. A distinct downfield shift, Δ, of 0.34 ppm of the α-C*H*-OSi was observed in the presence of one equiv EtZnCl (Table 6, entry 8). The α′-CH_3 protons exhibited a smaller shift (Δ = 0.19 ppm). Another 0.38 ppm downfield shift for the α-C*H*-OSi was measured upon addition of 3 more equiv of EtZnCl, vs a 0.19 ppm shift for the α′-CH_3 (entry 8). Significantly, a downfield shift of 0.29 ppm was measured for the diastereotopic Si(CH_3)$_2$ protons in the presence of 4 equiv of EtZnCl and the single resonance for the diastereotopic SiMe_2 groups in the free ketone split into two resonances separated by 0.017 ppm (see SI for spectra). With 4 equiv EtZnCl, the shifts in the $^{13}C\{^1H\}$ NMR spectra for the α-C*H*-OSi and α′-CH_3 resonances show less pronounced differences (Table 6, entries 8 and 9). The larger Δ′s for the α-C*H*-OSi, relative to the α′-CH_3 protons, in the ^1H NMR spectra of **1** + EtZnCl and the shift of the SiMe_2 resonance are consistent with chelation of both oxygens of the silyloxy ketone to EtZnCl. These results provide anecdotal support that the additions to α-silyloxy aldehydes proceed via a Cram-chelation mechanism. It is also noteworthy that smaller shifts were observed with EtZnCl than $MgBr_2$, consistent with the lower Lewis acidity of EtZnCl (compare entries 5 and 7).

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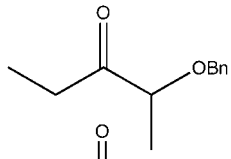
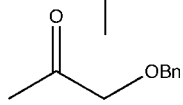
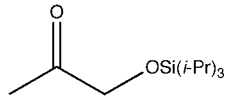
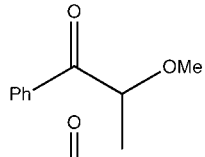
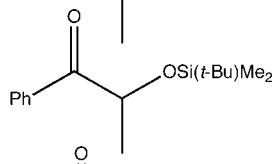
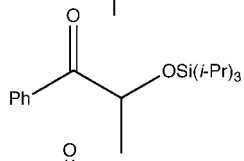
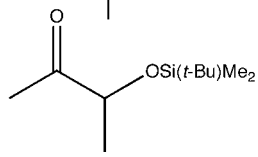
Table 6. ^{1}H and ^{13}C NMR Studies of Protected α-Hydroxy Ketones Binding to Lewis Acids[a]

entry	substrate	LA (equiv)	*C*=O	a-*C*–O	a'-*C*	a-C*H*-O	a'-C*H*
1		$MeTiCl_3$ (1)[b]	11.3[c]	3.1–8.3[d]	NR	NR	NR
2		$MgBr_2{\bullet}(OEt_2)_2$ (1)[e]	NR	NR	NR	0.48	0.21
3		$MgBr_2{\bullet}(OEt_2)_2$ (1)[e]	NR	NR	NR	0.20	0.22
4		$MgBr_2{\bullet}(OEt_2)_2$ (1)[e]	NR	NR	NA	0.81	NA
5		$MgBr_2{\bullet}(OEt_2)_2$ (1)[e]	NR	NR	NA	0.55	NA
6		$MgBr_2{\bullet}(OEt_2)_2$ (1)[e]	NR	NR	NA	0.19	NA
7		EtZnCl (1)	5.0	0.72	0.75	0.34	0.19
8		EtZnCl (4)	8.8	1.82	1.47	0.72	0.36

[a] NMR studies by Reetz (entry 1)[75] and Eliel and Frye (entries 2−6),[20] NA= Not applicable, NR= not reported, Δ values reported in ppm. [b] Mixture of two diastereomers formed. [c] Average of two diastereomers. [d] Minimum values, peaks not assigned in original report. m. [e] In CD_2Cl_2 solvent.

4. Summary and Outlook

We have developed the first general and highly diastereoselectivity method for the chelation-controlled addition of organometallic reagents to α-silyloxy aldehydes. These substrates normally provide Felkin addition products independent of the Lewis acid employed. With introduction of this method it is no longer necessary to switch protecting groups or add stoichiometric quantities of chiral auxiliaries to favor chelation-controlled addition of organometallic nucleophiles to α-silyloxy aldehydes. The generality of this procedure is demonstrated by the highly diastereoselective additions of alkyl, functionalized alkyl, and (*E*)-disubstituted, (*E*)-trisubstituted, and (*Z*)-disubstituted vinyl groups to a range of silyl protected α-hydroxy aldehydes. These results, in combination with our recent studies employing (*Z*)-trisubstituted vinylzinc additions to chiral aldehydes (Scheme 4), represent a powerful new method that is tolerant of functionality and suitable for late stage use in complex natural product synthesis.

^{1}H NMR studies with a substrate analogue indicate that RZnX chelates the carbonyl and *O*-silylated ether. These results provide circumstantial support for chelation-controlled additions in the presence of EtZnX Lewis acids. When combined with the observed high levels of chelation control, the considerable rate accelerations observed in the presence of RZnX, and higher diastereoselectivities with *iso*-propyl substituted aldehydes compared to their methyl substituted analogues, a compelling case for Cram-chelation control can be made. The approach described herein to chelation-controlled addition with substrates that rarely chelate is counterintuitive. Typically stronger Lewis acids are employed with weakly coordinating substrates to favor binding. In our approach, however, it is the combination of a weak Lewis acid and weak to moderate organozinc nucleophile[80,81] that favors chelation control. We are currently extending this strategy to related nucleophiles and electrophiles.

5. Experimental Section

Representative procedures are described herein. Full experimental details and characterization of all compounds are provided in the Supporting Information.

General Methods. All reactions were performed under a nitrogen atmosphere using oven-dried glassware and standard Schlenk or vacuum line techniques. The progress of all reactions was monitored by thin-layer chromatography. Toluene and dichloromethane were dried through alumina columns. Chiral aldehydes were prepared by literature method; Parrikh−Doering oxidation of the requisite primary alcohol was performed just prior to carbonyl addition reactions.[82,83] Alkyl zinc halides were prepared by literature methods.[60,84] Functionalized organozinc reagents were prepared from the corresponding alkyl iodide or from the alkene via hydroboration as outlined

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in the literature procedures.[64,65,85,86] All chemicals were obtained from Acros, Sigma-Aldrich, or GFS Chemicals unless otherwise described. The ^{1}H NMR and ^{13}C{^{1}H} NMR spectra were obtained using a Bruker AM-500 Fourier transform NMR spectrometer at 500 and 125 MHz, respectively. Chemical shifts are reported in units of parts per million (ppm) downfield from tetramethylsilane and all coupling constants are reported in hertz. The infrared spectra were obtained using a Perkin-Elmer 1600 series spectrometer. Thin-layer chromatography was carried out on Whatman precoated silica gel 60 F-254 plates and visualized by ultraviolet light or by staining with ceric ammonium molybdate stain. Silica gel (230−400 mesh, Silicycle) was used for air-flashed chromatography. Analysis of diastereomeric ratios was performed by gas chromatography of TMS derivatives using a Hewlett-Packard 6890 GC with a Beta-Dex Column or by ^{1}H NMR of the crude reaction products. High resolution mass spectra were measured using a Waters LCTOF- Xe Premier ESI mass spectrometer. Relative stereochemistry was determined by modified Mosher ester analysis.[87]

Cautionary Note. Dialkylzinc reagents and *tert*-butyllithium are pyrophoric. Extreme caution should be used in their handling and proper laboratory attire is highly recommended.

General Dialkylzinc Procedure. General Procedure A. A dry 10 mL Schlenk flask, which was evacuated under vacuum and backfilled with N_2 three times, was charged with the alkyl zinc chloride (0.35 mmol, neat solid), chiral aldehyde (0.35 mmol, neat), and toluene (1 mL). The flask was then cooled to 0 °C, and dialkylzinc (0.42 mmol) was added dropwise. The reaction mixture was gradually warmed to room temperature and monitored by TLC until completion (usually 30 min). The reaction mixture was quenched with saturated aq. NH_4Cl (2 mL) followed by addition of 2 N HCl (1 mL) and Et_2O (5 mL). The organic layer was separated and the aqueous solution extracted with EtOAc (3 × 10 mL). The combined organic layers were successively washed with $NaHCO_3$ and brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated in vacuo and purified by column chromatography on silica gel.

Additions to TIPS Protected Aldehyde. General Procedure B. A dry 10 mL Schlenk flask, which was evacuated and backfilled with N_2 three times, was charged with the alkyl zinc chloride (0.35 mmol, neat solid), dialkylzinc (0.42 mmol), and toluene (1 mL). The flask was then cooled to −50 °C followed by slow addition of aldehyde solution (0.35 mmol, in 0.5 mL toluene). The reaction was monitored by TLC until completion (usually 30 min). The reaction mixture was quenched with saturated aq. NH_4Cl (2 mL) followed by addition of 2 N HCl (1 mL) and Et_2O (5 mL). The organic layer was separated and the aqueous solution extracted with EtOAc (3 × 10 mL). The combined organic layers were successively washed with $NaHCO_3$ and brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated in vacuo and purified by column chromatography on silica gel.

Functionalized Dialkylzinc Procedure. General Procedure C. A dry 10 mL Schlenk flask, which was evacuated under vacuum and backfilled with N_2 three times, was charged with the functionalized dialkylzinc reagent (0.94 mL, 1 M in degassed CH_2Cl_2). The flask was cooled to −78 °C and trifluoromethanesulfonic acid (50 μL, 0.52 mmol) was added dropwise.[67] The flask was slowly warmed to room temperature and stirred for 45 min. The flask was the cooled to 0 °C and the aldehyde solution (0.35 mmol, in 0.3 mL degassed CH_2Cl_2) was added dropwise. The reaction was monitored by TLC until complete. The reaction mixture was quenched with saturated aq. NH_4Cl (2 mL) followed by addition of 2 N HCl (1 mL) and Et_2O (5 mL). The organic layer was separated and the aqueous solution extracted with Et_2O (3 × 10 mL). The combined organic layers were successively washed with $NaHCO_3$ and brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated in vacuo and purified by column chromatography on silica gel.

(*E*)-Di- and Trisubstituted Allylic Alcohol Procedure. General Procedure D. A dry 10 mL Schlenk flask, which was evacuated under vacuum and backfilled with N_2 three times, was charged with diethylborane (Et_2BH) (1 mL, 1 M in toluene) and dichloromethane (1 mL). The solution was cooled to 0 °C followed by slow addition of alkyne (1 mmol). After 5 min the reaction was warmed to room temperature and stirred for an additional 15 min. The solution was cool to −78 °C and dimethylzinc (0.6 mL, 2 M in toluene) was added. After stirring at −78 °C for 30 min, the reaction flask was warmed to −30 °C and EtZnCl (1.25 mmol) was added under a steady flow of N_2. Immediately thereafter, the aldehyde (0.833 mmol) was added neat. The reaction mixture stirred at −30 °C and was monitored by TLC until completion (usually 1 h). The reaction mixture was quenched with saturated aq. NH_4Cl (2 mL) and 2 N HCL (1 mL) and 5 mL Et_2O was added. The organic layer was separated, and the aqueous layer was extracted successively with Et_2O (2 × 5 mL). The combined organic layers were successively washed with $NaHCO_3$ and brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated in vacuo and purified by column chromatography on silica gel.

General Procedure for (*Z*)-Disubstituted Allylic Alcohols. General Procedure E. A dry 10 mL Schlenk flask, which was evacuated under vacuum and backfilled with N_2 three times, was charged with diethylborane (0.42 mL, 1 M toluene) and 1 mL dry THF. After cooling the flask to 0 °C, the bromoalkyne (0.42 mmol) was added dropwise and the flask was stirred at room temperature for 20 min. *t*-BuLi (0.25 mL, 1.7 M in pentanes) was added to the flask at −78 °C and stirred for 35 min, warmed to room temperature and stirred for an additional 40 min. The volatiles were then removed under vacuum over 30 min and the residue redissolved in toluene (1 mL). Dimethylzinc was slowly added to the reaction mixture at −78 °C and stirred for 30 min. The EtZnCl (67 mg, 0.52 mmol) was then added followed by the aldehyde solution (0.35 mmol, in 0.2 mL toluene). The reaction mixture stirred at −30 °C and was monitored by TLC until complete. The reaction mixture was quenched with saturated aq. NH_4Cl (2 mL) and 2 N HCL (1 mL) and 5 mL Et_2O was added. The organic layer was separated and the aqueous layer was extracted successively with Et_2O (2 × 5 mL). The combined organic layers were successively washed with $NaHCO_3$ and brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated in vacuo and purified by column chromatography on silica gel.

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Supporting Information Available: Procedures and full characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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