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β -Siloxy- α -Haloketones via Highly Diastereoselective Single and Double Mukaiyama-Aldol Reactions

Dr. Jakub Saadi and Dr. Hisashi Yamamoto^[a]

Department of Chemistry, The University of Chicago 5735 South Ellis Avenue, Chicago, IL 60635 (USA)

Keywords

α -haloketones; aldol reaction; cascade reactions; diastereoselectivity; polyketides

Halogens, in particular fluorine and chlorine play pivotal role in modern medicinal chemistry due to their strong impact on biological properties of organic molecules.^[1] In nature, organohalogens are mainly chlorine compounds of marine origin, and many of them exhibit potent antiproliferative or antibiotic properties.^[2] Recently, synthetic chemists turned their attention to chlorosulfolipids^[3, 14j] due to their unclear biological role and curious architecture resembling polyketides, a class of natural products that hold a prominent position among pharmaceuticals.^[4] For these reasons, it seems especially attractive for future medicinal research, to develop efficient synthetic methods for preparation of stereodefined, halogen-modified polyketide structures. β -Oxy- α -haloketones, which are valuable intermediates of epoxyketones,^[5, 13e, 13i] natural products,^[6] heterocycles,^[7] and carbohydrate mimetics,^[8] could also be very useful building blocks for the above mentioned task. Especially, terminal methyl ketones may potentially be utilized as a convenient linchpin for interconnection with aldehyde fragments, to efficiently gain molecular complexity through bi-directional assembly of polyketide subunits.^[14h-i] Methods for preparation of β -oxy- α -haloketones to date include: aldol reactions of metal enolates, which are especially efficient with bulkier ketones,^[5, 7b, 9] Mukaiyama-aldol reactions, which unfortunately generate only diastereoisomeric mixtures,^[10] oxyhalogenation of certain unsaturated ketones,^[11] enzymatic,^[12] and organocatalytic^[13] aldol reactions, which are particularly useful for conversion of aromatic aldehydes. Despite tremendous progress in this field, a truly flexible and highly diastereoselective method to access simple chloroacetone aldol products is still required.

Herein, we describe the first highly diastereoselective Mukaiyama-aldol reaction of chloroacetone and fluoroacetophenone, as well as the implementation of these substrates into the one-pot sequential-aldol protocol.^[14]

α -Chloroketone-derived “super-silyl” [tris(trimethylsilyl)silyl, TTMSS] enol ethers **2a-b** were prepared^[15] in excellent regio- and diastereoselectivities via rearrangement of lithium carbenoid species^[10a] generated from “super-silyl”-protected trichloromethyl alcohols **1a-b**, which are ready available by the nucleophilic addition of chloroform to aldehydes^[16a] or equivalents thereof^[16b-c] (Scheme 1). The fluorine-containing silyl enol ether **2c** was prepared directly from fluoroacetone **3**, which was accessible by sequential monodefluorination^[16d] of trifluoroacetophenone (Scheme 1).

^[a]Fax: (+1) 773-702-5059 yamamoto@uchicago.edu.

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In an analogous fashion, we have also prepared chloroacetone-derived silyl enol ethers bearing few other common silyl groups, and briefly compared their performance in the acid-catalyzed aldol reaction with benzaldehyde under conditions optimized previously for similar reactions (Table 1).^[14j] Results clearly show the superiority of the super-silyl group, which was essential for providing the product in excellent diastereoselectivity and yield.

Having starting materials in hand we have systematically explored the scope of the Mukaiyama-aldol reaction with silyl enol ether **2a**, which reacted smoothly with a remarkably broad range of aldehydes, furnishing β -siloxy- α -chloroketones **4-30** with exceptionally high *anti*-diastereoselectivities (Table 2).

Reactions with propanal and longer-chain, as well as bulkier, α -branched aliphatic aldehydes afforded products **4-9** in excellent diastereoselectivities and very good yields. The chloroacetaldehyde furnished bishalogenated **10** in very good yield and dr of 10:1. The 2-phenylpropanal provided **11a** having three contiguous stereocenters with a remarkably high diastereoselectivity. Reaction was also applicable to α,β -unsaturated and heterocyclic aldehydes giving products **12-15** in good yields and excellent diastereoselectivities. Indole-2-carboxyaldehyde, bearing an unprotected indole nitrogen atom, required 2 eq. of enol ether to achieve the full conversion to **16**, albeit in only 6:1 dr. Aromatic aldehydes, regardless of their steric or electronic properties, reacted very smoothly with **2a** affording products **17-30** in good to excellent yields and excellent diastereoselectivities.

To further demonstrate the flexibility of this method, pivalaldehyde, 2-naphthaldehyde, methyl benzaldehyde-4-carboxylate, and 3,5-dibromobenzaldehyde were reacted with the silyl enol ether **2c** yielding fluorinated ketones **31-34** respectively. Furthermore, benzaldehyde was also reacted with the silyl enol ether **2b**, furnishing chlorinated heptyl ketone **35** (Table 3). Silyl enol ethers **2b** and **2c** showed similar good reactivity as **2a**, albeit the corresponding products were afforded with slightly eroded diastereoselectivities.

Finally, we set out to establish if these halogenated, ketone-derived silyl enol ethers could be implemented into the one-pot sequential-aldol reaction^[14] and thus provide a rapid access to a new type of halogen-modified polyketide fragments. To demonstrate the utility of this protocol silyl enol ethers derived from chloro- and fluoroacetaldehyde,^[14j] as well as propanal^[14k] were chosen as partners in the first aldol step. To our delight, the one-pot sequential reaction of thus preformed *anti*-3-siloxy-2-functionalized aldehydes with **2a** or **2c** as second aldol-partners provided novel *syn-syn-anti*-configured 3,5-bissiloxy-2,4-bishaloketones **36-42** as well as a 3,5-bissiloxy-2-chloro-4-methylketone **43** in good to excellent yields and good to excellent diastereoselectivities (Table 4). The second aldol addition of (*Z*)-halo silyl enol ethers **2a/c** to the mono-aldol intermediates is, as expected, Felkin-selective.^[14j, 17]

In summary, we have developed a remarkably general and highly *anti*-stereoselective Mukaiyama aldol reaction of tris(trimethylsilyl)silyl enol ethers derived from α -halogenated ketones. Furthermore, we have successfully incorporated these silyl enol ethers into our one-pot sequential-aldol methodology which allows for a rapid, diastereoselective, and flexible construction of exotic polyketide-like fragments featuring four contiguous stereocenters. Overall, this methodology offers a step-economic access to a synthetically valuable and potentially pharmacophoric architectures, which are not easily accessible by other methods.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Scheme 1.

Synthesis of α -haloketone-derived silyl enol ethers. [a] Z/E ratio based on integration of the ¹H NMR signals of crude material.

Table 1

Influence of the silyl group on the aldol reaction.

Entry	R	Yield ^[a]	dr ^[a]
1	Me	54%	60:40
2	Et	74%	68:32
3	<i>i</i> -Pr	82%	86:14
4	SiMe ₃	97%	99:1

^[a]Yield and dr by integration of the ¹H NMR signals of crude material.

Table 2

Synthesis of β -siloxy- α -chloroketones.

Yields of isolated ketones. Dr based on integration of the 1H NMR signals of the crude reaction mixture.

[a] From previous examples of super-silyl enol ether addition to 2-phenylpropanal^[14a,f,k] we expect **11** to be the *anti,syn* diastereoisomer, however the stereochemical assignment was not performed in this case.

[b] 2 eq. of the silyl enol ether **2a** were used.

Table 3

Synthesis of β -siloxy- α -haloketones.

Yields of isolated ketones. Dr based on integration of the 1H NMR signals of the crude reaction mixture.

Table 4

One-Pot Sequential Double-Aldol Reactions.

Reactions performed directly on crude mixtures of α,β -functionalized aldehydes. Yields of isolated ketones, yields given over two steps. Dr based on integration of the ¹H NMR signals of purified materials.