Diastereoselective Aldol Reactions of Enolates Generated from Vicinally Substituted Trimethylsilylmethyl Cyclopropyl Ketones
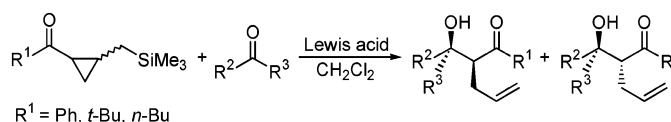
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ABSTRACT

R^1 = Ph, *t*-Bu, *n*-Bu

Vicinally substituted trimethylsilylmethyl cyclopropyl ketones undergo facile desilylative ring opening with Lewis acids under mild conditions. The enolates, thus generated, undergo aldol addition with aldehydes and ketones. The diastereoselectivity of the reaction with aldehydes depends on the nature of the Lewis acid used. The resulting aldol product is easily converted into a substituted tetrahydrofuran derivative.

The trimethylsilylmethyl function assists the ring-opening of cyclopropane. This is due primarily to the β-effect of the silicon atom.[1] The ring-opening of substituted (cyclopropylmethyl)trimethylsilanes with a variety of electrophiles yields substituted olefins with the extrusion of the silicon function.[2] Cyclopropanes bearing trimethylsilylmethyl and an electron-attracting group as vicinal substituents cause ring-opening to take place under mild conditions either with reagents such as CsF,[3a] BF$_3$·OEt$_2$,[3a] BF$_3$·AcOH,[3b,c] and TBAF,[3d] or under nucleophilic conditions.[3e] Surprisingly, however, sufficient efforts were not made to trap the intermediate enolate to make the reaction synthetically more meaningful. Only the γ,δ-unsaturated carbonyl compounds were obtained from these reactions. Attempts to trap the enolate formed from

the TBAF-induced ring-opening of methyl (2-trimethylsilylmethyl)cyclopropylcarboxylate with MeI were unsuccessful, as only methyl 4-pentenoate was isolated.[3d]

We planned to trap the intermediate enolate with electrophiles by using a suitable ring-opening Lewis acid. From our earlier exploration of the synthetic potential of cyclopropylmethylsilanes bearing bulky substituents on the silicon,[4] we discovered TiCl$_4$ to be an effective Lewis acid for the ring-cleavage, and we used this in the synthesis of substituted dihydrofurans.[4a] Since the aldol reaction is a powerful tool for constructing carbon−carbon bonds in a stereoselective manner and, moreover, new variants are being developed currently,[5] we wished to study the reactions of the cyclopropane derivatives **1a**−**c**[6] with carbonyl compounds under Lewis acid conditions. Related aldol-type reactions of substituted cyclopropanes bearing stronger donor substituents such as alkoxy and siloxy groups are known in

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the literature.[7] The aldol products formed from these reactions serve as useful intermediates for the synthesis of substituted tetrahydrofurans, γ-lactones, and γ-lactams. We present our results herein and comment upon the stereochemical aspects.

Our investigation began with the phenyl ketone **1a** (Table 1). **1a** underwent smooth ring-opening at −78 °C with TiCl$_4$

Table 1. Aldol Reactions of **1a**−**c** with Aldehydes and Ketones

1a: R^1 = Ph
1b: R^1 = t-Bu
1c: R^1 = n-Bu

5a: R^1 = Ph
5b: R^1 = t-Bu
5c: R^1 = n-Bu
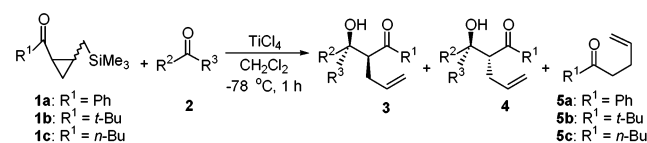
entry	silane	R^2	R^3	3:4 (yield in %)^a
1	**1a**	n-Pr	H	4:1 (72)
2	**1a**	Ph	H	5:1 (75)
3	**1a**	(furanyl)	H	10:1 (73)^b
4	**1a**	(MeO, Br aryl)	H	4:1 (70)
5	**1a**	(Ph-CH=CH)	H	12:1 (79)^b
6	**1a**	(ferrocenyl)	H	(69)^{c,d}
7	**1a**	Et	Et	(45)^d
8	**1a**	(cyclohexyl)		(50)^d
9	**1b**	n-Pr	H	10:1 (66)^b
10	**1b**	Ph	H	11:1 (70)^b
11	**1c**	n-Pr	H	2:1 (71)^b
12	**1c**	Ph	H	5:1 (74)^b

^{a} Isolated overall yield. ^{b} Diastereomeric ratio was estimated from the ^{1}H integrals of the isomeric mixture. ^{c} Product was a 2.6:1 mixture of trans- and cis-isomers of the α,β-unsaturated ketones formed from dehydration of the primary aldol products. ^{d} Reactions required warming to room temperature.

to give a deep red solution in anhydrous CH$_2$Cl$_2$. The aldol products were formed in good yields on treatment of the above titanium enolate with different aldehydes. Good syn diastereoselectivity was maintained throughout in the adducts

with different aliphatic, aromatic, and heteroaromatic aldehydes. The syn:anti ratios were generally ≥4:1 and as high as 12:1 when *trans*-cinnamaldehyde (entry 5) was used.[8] When the syn and anti isomers of **1a** were reacted separately with benzaldehyde under the above conditions, 5:1 and 4.7:1 syn:anti selectivity was observed, respectively. This demonstrated that the geometry of the starting cyclopropane derivative was not important in the overall diastereodetermination. The reactions were sluggish with ketones at −78 °C and required warming to 25 °C to obtain the products in decent yields.[9] The reaction with ferrocene carboxaldehyde was also slow at −78 °C. A 2.6:1 mixture of the trans and cis isomers of the α,β-unsaturated ketone derived from dehydration of the primary aldol product was formed on warming the reaction mixture to 25 °C. More than 2-fold increase in the syn selectivity was noticed when the *tert*-butyl ketone **1b** was employed as the nucleophilic partner. The enhancement in the syn selectivity indicates the involvement of the (Z)-enolate[10] that results in the syn aldol.

To demonstrate the usefulness of the present protocol, we examined the reactions of **1c** as well. The enolate generated from **1c** is equivalent to the enolate formed from the regioselective deprotonation of *n*-butyl homoallyl ketone, a reaction that is generally difficult to achieve. The yields of the aldol products were good with **1c** as well. However, the syn selectivity with butyraldehyde had diminished considerably in comparison to those from **1a** and **1b**. This is not surprising because the steric interactions of the *n*-butyl group in the enolate and the *n*-propyl group in butyraldehyde will not be significant in the transition state leading to the anti product. The γ,δ-unsaturated ketones **5a**−**c** were also isolated in 10−15% and ∼35% yields from the above reactions with aldehydes and ketones, respectively.

The stereochemical outcome of the aldol reaction of a Lewis acid enolate has been documented to be different from that of the Lewis acid-mediated reaction of a silyl enol ether.[11] Our system, being typical of a Lewis acid enolate, gave us an opportunity to examine the effect of different Lewis acids on the reaction diastereoselectivity (Table 2).

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(6) Cyclopropane derivatives **1a**−**c** were prepared conveniently in good yield by a rhodium-catalyzed carbene insertion reaction of the corresponding diazo-compound with allyltrimethylsilane. **1a**, **1b**, and **1c** were, respectively, 2.2:1, 1.5:1, and 1.7:1 mixtures of the anti and syn isomers and were used as such for reactions.

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Table 2. Effect of Lewis Acids on Reaction Diastereoselection^a

entry	silane	Lewis acid	aldehyde	3:4 (%)
1	**1a**	BF$_3$·OEt$_2$	n-PrCHO	1.3:1 (44)
2	**1a**	BF$_3$·OEt$_2$	PhCHO	1:2.5 (52)
3	**1b**	BF$_3$·OEt$_2$	n-PrCHO	2.2:1 (32)
4	**1b**	BF$_3$·OEt$_2$	PhCHO	1:1.7 (34)
5	**1a**	SnCl$_4$	PhCHO	2.0:1 (40)
6	**1a**	Et$_2$AlCl	PhCHO	1.2:1 (94)

^{a} All reactions were carried out at −30 °C for 3 h, and all yields and diastereomeric ratios are based on the isolated materials.

For this, we chose BF$_3$·OEt$_2$ since the syn selectivity was expected to be enhanced due to a tighter transition state. To our great surprise, there was a considerable erosion in the syn selectivity of **1a** with butyraldehyde (syn:anti = 1.3:1,

entry 1). Even more surprisingly, the selectivity reversed (syn/anti = 1:2.5, entry 2) in reaction with benzaldehyde. A similar trend was observed when the *tert*-butyl ketone **1b** was used (entries 3 and 4). The reactions involving BF$_3$·OEt$_2$ were carried out at −30 °C since the enolate formation from the cyclopropane derivative was very slow at −78 °C. The yields were generally low, and good amounts (35−45%) of the corresponding γ,δ-unsaturated ketones **5a/5b** were obtained.

To understand the above discrepancies, we carried out SnCl$_4$- and Et$_2$AlCl-assisted reactions of **1a** with benzaldehyde (entries 5 and 6, Table 2) where reversal in selectivity was observed with BF$_3$·OEt$_2$. Poor syn selectivity was noted with SnCl$_4$ (2:1), which improved to 5.2:1 when the reaction was warmed to 25 °C with a decrease in the yield. Examination of aliquots drawn at −30 and 25 °C and at 3 and 5 h from reaching 25 °C by ^{1}H NMR revealed enhancement in syn selectivity. Further, a similar examination of the aliquots drawn at −30 and 25 °C of the TiCl$_4$-assisted reaction showed hardly any change in selectivity. The yield, however, was somewhat reduced. These experiments suggest a possible retro-aldol in the SnCl$_4$-assisted reaction upon being warmed to 25 °C. Even though the selectivity observed with Et$_2$AlCl was only marginally syn (1.2:1), the yield of the reaction was excellent.[12]

Further, to understand the origin of the syn/anti diastereoselectivity,[13] the titanium enolate derived from **1a** was treated separately with Me$_3$SiCl and (EtO)$_2$P(O)Cl, 1.5 equiv each, at −78 °C to discern the geometry of the enolate. Both the attempts, however, were unsuccessful, as only 1-phenylpent-4-en-1-one was obtained. Hence, ^{1}H NMR study of the different metal enolates derived from **1a** was carried out at 25 °C in CD$_2$Cl$_2$. The geometries of the Ti-enolates were discerned from NOE experiments, and the ratio of the (Z)-

and (E)-enolates was estimated to be 2.1:1. The signal assignments for the Ti-enolates were used to determine the Z/E ratios of the other metal enolates. The Z/E ratios of the different metal enolates after 0.5 and 4 h of mixing are given in Table 3. These experiments reveal an equilibration of the

Table 3. Results of ^{1}H NMR Study of Different Metal Enolates of **1a** at 25 °C

Lewis acid	time (h)	enolate ratio (Z:E)	product ratio (syn:anti)
TiCl$_4$	0.5	2.1:1	
	4.0	1.9:1	2.6:1
BF$_3$·OEt$_2$	0.5	1:4.3	
	4.0	1:1.7	1.2:1
Et$_2$AlCl	0.5	1:1	
	4.0	1:1.3	>1:10
SnCl$_4$	0.5	1:1.5	
	4.0	1:1.5	1.5:1

enolates at 25 °C except for the tin-enolate. The boron enolate existed predominantly in the (E)-form. After 4 h, the metal enolates were treated with benzaldehyde for 1 h in the NMR tube itself and the syn:anti ratios of the aldol products were estimated from ^{1}H NMR. The following observations could be made from the above experiments: (a) the syn:anti ratios are less at 25 °C compared to those at the lower temperatures with TiCl$_4$ and SnCl$_4$, (b) the preferred anti selectivity (syn: anti = 1:2.5) observed at −30 °C is changed in favor of the syn selectivity (syn:anti = 1.2:1) at 25 °C with BF$_3$·OEt$_2$, and (c) with Et$_2$AlCl, interestingly, the selectivity changed from slightly syn (syn:anti = 1.2:1) to largely anti (syn:anti > 1:10) at 25 °C.

A closed chair transition state appears to be the most probable transition structure to explain the syn selectivity of the Ti-enolates (Scheme 1). Both BF$_3$·OEt$_2$ and SnCl$_4$

Scheme 1

show syn selectivity, although their enolates are more of the (E)-configuration. This could be because of the difference in the reactivities of the (Z)- and (E)-enolates; the (Z)-enolate reacts faster than the (E)-enolate. The preferred anti selectivities of the boron enolates of **1a** and **1b** with benzaldehyde at −30 °C may be because of a combination of the higher

(8) Syn and anti relationships in the aldol products were assigned on the basis of ^{1}H chemical shifts of the hydrogen on the carbinol carbon. The hydrogen resonated 0.06−0.12 ppm downfield in the syn isomer compared to the hydrogen in the corresponding anti isomer. Furthermore, this hydrogen appeared as a triplet (J = 1.7−6.3 Hz) and a doublet (J = 4.6−5.8 Hz) or a broad singlet, respectively, in the anti and syn aldol products obtained from arylaldehydes. For references related to the syn and anti assignments, see: (a) Ohtsuka, Y.; Koyasu, K.; Ikeno, T.; Yamada, T. *Org. Lett.* **2001**, 3, 2543. (b) Denmark, S. E.; Wong, K.-T.; Stavenger, R. A. *J. Am. Chem. Soc.* **1997**, *119*, 2333. (c) Hasegawa, E.; Ishiyama, K.; Kato, T.; Horaguchi, T.; Shimizu, T.; Tanaka, S.; Yamashita, Y. *J. Org. Chem.* **1992**, *57*, 5352. (d) Noyori, R.; Nishida, I.; Sakata, J. *J. Am. Chem. Soc.* **1981**, *103*, 2106. (e) House, H. O.; Crumrine, D. S.; Teranishi, A. Y.; Olmstead, H. D. *J. Am. Chem. Soc.* **1973**, *95*, 3310.

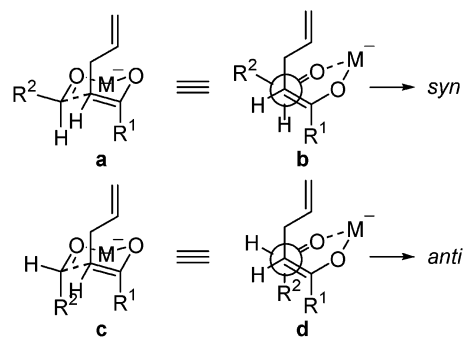(9) Mukaiyama, T.; Banno, K.; Narasaka, K. *J. Am. Chem. Soc.* **1974**, *96*, 7603.

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concentration of the (E)-enolates and the better reactivity of benzaldehyde. The reversal in selectivity with Et_2AlCl at room temperature may be due to the involvement of a boatlike transition state[13d] that explains the (Z)-enolate switch from the syn to the anti selectivity. However, more designed experiments are needed to ascertain the transition structures of the aldol reactions with $BF_3 \cdot OEt_2$, Et_2AlCl, and $SnCl_4$.

To demonstrate the synthetic utility of the present protocol, we have treated selected aldol products with *m*-CPBA following a literature protocol[14] to obtain the substituted tetrahydrofuranylmethanol derivatives.[15] The results are collected in Table 4. The yields were excellent from the ketone-derived aldol adducts. The stereorelationships of the substituents in the products were discerned from a series of NOE experiments for selected compounds and extended to others by comparing the spectral data.

In summary, we have shown that the enolate generated from the Lewis acid-assisted ring-opening of the vicinally substituted trimethylsilylmethyl cyclopropyl ketones could be effectively trapped with aldehydes and ketones. The aldol additions of Ti-enolates are syn selective and proceed possibly through a closed cyclic transition state. Importantly, the aldol products are convenient precursors to the preparation of substituted tetrahydrofuranylmethanol derivatives. The transition state structures of the present aldol reactions with different Lewis acids and double stereodifferentiation are interesting features to investigate in detail in the future.

Supporting Information Available: Experimental procedures and spectroscopic data of all the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Table 4. Conversion of Selected Aldol Products into Tetrahydrofuranylmethanol Derivatives
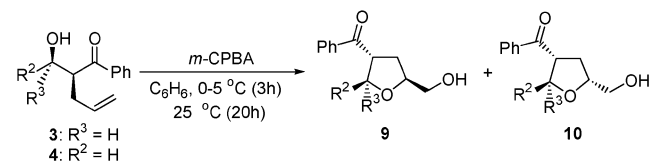
entry	R^2	R^3	9:10 (yield in %)
1	*n*-Pr	H	2.0:1 (71)
2	H	*n*-Pr	1.3:1 (69)[a]
3	Ph	H	2.5:1 (67)
4	H	Ph	2.2:1 (64)[a]
5	Et	Et	3.3:1 (90)
6			2.8:1 (92)

[a] Diastereomeric ratio was estimated from the ¹H integrals of the isomeric mixture.