Published in final edited form as:

J Am Chem Soc. 2011 September 14; 133(36): 14248–14251. doi:10.1021/ja2066169.

A Rapid, One-Pot Synthesis of β -Siloxy- α -Haloaldehydes

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Abstract

The Mukaiyama cross aldol reaction of α -fluoro-, α -chloro-, and α -bromoacetaldehyde-derived (*Z*)-tris(trimethylsilyl)-silyl enol ethers furnishing *anti*- β -siloxy- α -haloaldehydes is described. A highly diastereoselective, one-pot, sequential double aldol process, affording novel β,δ -bissiloxy- α,γ -bishaloaldehydes is developed. 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 acetaldehyde-derived enol ether in mono, double^{1a, 1c, 1e–f} and triple^{1g} cross-aldol processes. Furthermore, it enabled spectacularly rapid construction of a few naturally occurring polyketides.^{1c, 1i} The prospect of introducing halogen atoms into these biologically relevant structures seems especially exciting as halogens often have high impact on the molecule’s activity in the biological settings.² Halogenated polyketide-like structures have also received a lot of attention among synthetic community in the recent time.³ Furthermore, 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 one-pot.

The halogenated silyl enol ethers **3a–c** were prepared via highly stereoselective rearrangement of lithium carbenoid species⁷ 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% HNTf₂ as catalyst (eq 1). The reaction in dichloromethane afforded the desired α -chloroaldehyde with high efficiency but

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SUPPORTING INFORMATION

Experimental procedures, characterization of all compounds shown, including their ¹H, ¹³C and if applicable ¹⁹F 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>.

with modest diastereoselectivity. Remarkably, switching the solvent to toluene furnished the 3-siloxy-2-chloro-3-phenylpropanal quantitatively and with excellent *anti*-stereoselectivity (eq 1).

^a Yield and dr are based on the integration of the ¹H NMR signals of crude material.

(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, pentafluorophenyl-bis(triflyl)methane⁸ (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 NaBH₄ reduction. ^b Dr based on the integration of the ¹H NMR signals of crude material obtained after NaBH₄ reduction.

(eq 2)

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-position, were very well tolerated giving products **7–9**. 4-Nitro- and 4-trifluoromethyl-substituted benzaldehyde reacted remarkably efficiently and selectively (products **10–11**). Electron-rich 4-methoxybenzaldehyde and heterocyclic 2-furylcarboxyaldehyde gave α -haloaldehydes **12–13** with high stereoselectivity and slightly lower yields. Racemic 2-phenylpropanal afforded mixtures of stereoisomers **14a–c** with good yields and stereoselectivities. Cyclohexylcarboxyaldehyde afforded **15a–b** with very good *anti/syn* ratio, but only moderate yields. Octanal and pivaloaldehyde in reaction 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 examples of *syn*-selective aldol reactions were accomplished in dichloromethane using aluminum catalyst (see 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** were very efficient, furnishing products **18–20** in good yields and quite unexpected *syn-anti*-diastereoselectivities.^{9–11} Reaction of **4b** with the lithium enolate of acetone, as well as with acetone silyl enol ether, furnished desired δ -chloro- β -hydroxyketones **21** and **22** with good yields and good, complimentary *anti-anti*- and *syn-anti*-stereoselectivities, respectively. And reaction of **4b** with Rawal-Kozmin's diene¹² smoothly afforded the hetero-Diels-Alder product **23** as a single stereoisomer.

Taking advantage of the unique reactivity enabled by the “super-silyl” 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 equivalents of a second halogenated silyl enol ether in dichloromethane at $-78\text{ }^{\circ}\text{C}$. Addition of freshly prepared $\text{C}_6\text{F}_5\text{C}(\text{Tf})_2\text{AlMe}_2$ (1.5 mol%) was essential to ensure good yields.

The results are summarized in Table 3. Novel β,δ -bissiloxy- 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 monoaldol 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 in good yield; this was probably due to the exceptionally efficient kinetic resolution of the initially formed monoaldol product (eq 3).¹³

(eq 3)

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 the observed *anti* isomer formation by 1 kcal/mol (Figure 1). However, determination of the true nature of the preferred transition state may require more detailed investigation.

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. In addition, by switching solvent, all-*syn* double aldol product was also obtained.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported by the NIH grant (P50 GM086 145-01). J.S. thanks the Deutsche Forschungsgemeinschaft (DFG) for a postdoctoral fellowship (Sa 2108/1-1). The authors would like to thank Dr. Ian Steele for X-ray crystallography and Dr. Antoni Jurkiewicz for NMR expertise. The computations were performed using Research Center for Computational Science, Okazaki, Japan.

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13. Compare Table 2, product **5b'** for the corresponding monoaldol reaction under the same conditions.
14. Crystal Impact GbR Diamond software ver. 2.1d.
15. For full details see supporting information. (a) Gaussian 03, revision E.01. 2004 Wallingford, CT Gaussian Inc. (b) Gaussian 09, Revision B.01. 2009 Wallingford, CT Gaussian Inc.

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

^a The Z/E ratio is based on the integration of the ^1H NMR signals of crude material.

Scheme 1.
Synthesis of the halogenated silyl enol ethers.

Table 1

Aldol reactions with siloxy-vinyl halides 3a–c.^a

$\text{R-CHO} + \text{X-CH=CH-OSi} \xrightarrow[\text{toluene, -30 °C to RT, 3h}]{\text{C}_6\text{F}_5\text{CHTf}_2 \text{ 0.5 mol\%}}$ $\left[\begin{array}{c} \text{TTMSSO} \\ \\ \text{R-CH} \\ \\ \text{X} \end{array} \begin{array}{c} \text{O} \\ \\ \text{CH} \end{array} \right]$ $\text{Si} = \text{Si}(\text{TMS})_3$ 3a–c 4–18
X = F 4a 69%, 95:5 X = Cl 4b 86%, 96:4 X = Br 4c 77%, 97:3	X = F 5a 68%, >99:1 X = Cl 5b 72%, 95:5 (X = Cl 5b' 91%, 34:66) ^b X = Br 5c 85%, 98:2	X = F 6a 60%, 97:3 X = Cl 6b 68%, 99:1 X = Br 6c 63%, 99:1
X = Cl 7b 71%, 89:11 X = Br 7c 85%, 96:4	X = F 8a 82%, 96:4 X = Cl 8b 77%, 98:2 X = Br 8c 73%, 97:3	X = F 9a 82%, 97:3 X = Cl 9b 75%, >99:1 X = Br 9c 84%, 97:3
X = Cl 10b 79%, 96:4 X = Br 10c 89%, 95:5	X = F 11a 74%, 95:5 X = Cl 11b 76%, 97:3 X = Br 11c 77%, 95:5	X = F 12a 51%, 95:5 X = Cl 12b 66%, 98:2 X = Br 12c 41%, 97:3
X = Cl 13b 53%, 93:7	X = F 14a 62%, 69:21:8:2 X = Cl 14b 67%, 87:10:3:<1 X = Br 14c 64%, 88:9:3:<1	X = F 15a 58%, 91:9 X = Cl 15b 44%, 96:4 (X = Cl 15b' 71%, 19:81) ^b
X = Cl 16b 68%, 94:6	X = F 17a 63%, 85:15 X = Cl 17b 73%, 99:1	

^aYields of isolated alcohols after NaBH₄ reduction. Dr based on the integration of the ¹H NMR signals of crude alcohols.^bReaction conditions for **5b'** and **15b'**: C₆F₅C(Tf)₂AlMe₂ (1.5 mol%), CH₂Cl₂, –78 °C to RT, 8h.

Table 2One-pot sequential reactions with α -haloaldehydes.

$$\text{R-CHO} + \text{X-CH=CH-OSi} \xrightarrow[\text{then nucleophile}]{\text{C}_6\text{F}_5\text{CHTf}_2 \text{ 0.5 mol\%}, \text{toluene, } -30^\circ\text{C to RT, 3h}} \text{R-CH(SiO-)-CH(X)-CH(OR^2)-Nu}$$

$$\text{Si} = \text{Si}(\text{TMS})_3$$

entry	nucleophile	X	product	yield ^{a,b} , dr ^c
1		Br		71%, 94:6:<1:<1
2		Br		73%, 97:3:<1:<1
3	PhMgBr	Cl		69%, 99:1:<1:<1
4		Cl		72%, 87:13:<1:<1
5		Cl		77%, 94:6:<1:<1
6		Cl		74%, 99:<1:<1:<1 ^d

^a All reactions performed directly on crude mixtures of α -haloaldehyde; therefore yields over 2 steps.^b Yields of isolated material.^c Dr based on the integration of the ^1H NMR signals of crude material.^d Purified directly, dr of isolated material.

Table 3

One-pot sequential double aldol reactions.^a ^aYields of isolated alcohols after NaBH₄ reduction. Dr based on the integration of the ¹H NMR signals of purified alcohols.