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Diastereoselective Chelation-Controlled Additions to β-Silyloxy Aldehydes

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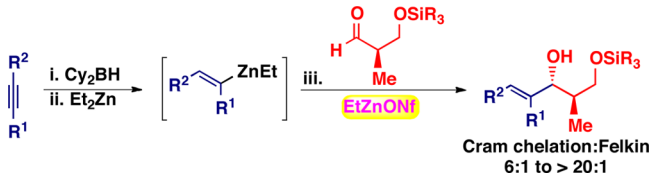
ABSTRACT



A general diastereoselective method for the addition of dialkylzincs and (*E*)-di- and (*E*)-trisubstituted vinylzinc reagents to β-silyloxy aldehydes is presented. This method employs alkyl zinc triflate and nonaflate Lewis acids and affords chelation-controlled products (6:1 to > 20:1 dr).

The traditional approach to complex molecule synthesis is to utilize existing substrate stereogenic centers to influence the introduction of new stereocenters.[1] In particular, this strategy has proven useful in the addition of organometallic reagents to protected α- and β-hydroxy aldehydes and ketones to afford diol moieties. For quite some time, the paradigm that rationalizes the stereochemical outcomes of these additions has encompassed the Felkin–Anh,[2] Cornforth–Evans,[3] and Cram-chelation[4] models.[5] According to these models, stereoinduction in such additions is dependent on the size of the protecting group.[6] Sterically undemanding protecting groups such as Me, Bn, and MOM promote chelation (Figure 1, Cram-chelation model).[7] In contrast, bulky silyl protecting groups disfavor chelation and give Felkin addition products (Figure 1). One major shortcoming in the application of this paradigm is that the protecting group is chosen to afford the desired stereochemistry during the carbonyl addition step and may not be best suited for the global protecting group strategy. To override substrate control, chemists have utilized chiral catalysts,[8] enantioenriched stoichiometric auxiliaries, and optically active stoichiometric additives.[9] Our approach is to develop methods to reverse the diastereoselectivity predicted by the

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aforementioned paradigm through introduction of Lewis acids capable of chelating substrates that normally undergo Felkin addition.

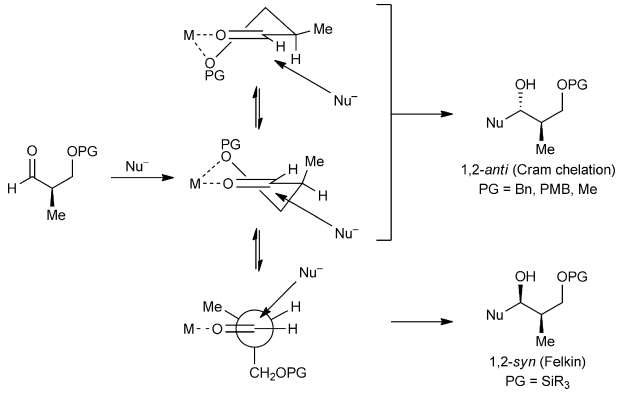
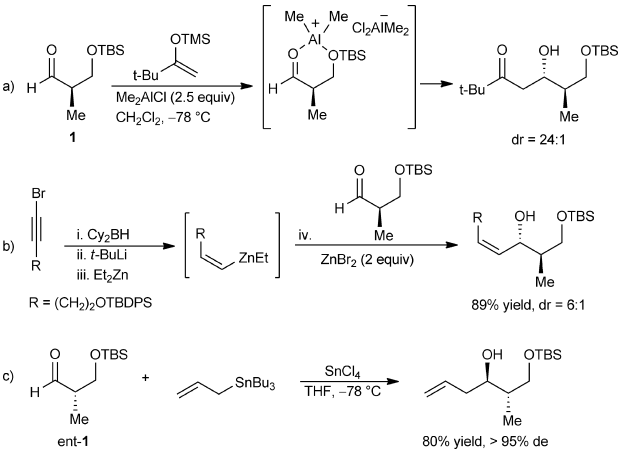


Figure 1. Models for 1,2-asymmetric induction for protected α-methyl β-hydroxy aldehydes.

To date, few exceptions to the current stereoinduction models have been reported.[6f,7c,10] In particular, there are limited examples of methods to promote chelation in additions to β-silyloxy aldehydes and ketones. Evans and co-workers have demonstrated the remarkable ability of Me_2AlCl and $MeAlCl_2$ to chelate β-silyloxy aldehydes in Mukaiyama aldol reactions.[7c] As shown in Scheme 1a, the active Lewis acid results from the disproportionation of $MeAlCl_2$. Somfai and co-workers have disclosed interesting studies to elucidate the origin of reversed diastereoselectivity of Mukaiyama aldol additions to α-silyloxy and chloro aldehydes.[11] En route to developing methods for the *in situ* generation of (*Z*)-vinylzinc reagents, our group observed unexpected chelation-controlled additions to β-silyloxy aldehydes in the presence of $ZnBr_2$, albeit in modest selectivity (Scheme 1b).[12] In efforts toward the synthesis of mycolactone polyketides, Burkart observed high selectivity for the chelation-controlled product in the allylation of aldehyde ent-**1** using allyltrichlorostannane (Scheme 1c).[13]

Scheme 1. Previous Examples of β-Chelation to β-Silyloxy Aldehydes



More recently, we have shown that alkyl zinc halides and triflates are viable Lewis acids to chelate α-silyloxy aldehydes and ketones to enable chelation-controlled additions to these substrates.[14] Given the high levels of diastereoselectivity of these reactions and their generality, we set out to determine whether highly diastereoselective additions of organozinc reagents to β-silyloxy aldehydes could be achieved. We perceived this to be a challenge considering that α-chelation is more favorable than β-chelation and usually furnishes a product of higher dr.[15] Furthermore, general chelation-controlled additions of organometallic reagents to β-silyloxy aldehydes are unknown.

Initially, we investigated the reaction of diethylzinc with aldehyde **1**. Interestingly, in the absence of EtZnX Lewis acids, the reaction of diethylzinc (1.2 equiv) with (*R*)-3-TBS-2-methylpropanal **1** provided the chelation controlled product with 3.5:1 dr in $<10\%$ yield (Table 1, entry 1). The absolute stereochemistry of the major diastereomer was ascertained through comparison to literature data[16] and confirmed by modified Mosher ester analysis.[17] To achieve synthetically useful diastereoselectivities and yields, Lewis acids that could chelate the substrates were utilized. Additions employing 25−150 mol %

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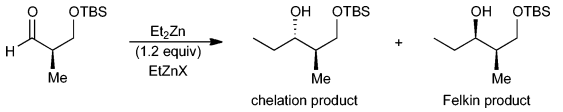
Table 1. Optimization of Diethylzinc Addition to **1**



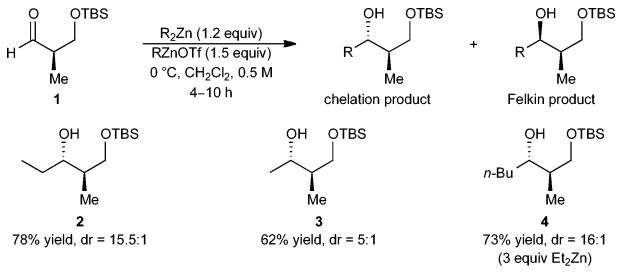
entry	temp (°C)	concentration (M)[a]	LA (mol %)[b]	dr[c]	yield (%)[d]
1	0	0.2	0	3.5:1	<10
2	0	0.2	EtZnCl (25)	5.7:1	50
3	0	0.2	EtZnCl (50)	5.7:1	61
4	0	0.2	EtZnCl (100)	7.4:1	77
5	0	0.2	EtZnCl (150)	6.5:1	83
6	–15	0.2	EtZnCl (150)	6.9:1	83
7	–30	0.2	EtZnCl (150)	5.2:1	61
8	0	0.5	EtZnCl (150)	8.9:1	89
9	0	0.5	EtZnBr (150)	7.9:1	85
10	0	0.5	EtZnOTf (150)	15.5:1	78
11	0	0.5	EtZnONf (150)	10:1	87
12	0	0.5	$EtZnN(Tf)_2$ (150)	6:1	72

[a] Concentration is with respect to the aldehyde. [b] mol % of Lewis acid is with respect to the aldehyde. [c] dr determined by ^{1}H NMR of the unpurified product or by GC analysis of the TMS-protected product derivatives and refers to the ratio of chelation/Felkin addition products. [d] Refers to yield of isolated, purified product.

of EtZnCl led to chelation-controlled products with slightly improved dr (entries 2–5). Lowering the temperature did not improve the diastereoselectivity of the reaction (entries 6 and 7). Furthermore, increasing the concentration of the reaction afforded the addition product in 89% yield with 8.9:1 dr (entry 8). Encouraged by these results, we next surveyed other zinc Lewis acids (entries 9–12). Employing either EtZnOTf or EtZnONf gave the expected addition product with 15.5:1 and 10:1 dr, respectively (entries 10 and 11). These Lewis acids can be prepared simply by reaction of the dialkylzinc with the sulfonic acid at low temperature.[18]

The optimized reaction conditions in Table 1 (entry 10) were applied to the addition of other dialkylzincs to aldehyde **1**. It is important to note that R groups on the dialkylzinc and Lewis acid must be the same due to expeditious alkyl exchange. As shown in Scheme 2, the addition of dimethylzinc to afford **3** was less selective (dr = 5:1) and can be attributed to the smaller size of the nucleophile, resulting in a reduced energy difference between the transition states leading to the chelation or Felkin addition products. Additionally, MeZnOTf has limited solubility in dichloromethane. Addition of di-*n*-butylzinc to aldehyde **1** occurred to give **4** with comparable dr to diethylzinc (16:1). An excess of di-*n*-butylzinc (3 equiv) was

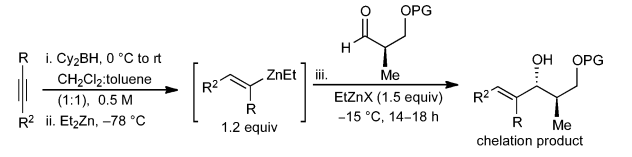
Scheme 2. Chelation-Controlled Addition of Dialkylzincs to **1**



required due to the facile formation of a reduction side product via a β-hydride reduction mechanism.[19]

Chiral allylic alcohols are important structural motifs that are commonly used as key intermediates in synthesis and are found in many natural products.[1c,20] To broaden the substrate scope of our method, we studied the addition of (*E*)-vinylzinc reagents to silyl-protected β-hydroxy

Table 2. Generation of (*E*)-Di- and Trisubstituted Allylic Alcohols



entry	PG	alkyne	dr[a], EtZnONf (yield)	dr[a], EtZnOTf (yield)	major product
1	TBS	*n*-Bu—≡—H	10:1 (61%)	4.8:1 (83%)	**5**
2		—≡—H	5.8:1 (66%)	2.3:1 (50%)	**6**
3		*t*-Bu—≡—H	10:1 (70%)	3.6:1 (78%)	**7**
4		*t*-Bu—≡—Me	20:1 (80%)	11:1 (77%)	**8**
5[b]		*i*-Pr—≡—Me	17:1 (78%)	7.8:1 (77%)	**9**
6	TES	*n*-Bu—≡—H	11:1 (65%)	7.8:1 (84%)	**10**
7		—≡—H	9:1 (78%)	4.6:1 (67%)	**11**
8		*t*-Bu—≡—H	18:1 (71%)	10:1 (45%)	**12**
9		*t*-Bu—≡—Me	> 20:1 (76%)	17.5:1 (76%)	**13**

[a] dr determined by ^{1}H NMR of the unpurified product and refers to the ratio of chelation/Felkin addition products. [b] The relative stereochemistry was determined by modified Mosher ester analysis (see Supporting Information).

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aldehydes. The (*E*)-vinylzinc reagents were generated *in situ* using the Srebnik/Oppolzer procedure.[21] Hydroboration of alkynes and subsequent B to Zn transmetalation with Et_2Zn gave the (*E*)-vinylzinc intermediates. These vinylzinc reagents were then added to β-silyloxy aldehydes in the presence of EtZnX Lewis acids. It is well precedented that vinyl- and arylzinc reagents add to aldehydes significantly faster that alkylzinc reagents.[22]

After extensive screening, we found that optimal yields and diastereoselectivities were achieved at −15 °C in 1:1 toluene to dichloromethane solvent. Similar to the addition of dialkylzincs, initially EtZnOTf proved to be the most effective Lewis acid, providing the chelation-controlled addition product with moderate to good dr (Table 2). However, employing EtZnONf further improved the diastereoselectivity of the reaction. For example, a 2-fold increase in the dr of product **5** is seen in entry 1 when EtZnONf is used compared to the same reaction using EtZnOTf (dr = 10:1 vs 4.8:1). It is conceivable that this improved diastereoselectivity is due to the greater solubility of EtZnONf in dichloromethane at low temperature. As shown in Table 2, a variety of terminal alkynes can be employed in the reaction with 1.5 equiv of EtZnONf and both TBS or TES-protected 3-hydroxy-2-methylproponal. The (*E*)-disubstituted allylic alcohol products were furnished with ≥ 5.8:1 dr and 61−80% yield (entries 1−3 and 6−8). Lower yields were observed in some cases owing to the formation of ethyl addition byproducts (entries 2 and 8 using EtZnOTf). Furthermore, when internal alkynes were utilized in the reaction, (*E*)-trisubstituted allylic alcohols were generated with ≥ 17:1 dr (entries 4, 5, and 9). Reactions with less sterically hindered TES-protected 3-hydroxy-2-methylproponal generally yielded products with higher dr, most likely due to more favorable chelate formation.

In summary, chelation-controlled addition of organozinc reagents to TBS and TES-protected β-hydroxy aldehydes can be accomplished in the presence of EtZnOTf or EtZnONf. Our method represents an alternative approach to the use of stoichiometric amounts of chiral auxiliaries to reverse the diastereoselectivity in additions of organometallic reagents to α-chiral β-silyloxy aldehydes.

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

The authors declare no competing financial interest.

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