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Rapid, One-Pot Synthesis of β-Siloxy-α-haloaldehydes

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Supporting Information

ABSTRACT: The Mukaiyama cross-aldol reaction of α-fluoro-, α-chloro-, and α-bromoacetaldehyde-derived (*Z*)-tris(trimethylsilyl)silyl enol ethers is described, furnishing *anti*-β-siloxy-α-haloaldehydes. A highly diastereoselective, one-pot, sequential double-aldol process is developed, affording novel β,δ-bissiloxy-α,γ-bishaloaldehydes. Reactions are catalyzed by $C_6F_5CHTf_2$ and $C_6F_5CTf_2AlMe_2$ (0.5−1.5 mol %) and provide access to halogenated polyketide fragments.

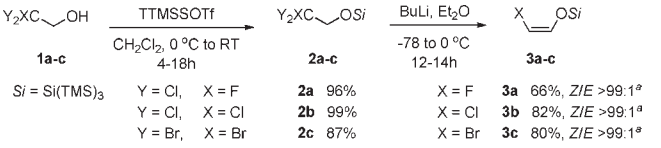
Recently our group has actively developed a highly efficient methodology employing catalytic, sequential one-pot Mukaiyama aldol reactions of "super-silyl" [tris(trimethylsilyl)silyl, TTMSS] enol ethers.[1] High steric shielding provided by the super-silyl group and its unique electronic properties allowed us to tame the reactivity of an acetaldehyde-derived enol ether in mono, double,[1a,c,e,f] and triple[1g] cross-aldol processes. Furthermore, it enabled spectacularly rapid construction of a few naturally occurring polyketides.[1c,i] The prospect of introducing halogen atoms into these biologically relevant structures seems especially exciting, as halogens often have a high impact on a molecule's activity in biological settings.[2] Recently, halogenated polyketide-like structures have also received a lot of attention among the synthetic community.[3] In addition, halogen atoms could also be potentially exploited as chemically reactive functional groups as a means to introduce more complex functionalities.

Herein, we describe the first cross-aldol reactions of α-haloacetaldehyde-derived silyl enol ethers, affording β-siloxy-α-haloaldehydes[4−6] with excellent *anti*-stereoselectivities, and the first sequential double-aldol reaction of such enol ethers, furnishing novel β,δ-bissiloxy-α,γ-bishaloaldehydes in a one-pot reaction.

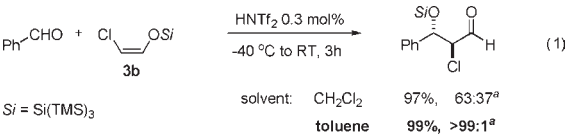
The halogenated silyl enol ethers **3a**−**c** were prepared via highly stereoselective rearrangement of lithium carbenoid species[7] generated from readily available silylated trihaloethanols **2a**−**c** (Scheme 1).

With the starting materials in hand, we screened for the best reaction conditions using benzaldehyde and **3b** as model substrates and 0.3 mol % $HNTf_2$ as catalyst (eq 1). The reaction in dichloromethane afforded the desired α-chloroaldehyde with high efficiency but with modest diastereoselectivity. Remarkably, switching the solvent to toluene furnished the 3-siloxy-2-chloro-3-phenylpropanal quantitatively

Scheme 1. Synthesis of the Halogenated Silyl Enol Ethers



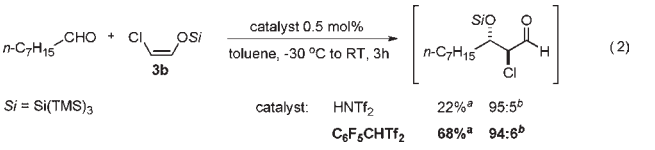
[a] *Z*/*E* ratio based on integration of the ^{1}H NMR signals of crude material.



[a]Yield and dr based on integration of the ^{1}H NMR signals of crude material.

and with excellent *anti* stereoselectivity (eq 1).

Further experiments indicated that the conditions established for benzaldehyde work well with various aromatic aldehydes; however, reactions with aliphatic aldehydes proved sluggish. Thus, we performed an additional screening of other potential catalysts for this reaction to also enable high reactivity with aliphatic aldehydes. Gratifyingly, pentafluorophenylbis(triflyl)-methane[8] (0.5 mol %) afforded the desired α-chloroaldehyde from octanal in good yield and excellent *anti* stereoselectivity (eq 2).



[a]Isolated yield of the corresponding alcohols obtained after $NaBH_4$ reduction. [b]Dr based on integration of the ^{1}H NMR signals of crude material obtained after $NaBH_4$ reduction.

Employing the conditions optimized for *anti* selectivity, we have systematically prepared a series of *anti*-β-siloxy-α-haloaldehydes **4**−**17** using the starting materials **3a**−**c** (Table 1). Most aromatic aldehydes reacted smoothly with compounds **3a**−**c**, affording products in good yields and excellent stereoselectivities. Sterically hindered 2-methylbenzaldehyde afforded products **6a**−**c**. Halides at the 2-, 3-, and 4-positions were very well tolerated, giving products **7**−**9**. 4-Nitro- and 4-trifluoromethyl-substituted

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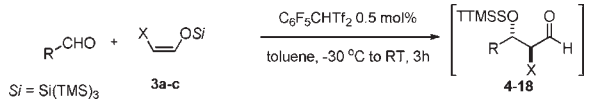
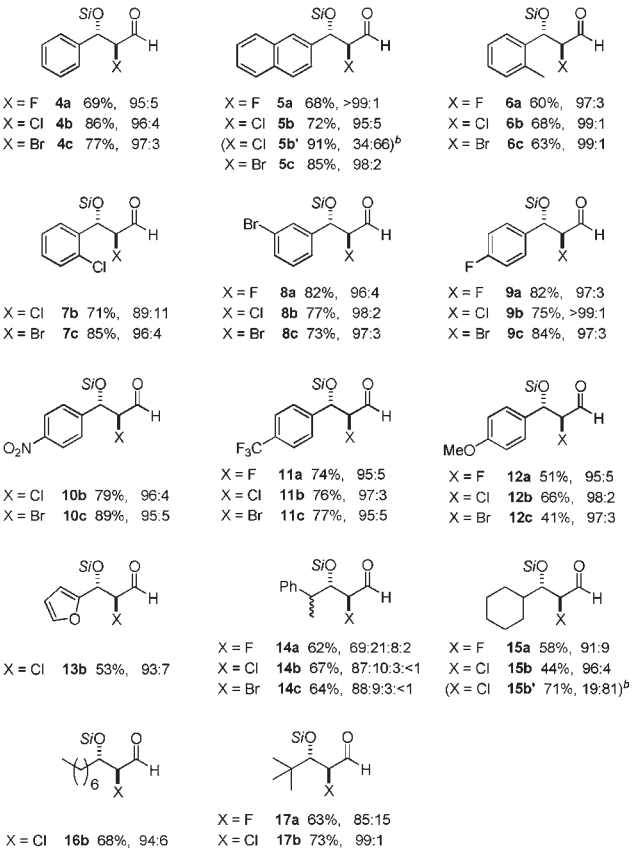
Table 1. Aldol Reactions with Siloxy-vinyl Halides 3a−c[a]



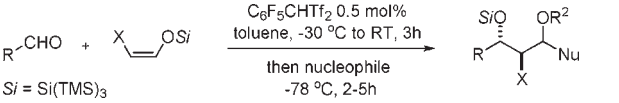


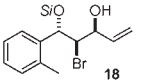
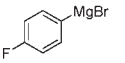
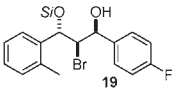
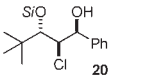
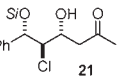
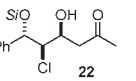
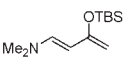
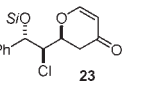
[a] Yields of isolated alcohols after $NaBH_4$ reduction. Dr based on integration of the ^1H NMR signals of crude alcohols. [b] Reaction conditions for **5b′** and **15b′**: $C_6F_5C(Tf)_2AlMe_2$ (1.5 mol %), CH_2Cl_2, −78 °C to RT, 8 h.

benzaldehyde reacted remarkably efficiently and selectively (products **10** and **11**). Electron-rich 4-methoxybenzaldehyde and heterocyclic 2-furylcarboxyaldehyde gave α-haloaldehydes **12** and **13** with high stereoselectivity and slightly lower yields. Racemic 2-phenylpropanal afforded mixtures of stereoisomers **14a−c** in good yields and stereoselectivities. Cyclohexylcarboxyaldehyde afforded **15a,b** with very good *anti*/*syn* ratios but only moderate yields. Reaction of octanal and pivaloaldehyde with **3b** furnished chlorinated **16b** and **17b** with excellent stereoselectivities. Pivaloaldehyde also reacted well with **3a**, but the fluorinated product **17a** was formed with only moderate stereoselectivity. In addition, two *syn*-selective aldol reactions were accomplished in dichloromethane using aluminum catalyst (see Table 1, footnote *b*), giving products **5b′** and **15b′**, albeit with moderate diastereoselectivities.

Next, a few possibilities of subsequent, one-pot transformations of the obtained β-siloxy-α-haloaldehydes were briefly investigated (Table 2). Addition of vinyl and aryl Grignard reagents to **6c** and **17b** was very efficient, furnishing products **18−20** in good yields and quite unexpected *syn*−*anti* diastereoselectivities.[9−11] Reaction of **4b** with the lithium enolate

Table 2. One-Pot Sequential Reactions with α-Haloaldehydes



entry	nucleophile	X	product	yield[a,b], dr[c]
1		Br	 **18**	71%, 94:6:<1:<1
2		Br	 **19**	73%, 97:3:<1:<1
3	PhMgBr	Cl	 **20**	69%, 99:1:<1:<1
4		Cl	 **21**	72%, 87:13:<1:<1
5		Cl	 **22**	77%, 94:6:<1:<1
6		Cl	 **23**	74%, 99:<1:<1:<1[d]

[a] All reactions performed directly on crude mixtures of α-haloaldehyde; therefore, yields are given over two steps. [b] Yields of isolated material. [c] Dr based on integration of the ^1H NMR signals of crude material. [d] Purified directly; dr of isolated material.

of acetone, as well as with acetone silyl enol ether, furnished the desired δ-chloro-β-hydroxyketones **21** and **22** with good yields and good, complementary *anti*−*anti* and *syn*−*anti* stereoselectivities, respectively. Reaction of **4b** with Rawal−Kozmin's diene[12] smoothly afforded the hetero-Diels−Alder product **23** as a single stereoisomer.

Taking advantage of the unique reactivity enabled by the supersilyl group, we tried to expand this reaction to the sequential double Mukaiyama aldol reaction with the halogenated silyl enol ethers in a single pot. Remarkably, the second aldol step works exclusively in dichloromethane rather than toluene. Thus, after the first aldol reaction (*anti*-selective), the toluene was evacuated under vacuum from the crude α-haloaldehyde reaction mixtures, followed by the addition of 1.5 equiv of a second halogenated silyl enol ether in dichloromethane at −78 °C. Addition of freshly prepared $C_6F_5C(Tf)_2AlMe_2$ (1.5 mol %) was essential to ensure good yields.

The results are summarized in Table 3. Novel β,δ-bis-siloxy-α,γ-bishaloaldehydes **24−31** having four stereocenters were isolated with remarkably high stereoselectivities. Significantly, this sequential process offers the possibility to introduce two different halogen atoms into the polyketide fragment in a regiocontrolled fashion. The second aldol addition of (*Z*)-halo silyl enol ether to the mono-aldol intermediates is, as expected, Felkin-selective and furnishes *syn*−*syn*−*anti*-configured products.[9−11]

Amazingly, if both aldol steps were performed only in dichloromethane as solvent, all-*syn* product **32** was obtained in high diastereoselectivity and good yield; this was probably due to

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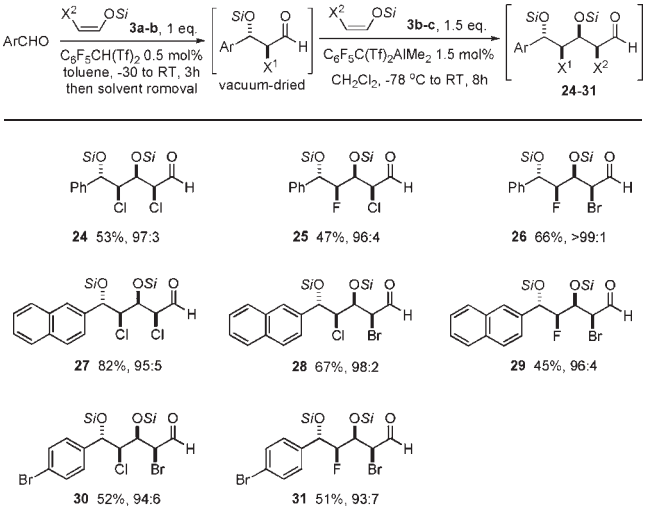
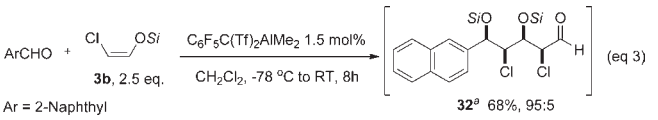
Table 3. One-Pot Sequential Double-Aldol Reactions[a]



[a] Yields of isolated alcohols after $NaBH_4$ reduction. Dr based on integration of the ^1H NMR signals of purified alcohols.

the exceptionally efficient kinetic resolution of the initially formed mono-aldol product (eq 3).[13]



[a] Yield of isolated alcohol after $NaBH_4$ reduction. Dr based on integration of the ^1H NMR signals of purified alcohol.

To address the observed *anti* stereoselectivity of the (*Z*)-silyl enol ether additions in toluene, DFT calculations at the B3LYP levels were made.[15] The B3LYP/6-31G(d)-optimized transition-state structure showed a preference for formation of the observed *anti* isomer by 1 kcal/mol (Figure 1). However, determination of the true nature of the preferred transition state may require more detailed investigation.

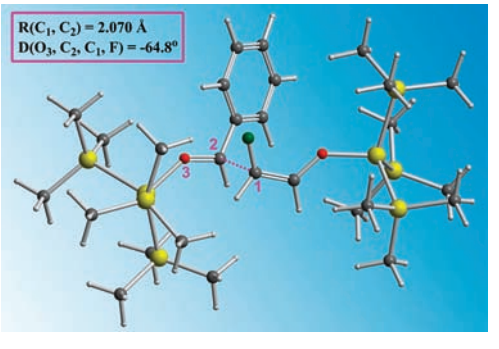


Figure 1. B3LYP/6-31G(d)-optimized transition-state structure of the fluoroacetaldehyde-derived (*Z*)-silyl enol ether addition to benzaldehyde, affording *anti* product.

In summary, we have developed the first Mukaiyama cross-aldol addition of silyl enol ethers derived from α-halogenated acetaldehydes. Furthermore, we have successfully applied this reaction in a sequential manner, allowing for rapid, highly stereoselective construction of novel halogenated polyketide-like fragments. The first aldol addition of the (*Z*)-halo silyl enol ethers furnishes *anti*-β-siloxy-α-haloaldehydes. The subsequent addition is Felkin-selective and yields *syn*−*syn*−*anti*-configured β,δ-bissiloxy-α,γ-bishaloaldehydes. Moreover, by switching solvent, all-*syn* double-aldol product was also obtained.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures; characterization of all compounds shown, including their ^1H, ^{13}C, and if applicable ^{19}F NMR spectra; crystallographic data; computational details; and complete ref 15. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Compare Table 2, product **5b′** for the corresponding mono-aldol reaction under the same conditions.

(14) *Crystal Impact GbR Diamond*, ver. 2.1d.

(15) For full details see Supporting Information. (a) Frisch, M. J.; et al. *Gaussian 03*, revision E.01; Gaussian Inc.: Wallingford, CT, 2004; (b) *Gaussian 09*, Revision B.01; Gaussian Inc.: Wallingford, CT, 2009.