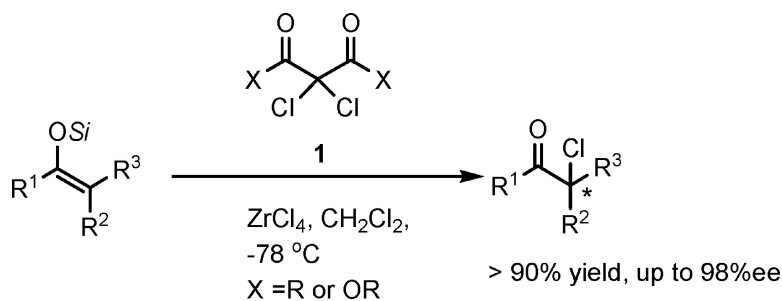


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Lewis Acid-Mediated Selective Chlorinations of Silyl Enolate

Yanhua Zhang, Kazutaka Shibatomi, and Hisashi Yamamoto*

Department of Chemistry, University of Chicago, 5735 South Ellis Avenue, Chicago, Illinois 60637

Received July 28, 2004; E-mail: yamamoto@uchicago.edu

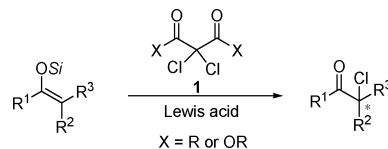
The selective halogenation of carbonyl compounds is a highly useful synthetic operation for multistep synthesis since the resulting α -halo carbonyl compounds may serve as precursors of various derivatives.¹ Although many research groups have made important contributions to the steady improvement of this methodology, their diastereo- and/or enantioselective versions have rarely been investigated.^{2,3} Obviously, a general and more efficient methodology is required. The electrophilic halogenation of simple silyl enolate is one of the simplest solutions by which to achieve the above goal.⁴ Described herein (Scheme 1) is a new method involving the efficient, widely applicable, and highly selective α -chlorination of simple silyl enolate with Lewis acid and an α,α -dichloro-1,3-dicarbonyl controller unit.

As a chlorinating reagent for silyl enolates, α,α -dichloro-1,3-dicarbonyl compound (**1**) was synthesized from the corresponding 1,3-dicarbonyl compound by the reaction shown in Scheme 2.⁵

Although α,α -dichlorinated 1,3-dicarbonyl compounds are very weak chlorinating reagents,⁶ we considered that the use of a suitable Lewis acid would substantially increase the electrophilicity of the chlorine atoms on **1** to react with the weak nucleophilic substrates under mild conditions. Thus, the diastereoselective chlorination of silyl enolate was first examined with **1** in the presence of various Lewis acids, and we were pleased to find that $ZrCl_4$ uniquely revealed high reactivity and selectivity⁷ (Table 1, left eq). The chlorination did not proceed at all in the absence of a Lewis acid at 0 °C to room temperature, but in the presence of $ZrCl_4$, the reaction proceeded smoothly, even at -78 °C.⁸ Moreover, diastereoselectivity of the reaction was significantly influenced by the size of the X group of **1** and the Si group of enolate (Table 1). Finally, treatment of the silyl enolate of 4-*tert*-butylcyclohexanone with 1 equiv of $ZrCl_4$ and **1** in dichloromethane at -78 °C quantitatively gave 2-chloro-4-*tert*-butylcyclohexanone, with a ratio up to 19:1 (*trans*:*cis*). The selectivity of this method, as well as the reactivity, is much higher than that of the reported reaction¹⁰ (Table 1, right eq). In most cases, α -monochlorinated 1,3-dicarbonyl compound was recovered in >90% yields and can be re-used after chlorination by the reaction shown in Scheme 2.

Encouraged by these results, we prepared several optically active chlorinating reagents (**1a–d**), most of which have aromatic substituents at the 2-position of cyclohexanol, to perform asymmetric chlorination of silyl enolate. The structural optimization of chiral malonic esters and the scope of substrates are summarized in Table 2.¹¹ The yields of all α -chloroketones were >90%; as expected, the larger the sterical substituents at the 2-position of cyclohexanol, the higher the enantioselectivity they gave (entry 1, 42% ee with **1a**; entry 2, 67% ee with **1b**; entry 3, 80% ee with **1c**). However, the most bulky chlorinating reagent, **1d**, was not the best choice, except for substrate **4** (entries 8–10, up to 98% ee). In most cases, **1c** gave a corresponding product with the highest enantioselectivity. It was also noteworthy that the steric hindrance of the silyl group had a significant influence on the asymmetric induction (entries 3, 4, 6, and 13–16) (Table 1 also indicated the

Scheme 1



Scheme 2

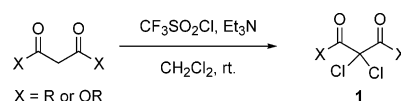


Table 1. Diastereoselective Chlorinations with $ZrCl_4$ and α,α -Dichlorinated 1,3-Dicarbonyl Compounds

entry	1	Si	<i>trans</i> : <i>cis</i> ^a
1		TMS TBDMS	3.5:1 8.7:1
2		TMS TBDMS	2.6:1 4.8:1
3		TMS TBDMS	3.3:1 7.9:1
4		TMS TBDMS	5.7:1 14:1
5		TMS TBDMS	14:1 19:1

^a Determined by GC analysis. Yields of the reaction are >90%.

effects of silyl groups). Although the reaction of trimethylsilyl enolate **6a** with **1c** afforded only 31% ee of **13** (entry 13), the use of *tert*-butyldimethylsilyl enolate afforded **13** with 87% ee (entry 14). The reaction of silyl enolate, having a five- or seven-membered ring, also afforded the corresponding α -chloroketones in high enantioselectivity (entries 8–12, up to 98% ee). Up to 90% ee was obtained for acyclic substrates (entries 17 and 18). One unique advantage of this reaction is that we can obtain α -chlorinated product with opposite configuration by simply changing the R group on **1** to its opposite isomer.

The exact reaction mechanism is not yet clear. However, we assume that the high asymmetric induction observed came from the high reactivity of the Lewis acid ($ZrCl_4$) as well as the unique structural feature of chiral malonic ester. After the coordination of zirconium with two carbonyl oxygens, a C_2 symmetrical six-membered ring is apparently generated, and the carbon–chlorine

Table 2. Asymmetric Chlorinations of Silyl Enolate with $ZrCl_4$ and Chiral α,α -Dichlorinated Malonic Ester^a

1a
1b: Ar = Ph
1c: Ar = 1-naphthyl
1d: Ar = 9-phenanthryl

entry	substrate	Si	1	product	time(h)	% ee ^b
1	(2a)	TMS	1a		2	42
2	(2a)	TMS	1b		1.5	67
3	(2a)	TMS	1c		2	80
4	(2b)	TBDMS	1c		2	88
5	(2b)	TBDMS	1d		(9) 1.5	77
6	(2c)	DMTS ^c	1c		1.5	86

7	(3)	TMS	1c		2	48

8	(4a)	TBDMS	1c		1.5	86
9	(4a)	TBDMS	1d		5	92
10	(4b)	DMTS	1d		(11) 1.5	98

11	(5)	TBDMS	1c		2	68
12	(5)	TBDMS	1d		4	55

13	(6a)	TMS	1c		4.5	31
14	(6b)	TBDMS	1c		5	87
15	(6c)	TIPS	1c		5	83
16	(6d)	DMTS	1c		(13) 1.5	84

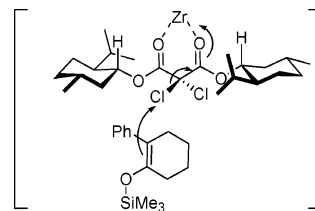
17	(7)	TBDMS	1d		3	80

18	(8)	TBDMS	1d		1	90 ^d

^a Reactions were carried out at $-78\text{ }^\circ\text{C}$ in dichloromethane in the presence of 1 equiv of $ZrCl_4$ and chiral α,α -dichlorinated malonic ester. Yields of the reaction are $>90\%$. ^b Determined by HPLC analysis, except for special demonstration. ^c DMTS is dimethylhexylsilyl. ^d Determined by GC analysis.

bonding was weakened. Those two chlorine atoms are equivalent, either one can be released as a cation, which reacted with silyl enolate in the cage formed by two chiral functional groups and gave the expected α -chlorinated product. When all of these results are taken into account, the transition state assembly shown in Scheme 3 is most likely.

In summary, we have described a new concept of enantioselective α -chlorination of ketones through chlorination of corresponding silyl enolates using α,α -dichlorinated malonic ester as a chlorine source and chirality controller in the presence of a Lewis acid. We believe that the idea expressed herein provides a useful new

Scheme 3. Proposed Transition State

paradigm for enantioselective chlorination of carbonyl compounds, which could further expand the use of Lewis acids in organic synthesis. Obviously, the next steps include rendering the suitable ligand systems amenable to multiturnover and asymmetric catalysis.

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

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- To the solution of optically active α,α -dichlorinated malonate ester (0.5 mmol) in CH_2Cl_2 (2.0 mL), cooled to $-78\text{ }^\circ\text{C}$, was added $ZrCl_4$, followed by the solution of silyl enolate (0.5 mmol) in CH_2Cl_2 (2.0 mL) under a nitrogen atmosphere. The reaction was stirred at $-78\text{ }^\circ\text{C}$ until all of the starting material was consumed and was then quenched by a saturated $NaHCO_3$ aqueous solution. Extraction with CH_2Cl_2 , followed by flash column chromatography on silica gel, gave pure α -chlorinated product.

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