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Synthesis of β-Hydroxy-α-haloesters through Super Silyl Ester Directed *Syn*-Selective Aldol Reaction

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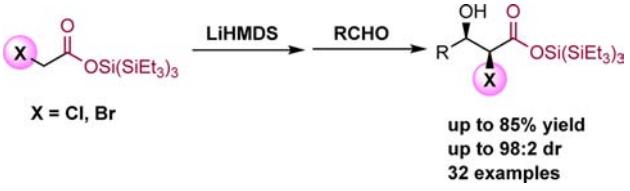
ABSTRACT



Super silyl haloesters including chloro- and bromoacetate were synthesized and utilized for aldol reactions to give *syn*-β-hydroxy-α-haloacetates in good yields with high diastereoselectivities. β-Hydroxy-α-fluoroacetate was obtained by lithiation of super silyl bromofluoroacetate. Sequential Darzens reactions provided *cis*-glycidic esters in moderate yields.

Halogenated compounds are of great interest in medicinal chemistry and material science due to their biological properties.[1] In particular, fluorine and chlorine atoms are often found in bioactive natural products and pharmaceuticals. Furthermore, their synthetic significance is proven by the recent development of transition metal catalyzed reactions which enable facile transformation of halogen atoms into a variety of functional groups. In this context, catalytic stereoselective halogenation is a valuable synthetic approach to α-halocarbonyl compounds, which are useful chiral building blocks, and has been explored over the years.[2]

In our continuous studies on tris(trialkylsilyl)silyl (super silyl) chemistry,[3] we developed a Mukaiyama aldol reaction using super silyl halogenated enol ethers to construct β-siloxy-α-halocarbonyls in good yields with high diastereoselectivities.[4] It successfully installs a series of halogen atoms into a polyketide structure[5] and can be an alternative for direct halogenation. Moreover, we found that super silyl ester, a new class of protected carboxylic acids, demonstrated high stability and stereocontrol to achieve diastereoselective aldol and Mannich reactions.[6] Encouraged by these results, we decided to utilize this protocol to provide β-hydroxy-α-haloesters, which is complementary to our reported method[4] for the synthesis of β-siloxy-α-haloaldehydes and ketones, leading to the design diversity of halogenated polyketide motifs.

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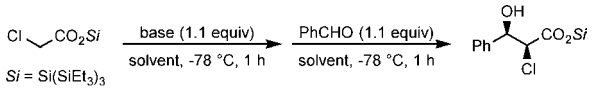
Herein, we report aldol reactions with super silyl haloacetate to give β-hydroxy-α-haloacetate in good yield with high *syn*-selectivity. While there are many examples of aldol reactions with α-halocarbonyls,[7–9] the application of a haloester is limited[7] and a versatile method for *syn*-selective reaction is desirable. The resulting products are attractive precursors for glycidic esters.

Table 1. Screening of Reaction Conditions

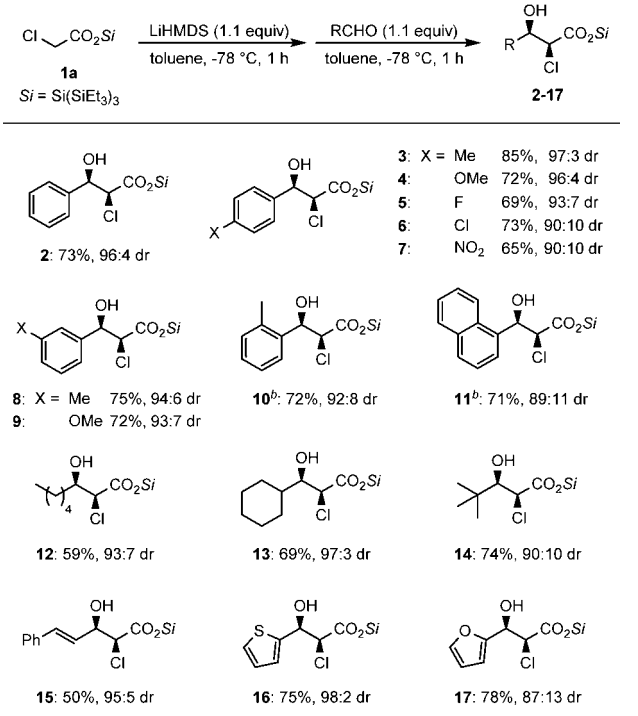


entry	base	solvent	yield (%)[a]	dr (*syn*/*anti*)[b]
1	*n*-BuLi	THF	32	74:26
2	LiHMDS	THF	60	72:28
3	LiHMDS	Et_2O	0	N.D.
4	LiHMDS	toluene	73	96:4
5	NaHMDS	toluene	71	92:8
6	KHMDS	toluene	67	89:11
7[c]	LiHMDS	toluene	trace	74:26

[a] Yield of isolated product. [b] Determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [c] Triisopropylsilyl(TIPS) chloroacetate was used.

Given the optimal conditions from our previous study,[6a] we first examined an aldol reaction of super silyl chloroacetate with benzaldehyde using *n*-butyllithium as a base in THF. Unfortunately, it resulted in poor yield with moderate *syn*-diastereoselectivity owing to the dehalogenated side reaction through Li/Cl exchange (Table1, entry 1). The stereochemistry of the product was confirmed by the ^{1}H NMR after deprotection.[10] The use of LiHMDS suppressed the side reaction to improve the yield (entry 2). Among the screened solvents, toluene was found most suitable for achieving the highest yield (73%) and diastereoselectivity (96:4) (entry 4). In order to survey the size effect of the base, NaHMDS and KHMDS were used to give a slightly lower diastereoselectivity (entries 5, 6). Triisoproylsilyl chloroacetate was employed to furnish a trace amount of the aldol adduct, indicating the unusual stability and stereodirecting property of super silyl ester (entry 7).

Scheme 1. Aldol Reaction with Super Silyl Chloroacetate[a]



[a] The yields of isolated products are shown. The dr is determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [b] 1.0 equiv of HMPA was used as an additive.

The substrate scope of aldehydes was then investigated under the optimized conditions (Scheme 1). Both electron donating and withdrawing groups on aryl aldehydes were tolerant and gave *syn*-aldol products (**3**–**7**) in good yields.

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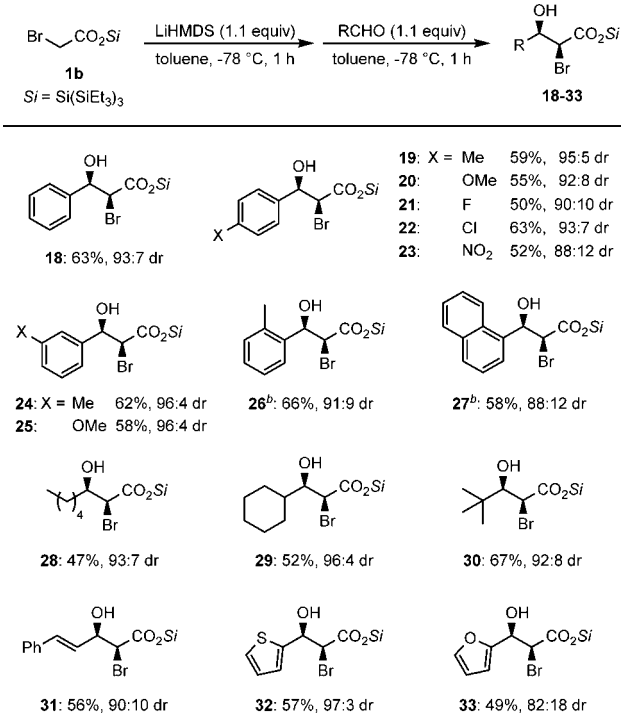
(10) See the Supporting Information for details.

While substituents on *para*- and *meta*-positions gave comparable results, the addition of HMPA was required for *ortho*-substituted aldehydes such as *ortho*-tolualdehyde and 1-naphthaldehyde to afford the satisfying *syn*/*anti* ratio (**10**, **11**). To our delight, aliphatic aldehydes including sterically bulky pivalaldehyde worked as well to provide **12**–**14** with good to excellent *syn*-selectivities. Cinnamaldehyde reacted with lithium enolate to give **15** without causing conjugate addition. The reaction was also applicable for heteroaromatic aldehydes to give *syn*-aldol products **16** and **17** in good yields.

Next, an aldol reaction with super silyl bromoacetate was tested (Scheme 2). Gratifyingly, the reaction gave β-hydroxy-α-bromoacetate in moderate to good yields with high *syn*-selectivities, leaving the reactive bromo-group intact. Although the yields are lower than chloroacetate, the substrate scope of aryl aldehydes was broad as well. The addition of HMPA was necessary for *ortho*-substituted aryl aldehydes to achieve high diastereoselectivity (**26**, **27**). The reaction with aliphatic aldehydes proceeded to furnish *syn*-aldol products (**28**–**30**). 2-Thienyl aldehyde was applied to give **32** in 57% yield with excellent diastereoselectivity (97:3).

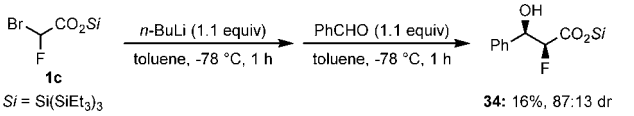
Scheme 2. Aldol Reaction with Super Silyl Bromoacetate[a]



[a] The yields of isolated products are shown. The dr is determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [b] 1.0 equiv of HMPA was used as an additive.

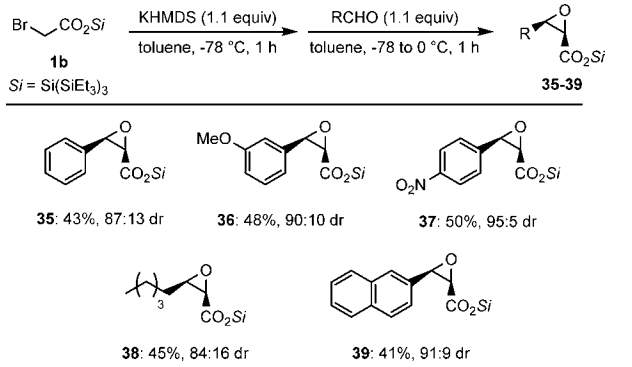
Synthesis of super silyl fluoroacetate was avoided due to the high toxicity of fluoroacetic acid. Instead, super silyl bromofluoroacetate was used to provide β-hydroxy-α-fluoroacetate (Scheme 3). *n*-Butyllithium was added to form a lithium fluoroacetate enolate intermediate through Br/Li exchange, and a sequential reaction with benzaldehyde accomplished β-hydroxy-α-fluoroacetate (**34**). Unfortunately, the reaction resulted in a low yield (16%) because of the instability of the starting material, but promising *syn*-selectivity (87:13) was observed.

Scheme 3. Aldol Reaction with Super Silyl Bromofluoroacetate



Although detailed mechanistic studies are required, the reaction is thought to proceed through the same manner as an aldol reaction of super silyl propionate,[6a] an anticlinal open transition state with *Z*-enolate, to give high *syn*-selectivity. However, the Zimmerman–Traxler-type cyclic transition state cannot be ruled out because the coordination of THF plays a crucial role in stabilizing *Z*-enolate in the case of super silyl propionate and the use of noncoordinating solvent may change the preferred enolate.

Scheme 4. Darzens Reaction with Super Silyl Bromoacetate[a]



[a] The yields of isolated products are shown. The dr is determined by ^{1}H NMR spectroscopy of the crude reaction mixture.

Finally, a one-pot ring closing reaction from an aldol adduct, known as the Darzens reaction,[11] was examined (Scheme 4). The resulting glycidic ester is the prevalent intermediate for total synthesis. While *trans*-glycidic esters are easily accessible by Darzens reaction or transition metal catalyzed epoxidation, the *cis*-selective Darzens reaction has been less explored.[12] By switching from LiHMDS to KHMDS and warming up to 0 °C after the addition of benzaldehyde, the desired *cis*-glycidic ester **35**

(11) For a review, see: Rosen, T. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Heathcock, C. H., Eds.; Pergamon: Oxford, 1991; Vol. 2, pp 409–439.

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was obtained in 43% yield with 87:13 dr. The reaction proceeded smoothly with aryl aldehydes bearing electron donating and withdrawing groups and aliphatic aldehyde. Sterically hindered 2-naphthaldehyde gave **39** in 41% yield with 91:9 *syn*-selectivity.

In summary, an aldol reaction of super silyl haloacetates was developed to give β-hydroxy-α-haloacetates in good yields with high *syn*-diastereoselectivities. Furthermore, a Darzens reaction provides a concise synthetic route for *cis*-glycidic esters. Combined with a Mukaiyama aldol reaction of super silyl halogenated enol ethers,[4] these reactions realized stereoselective installation of halogen atoms (Cl, Br, F) into the α-position of carbonyl compounds such as aldehyde, ketone, and ester, which serve as useful tools for screening complex molecules including polyketide analogues to investigate their potential bioactivity.

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Supporting Information Available. Complete experimental procedures, characterization data of the prepared compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.