ORGANIC LETTERS

2013
Vol. 15, No. 24
6174–6177

Chelation-Controlled Additions to α-Silyloxy Aldehydes: An Autocatalytic Approach

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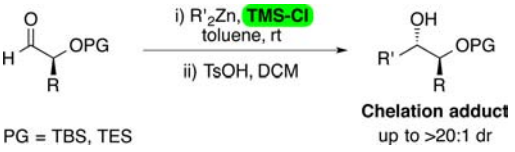
Received October 21, 2013

ABSTRACT



The Felkin–Anh model has been widely accepted to describe stereochemical outcomes in nucleophilic additions to α-silyloxy carbonyl compounds. Herein, it is demonstrated that chelation-controlled additions can be performed using dialkylzinc reagents in the presence of chlorotrimethylsilane with good to excellent diastereoselectivities. Ethyl zinc chloride, the Lewis acid responsible for promoting chelation, is generated *in situ* in an autocatalytic fashion. This approach circumvents its use in stoichiometric amounts.

Autocatalytic reactions constitute a rare class of transformations in which a reaction product catalyzes its own formation. Since its first suggestion by Franck in 1953,[1] the development of asymmetric versions of autocatalysis has attracted much attention.[2] Soai's pioneering work in this field has inspired many studies of enantioselective and asymmetric amplification processes.[2,3] Interesting works have also appeared on self-replicating systems.[2c,4] Despite the important advantages of such processes, applications of autocatalysis to diastereoselective transformations have received less attention.[5]

Controlling the configuration of newly formed stereogenic centers using existing stereochemistry is one of the most widely utilized strategies in small and complex molecule synthesis.[6] In particular, nucleophilic additions of organometallic reagents to chiral aldehydes and ketones have been studied extensively. Within this framework, the

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10.1021/ol4030259
Published on Web 11/19/2013

Felkin–Anh and Cram chelation models have been used for quite some time to rationalize stereochemical outcomes in additions to protected α-hydroxy carbonyl derivatives.[7–9] According to these models, the preferred pathway is dependent on the size of the protecting group (Figure 1). Small protecting groups, such as methyl or benzyl, favor chelation (Cram-chelate model)[7a,9b] while bulky ones, including silyls, typically proceed via a nonchelation pathway, leading to Felkin–Anh products.[7,8d]

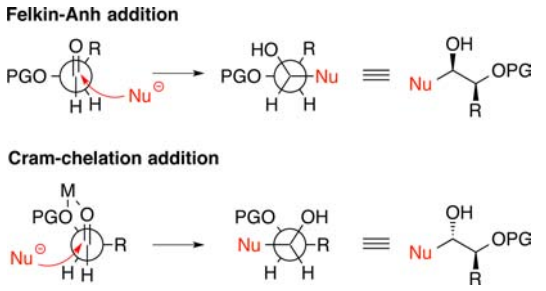
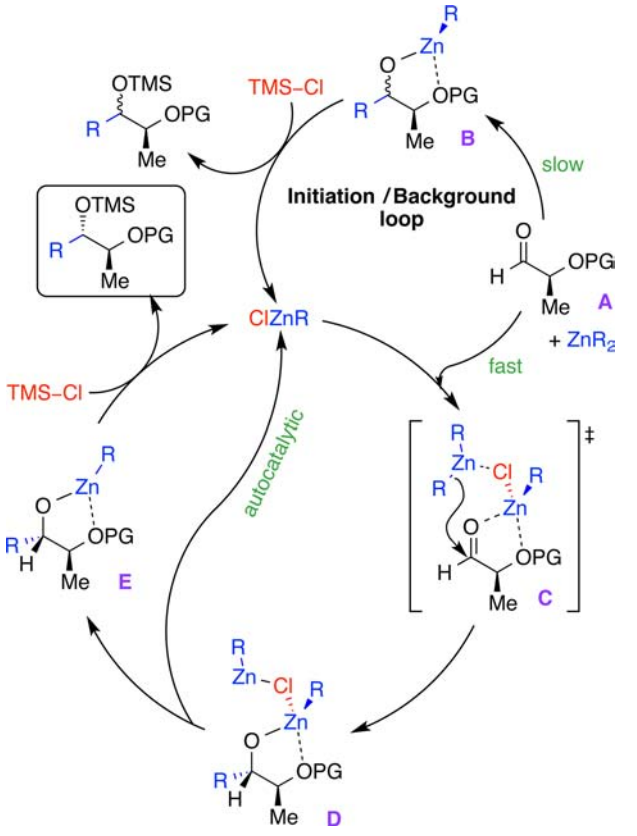


Figure 1. Felkin–Anh and Cram-chelate models.

Our group recently highlighted exceptions to this paradigm, reporting highly diastereoselective chelation-controlled additions of organozinc reagents to α- and β-silyloxy aldehydes,[10] α-silyloxy ketones,[11] and α-halo imines.[12] In each case, stoichiometric amounts of an alkyl zinc halide or sulfonate Lewis acids were employed to promote chelation. The long reaction times needed to synthesize alkyl zinc halides,[13] and the necessity to handle them in a glovebox, prompted us to consider an alternative approach. Herein, a conceptual advance, an autocatalytic strategy, to furnish chelation products under reaction conditions that generate the alkyl zinc halide *in situ* from inexpensive and readily available chlorotrimethylsilane (TMS–Cl) is presented.

Scheme 1 introduces the proposed mechanism for this transformation. The process is initiated with an unselective addition of the dialkylzinc reagent to aldehyde **A** to form zinc alkoxide **B**. Adduct **B** undergoes reaction with

Scheme 1. Proposed Mechanism for the Chelation-Controlled Addition *via* Autocatalytic Generation of Alkyl Zinc Chloride



TMS–Cl to generate alkyl zinc chloride. This addition pathway eventually becomes the background reaction. As Eliel and Frye demonstrated, the rate of addition to carbonyls is increased by chelation.[14] Therefore, the diastereoselective chelation-controlled pathway using RZnCl is expected to overcome the nonselective background addition. After the addition takes place *via* transition state **C**,[10] the resulting intermediate **D** can fragment into RZnCl and zinc alkoxide **E**. Further reaction with TMS–Cl yields the TMS-protected chelation product and generates a second molecule of RZnCl, making the overall process autocatalytic.

Initially, the addition of diethylzinc to aldehyde **1** (Table 1) has been investigated. The reactions were performed at 0 °C to minimize the background reaction. The choice of the solvent proved to be very important for the diastereoselectivity of the reaction (Table 1, entries 1–3). As expected from our previous reports,[10,11] the use of toluene (entry 3) furnished the product with higher selectivity than DCE or DCM (entries 1–2), albeit with lower yields. It is noteworthy that these reactions were performed in the presence of 20 mol % triethylamine, as our previous studies on tandem asymmetric additions/diastereoselective cyclopropanations suggested triethylamine facilitated

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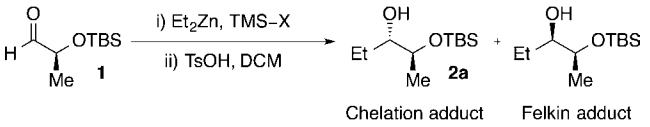
Table 1. Optimization of the Chelation-Controlled Addition of Diethylzinc to Aldehyde **1**



entry	aldehyde add. time (h)	Et_2Zn (equiv)[a]	X	TMS–X (equiv)[a]	solvent	temp (°C)	concn (M)[a]	dr[b]	yield (%)[c,d]
1	–	1.2	Cl	1.2	DCE	0	0.2	1.6:1[e]	54[e]
2	–	1.2		1.2	DCM	0	0.2	2:1[e]	45[e]
3	–	1.2		1.2	toluene	0	0.2	5:1[e]	33[e]
4	–	1.2		1.2	toluene	0	0.2	8:1	27
5	–	1.2		1.2	toluene	0	0.1	19:1	37
6	–	1.2		3	toluene	0	0.1	10:1	43
7	1	1.2		1.2	toluene	0	0.1	11:1	37
8	1	2.5		1.2	toluene	0	0.1	13:1	51
9	2	2.5		1.2	toluene	0	0.2	16:1	40
10	2	2.5	Br	1.2	toluene	0	0.2	1:1.4	24
11	2	2.5	I	1.2	toluene	0	0.2	1:1	88
12	2	2.5		1.2	toluene	−78	0.2	1:1.2	36
13	–	**1.2**	**Cl**	**1.2**	**toluene**	**rt**	**0.1**	**17:1**	**75 (70)**
14	**2**	**2.5**		**1.2**	**toluene**	**rt**	**0.2**	**14:1**	**81 (73)**

[a] With respect to the aldehyde. [b] dr = chelation:Felkin adducts as ascertained by ^{1}H NMR of the unpurified product. [c] Yield of unpurified product determined by ^{1}H NMR. [d] Values in parentheses refer to isolated yields. [e] Reaction performed in the presence of 20 mol % NEt_3 with respect to the aldehyde.

reactions of zinc alkoxide by breaking up alkoxy zinc aggregates.[15] It was anticipated that triethylamine would have a similar effect in this system, thus catalyzing the formation of both the TMS-protected adduct and EtZnCl. Unfortunately, the reaction was slower (about 6 h instead of 4 h) and less selective when triethylamine was employed (entry 4 vs 3), probably because of a competing coordination process with the EtZnCl.

Concentration was also an important factor. Diluting the media from 0.2 to 0.1 M afforded chelation product **2a** with excellent dr (19:1, entry 5). However, the yield of the reaction was only 37%. This low yield seems to result from a competitive addition of the zinc alkoxide to the starting aldehyde (see Supporting Information). To facilitate the reaction of the zinc alkoxide with the TMS−Cl and avoid this competitive pathway, a larger excess of TMS−Cl was used (entry 6). Unfortunately, a drastic drop in product dr was observed without a significant increase in yield. Slow addition of aldehyde **1** was then performed to ensure the contact time between the zinc alkoxide and the aldehyde was minimal (entries 7−9). These conditions gave, at best, comparable results, with only slightly improved yields (entries 8−9). To facilitate the reaction with the zinc alkoxide, more reactive trimethylsilyl sources were investigated. The reaction with TMS−Br gave a poor yield and diastereoselectivity (entry 10). The reaction with TMS−I led to an improved yield of 88%, but with no diastereoselectivity (entry 11). Performing this reaction at −78 °C did not improve the dr of the product (entry 12). It is noteworthy that TMS−OTf was also tested in the reaction, but gave a complex mixture of products. Collectively, these results suggested that fast reaction of the zinc alkoxide with TMS−X could be key to increase the yield and that temperature can play an important role to this end. Thus, the two best conditions (entries 5 and 9) were repeated at rt. To our delight, an increase in yield to 70% and 73% respectively was observed with minimal erosion of the dr (entries 13−14). Both slow and fast addition of the aldehyde gave comparable results.

The optimized reaction conditions (Table 1, entries 13−14) were then used to explore the substrate scope of the reaction (Table 2). First, the influence of the protecting group was investigated. The reaction of the TES-protected hydroxy aldehyde proceeded efficiently, with a very high diastereoselectivity, in good yield (entry 2). Note that the results in Table 2 refer to the fully deprotected product **2b**. When a bulky TIPS-protected substrate was employed, no selectivity was observed (entry 3). Similar results were encountered in our previous studies where the temperature had to be lowered to −50 °C to achieve high diastereoselectivity.[10a] However, in the autocatalytic process, performing the reaction below 0 °C resulted in an unacceptable decrease in yield. The nature of the α-substituent of the aldehyde was then investigated. Reaction of the substrate bearing an α-phenyl group afforded **2d** in 70% isolated yield with >20:1 dr (entry 4). Surprisingly, with an isopropyl α-substituent, the addition product **2e** was

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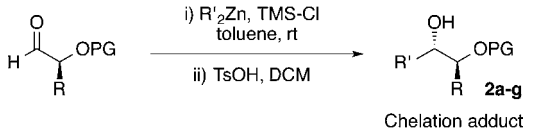
Table 2. Substrate Scope of the Reaction



entry	PG	R	R′	2	method[a]	dr[b]	yield (%)[c,d]
1	TBS	Me	Et	**2a**	A	17:1	75 (70)
					B	14:1	81 (73)
2	TES	Me	Et	**2b**	A	>20:1[e]	80 (72)[e]
					B	>20:1[e]	70[e]
3	TIPS	Me	Et	**2c**	A	1.2:1	86 (80)
					B	1:1	83
4	TBS	Ph	Et	**2d**	A	>20:1	72 (70)
					B	14:1	55
5	TBS	*i*-Pr	Et	**2e**	A	4:1	85 (80)
					B	4:1	85
6	TBS	Me	Me	**2f**	A	5:1	78 (72)
					B	5:1	50
7	TBS	Ph	Me	**2g**	A	5:1	75 (71)
					B	6:1	70

[a] Method A: addition of Et_2Zn (0.24 mmol, 0.12 mL, 2 M in toluene) to a solution of aldehyde (0.2 mmol) and TMS−Cl (0.24 mmol, 30.5 μL) in dry toluene (2 mL); Method B: slow addition of the aldehyde (0.2 mmol, 0.2 mL, 1 M in toluene) over 2 h to a solution of Et_2Zn (0.50 mmol, 0.25 mL, 2 M in toluene) and TMS−Cl (0.24 mmol, 30.5 μL) in dry toluene (1 mL). [b] dr = chelation:Felkin adducts as ascertained by ^{1}H NMR of the unpurified product. [c] Crude yield determined by ^{1}H NMR. [d] Values in parentheses refer to isolated yields. [e] dr and yield determined for the fully deprotected diol.

obtained in 80% yield, but the selectivity was unexpectedly modest (dr = 4:1 favoring chelation, entry 5). Finally, the use of dimethylzinc as a nucleophile was explored. The chelation products **2f**−**g** were furnished in reasonable yields but with moderate selectivities favoring chelation (entries 6−7).

To probe the proposed autocatalytic mechanism, a kinetic study using ^{1}H NMR has been considered (Figure 2). To this end, the diethylzinc addition reaction to aldehyde **1** was performed in an NMR tube using toluene-d_8 as solvent. The sample was prepared and sealed in a glovebox, and the ^{1}H NMR spectra were recorded at rt at 10-min intervals. Consistent with the proposed mechanism, the initiation step was slow due to the absence of EtZnCl. As the reaction proceeded and the concentration of EtZnCl increased, the rate of the addition quickly amplified before slowing down due to the diminishing

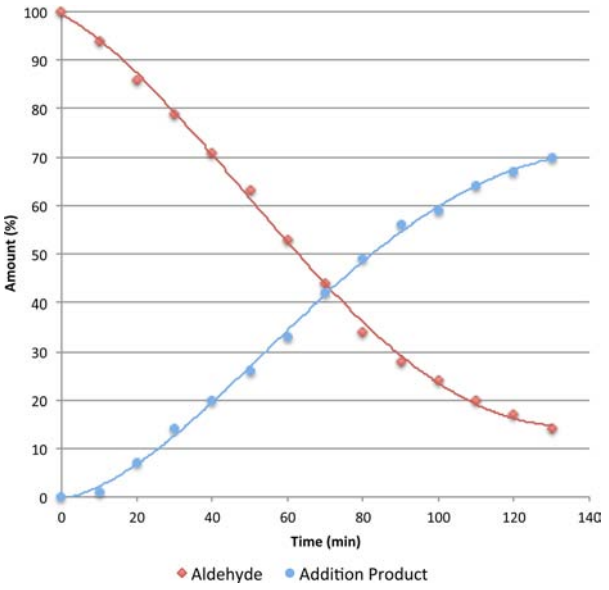


Figure 2. Kinetic study of the addition of diethylzinc to **1**.

concentration of aldehyde. The sigmoid curve obtained is typical of second-order autocatalytic reactions.[16] Comparison with the kinetics in the presence of a stoichiometric amount of EtZnCl was complicated because reactions performed under these conditions are generally complete in less than 30 min.[10a] The faster reaction rate in the presence of stoichiometric EtZnCl is consistent with the absence of an induction period.

In summary, it has been demonstrated that α-silyloxy aldehydes can undergo chelation-controlled addition of dialkylzinc reagents using TMS−Cl to generate EtZnCl *in situ*. The significance of this work is the conceptual novelty of using autocatalytic Lewis acid generation to control the diastereoselectivity in a classic reaction: the chelation-controlled addition of alkyl groups to α-silyloxy carbonyl compounds.

Acknowledgment. L.R. thanks the "Région Rhône-Alpes" for its Explora'Pro fellowship. P.J.W. acknowledges the NSF (CHE-1152488), and G.R.S. thanks the Dean's Scholar Fund.

Supporting Information Available. Experimental procedure 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.