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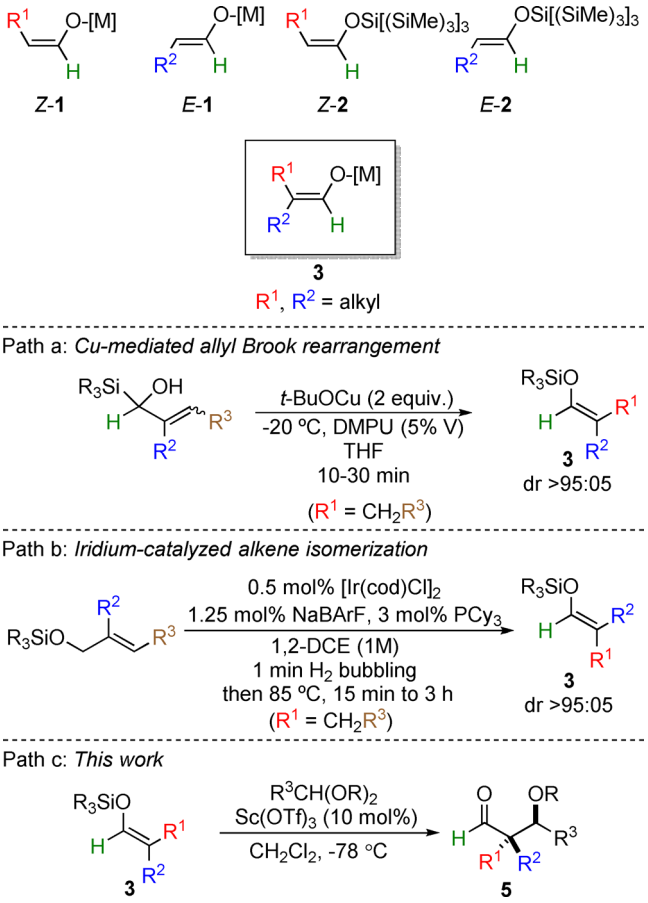
Stereoselective $Sc(OTf)_3$-Catalyzed Aldol Reactions of Disubstituted Silyl Enol Ethers of Aldehydes with Acetals

*Peter-Yong Wang, Itai Massad, and Ilan Marek**

Abstract: *Facile and modular access to stereodefined disubstituted aldehyde-derived silyl enol ethers allowed their successful application in a stereoselective aldol reaction affording the products with excellent yields and diastereomeric ratios. The counter-intuitive stereochemical behavior of this Mukaiyama-aldol reaction is accounted for by a non-classical open transition state.*

The aldol reaction prominently stands as one of the most powerful transformations in stereoselective synthesis.[1] While a plethora of stereoselective variants exist, providing a broad range of differently substituted and functionalized structures,[2] the formation of aldol products resulting from aldehyde-derived enolates remains a significant challenge, due to the difficulties in their stereoselective preparation (Scheme 1, *Z*-**1** and *E*-**1** respectively).[3] The preparation of tris(trialkylsilyl)-silyl enol ethers *Z*-**2** and *E*-**2** by Yamamoto, along with their successful engagement in the triflimide-catalyzed Mukaiyama-aldol reaction, represents a notable step forward in the field.[4] A yet more complex class of substrates are stereodefined disubstituted enolates of aldehydes **3** ($R^1 \neq R^2 =$ alkyl), which remained synthetically elusive for decades, as very few strategies are able to form such enolates stereoselectively.[5] The only stereocontrolled approaches towards such disubstituted aldehyde-derived enolates **3** ($R^1 =$ Me, $R^2 =$ Et)[6] were reported by Nakamura and Kuwajima[5] via a stereoselective conjugate addition of Me_2CuLi to methacrolein and by Ready through a tandem carbometallation–stereoretentive oxidation of terminal alkynes.[7]

Furthermore, the only investigation concerning the aldol addition of disubstituted Li-, B- and Zr-enolates of aldehydes **3** ($R^1 =$ Me, $R^2 =$ Et) to aldehydes resulted in rather low yields and diastereomeric ratios (*syn*:*anti* = 31:69 in 35% yield), providing important mechanistic insights but limited synthetic utility.[8] While yields could be improved when silyl enol ether of aldehyde **3** ($R^1 =$ Me, $R^2 =$ Et, [M] = $SiMe_3$) was treated with aldehydes in the presence of $BF_3{\cdot}Et_2O$ as a Lewis acid, diastereoselectivity remained modest (*syn*:*anti* = 76:24 in 64% yield).[8] Thus, both the stereoselective preparation of disubstituted aldehyde-derived enolates and their application in the aldol reaction are still in their infancy.



Scheme 1. Stereoselective preparation of disubstituted enolate derivatives of aldehydes.

In this context, we have recently reported two complementary approaches toward stereodefined disubstituted aldehyde-derived silyl enol ethers **3** by using an allyl-Brook rearrangement of allylic silyl carbinols (Scheme 1, path a)[9] or through iridium-catalyzed alkene isomerization of allyl silyl ethers (Scheme 1, path b).[10] In both cases, either geometrical isomer of a given enolate was accessible as a single regio- and stereoisomer from readily available starting materials.

With a flexible route towards disubstituted silyl enol ethers of aldehydes **3** in hand, we set out to investigate their reactivity in the Mukaiyama-aldol reaction (Scheme 1, path c) as a new approach towards aldol products **5** possessing quaternary carbon stereocenters within acyclic systems.[11,12] Aiming to develop an easy and reproducible approach to aldol products, robust silyl enol ethers **3** possessing $PhMe_2Si$-

[*] P.-Y. Wang, I. Massad, Prof. Dr. I. Marek
Schulich Faculty of Chemistry, Technion—Israel Institute of Technology
Technion City, Haifa 3200009 (Israel)
E-mail: chilanm@technion.ac.il
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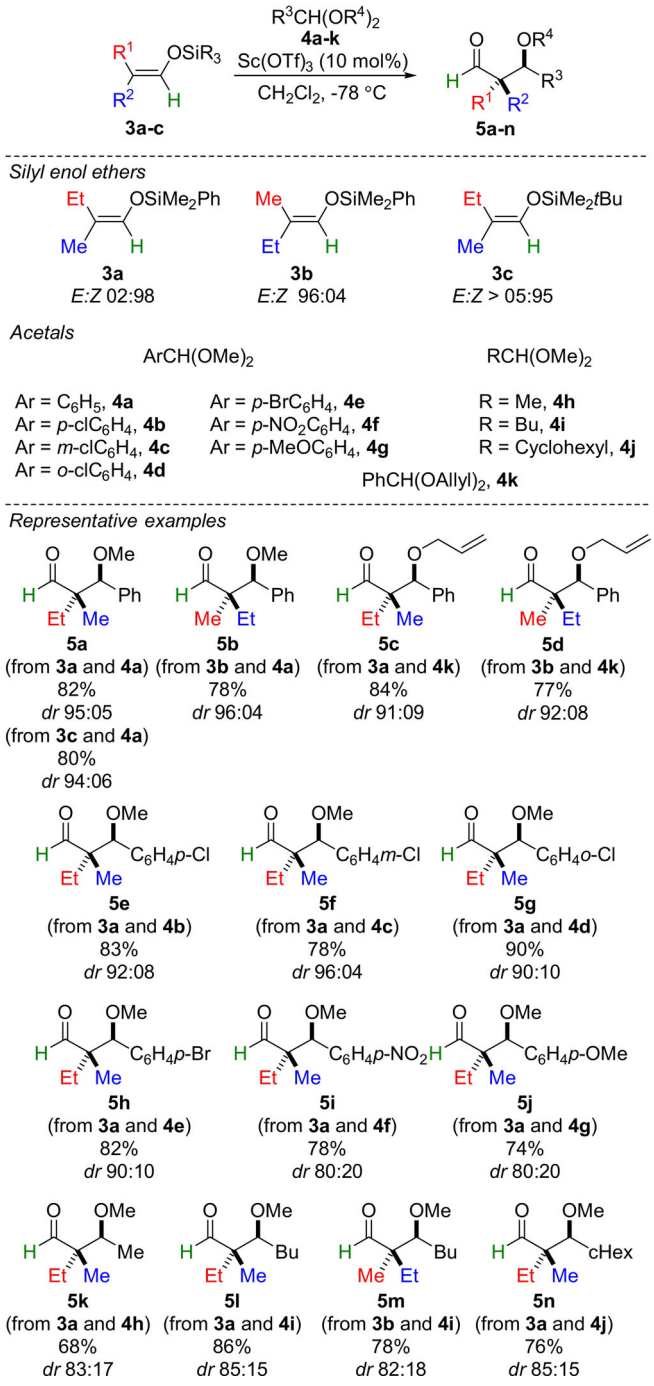
or tBuMe$_2$Si- groups were chosen as substrates. However, these stable and isolable silyl enol ethers **3a–c** are known to be rather weak nucleophiles which react with simple carbonyl compounds only in the presence of strong Lewis or Brønsted acids.[13] Following a screening of potential Lewis acids[14] (see the supporting information), we were delighted to observe that Sc(OTf)$_3$ catalyzed a smooth and selective Mukaiyama-aldol reaction with acetals **4** at low temperature in CH_2Cl_2 to provide the expected products **5** in high yield and diastereoselectivity (Scheme 2).[15] When silyl enol ether **3a** was reacted with acetal **4a** under the experimental conditions described in Scheme 2, Mukaiyama-aldol product **5a** was isolated in 82% yield with excellent diastereoselectivity (95:05 *dr*). Importantly, the complementary diastereomer is accessible as well, with similar diastereoselectivity and yield, by simply inverting the stereochemistry of the starting enol silyl ether (**3b** provides **5b** in 78% yield and 96:04 diastereomeric ratio, Scheme 2). The relative stereochemistry of **5b** has been determined by comparison with a previously reported product[10] and all other configurations were assigned by analogy. This transformation is stereoselective, as the two starting silyl enol ethers **3a** and **3b** are of *E*:*Z* ratios of 02:98 and 96:04 and provide the two aldol products with 95:05 and 96:04 diastereomeric ratios, respectively. Notably, even for the simplest monosubstituted enolates, stereospecific transformations with acetals as proelectrophiles are very rare.[16] TBS-silyl enol ether **3c** reacted with acetal **4a** delivering **5a** with very similar selectivity, suggesting that the nature of the silyl group does not dramatically influence the mechanism of the reaction. To access free aldol products (R^4 = H), acetal **4k** possessing a removable allyl group[17] was also tested, and we were pleased to observe similar selectivities and yields for the diastereomeric pair **5c** and **5d** (from **3a** and **3b**, respectively). Aromatic aldehydes featuring substitution at either the para, meta or ortho-position proceed with satisfactory levels of diastereoselectivity (Scheme 2, compare **5e** with **5f** and **5g**). Disappointingly, electron withdrawing or donating groups slightly decrease the selectivity of the reaction (Scheme 2, **5i** and **5j**, respectively). Still, we were pleased to observe that acetals derived from aliphatic aldehydes smoothly participated in the Sc-catalyzed Mukaiyama-aldol reaction, and that increasing the steric hindrance of the acetal (R = Me, to Bu and c-Hex) doesn't impede reactivity (Scheme 2, compare **5k** with **5l** and **5n**), although the diastereoselectivity is slightly lower in these cases (Scheme 2, **5k–5n**). Still, both diastereomers (**5l** and **5m**) of a given aldol product could be accessed from the two stereomeric enolates **3a** and **3b**. Acetals are the reactive partners of choice for the addition of these disubstituted silyl enol ethers, as the corresponding aldehydes do not react under the same experimental conditions.[16]

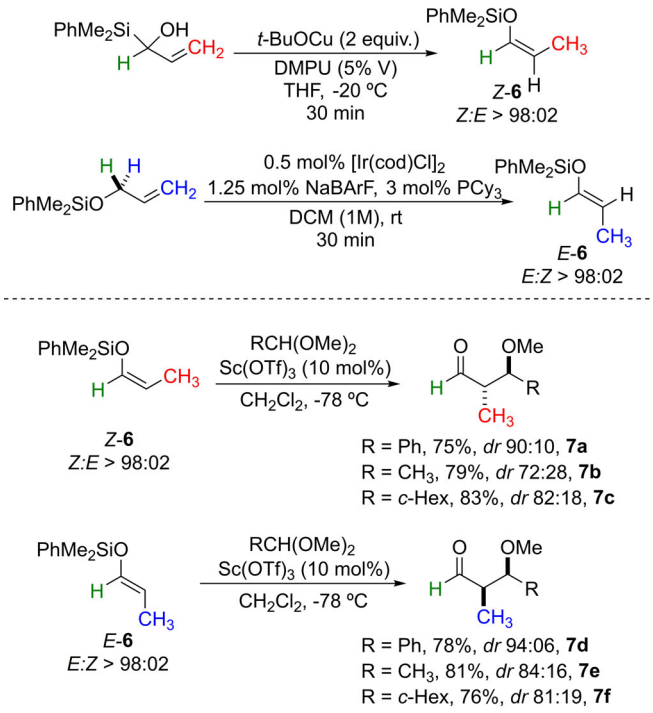


Scheme 2. Sc(OTf)$_3$-catalyzed Mukaiyama-aldol reaction of disubstituted enolates of aldehydes with acetals.

We next wondered whether this Mukaiyama-aldol reaction performs equally well for the less sterically demanding monosubstituted silyl enol ethers **6**. The two stereoisomers *E*- and *Z*-**6** were readily synthesized by using the complementary procedures that we have previously developed for the preparation of disubstituted enolates of aldehydes (Scheme 3).[9,10] The excellent stereoselectivity in both cases shows that these two methods can also be successfully applied to enolates of different substitution patterns.

Under the standard reaction conditions, *Z*-enolate **6** provided the *anti*-aldol derivatives **7a–c**, whereas the *E*-isomer gave the *syn* products **7d–f** in good yields with moderate to good selectivities. The relative stereochemistry of the aforementioned products can be determined by careful analysis of ^{1}H NMR *J* coupling constants ($J_{anti} > J_{syn}$)[18] and chemical correlation with published structures.[17]

Two striking aspects of the stereoselection in this aldol addition attracted our attention. First, the reaction is stereo-



Scheme 3. Sc(OTf)$_3$-catalyzed Mukaiyama-aldol reaction of monosubstituted enolates of aldehydes with acetals.

selective, with each stereoisomer of the enolate leading to a different diastereomer of the product. Such behavior is characteristic to aldol reactions proceeding through cyclic transition states, which is unlikely for this system (discussion follows). Second, the above stereoselectivity is opposite to the classical stereochemical outcome for aldol reactions, as in our case the *Z* enolates provide the *anti*-products whereas the *E* enolates give the *syn* structures (in reactions proceeding through a chair-like transition state, *Z* enolates usually yield *syn* products and *E* enolates give *anti* products).[19]

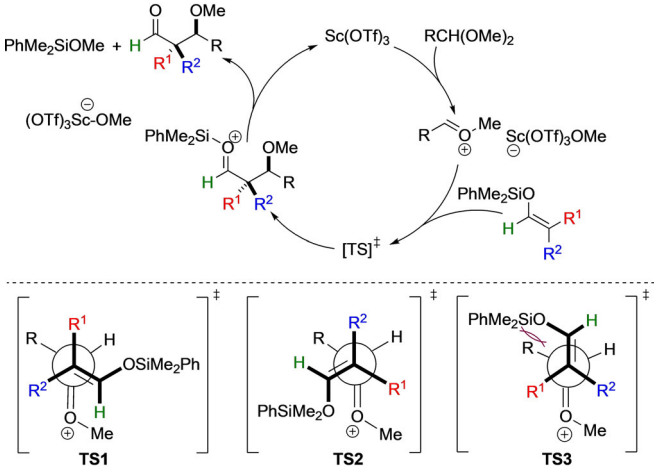
To rationalize the observed reactivity, we propose the catalytic cycle depicted in Scheme 4.[20] Following activation of the acetal by Sc(OTf)$_3$, the silyl enol ether reacts with the in situ generated oxocarbenium ion to provide the Mukaiyama-aldol product in its silylated form, which yields the product by reaction with MeO^-, as supported by the detection of $PhMe_2SiOMe$ in the crude reaction mixture. ^{29}Si NMR investigations do not show any indication of transmetalation of silyl enol ethers into Sc-enolates under our experimental conditions, discounting the possibility of a cyclic transition state.[21]

Seeking to gain insight into the surprising stereochemical behavior of the reaction, we considered the three possible open transition state structures detailed in Scheme 4. We believe the diastereoselectivity of this Mukaiyama-aldol reaction is most convincingly explained by an open transition state wherein the electrophilic oxocarbenium ion reacts with the silyl enol ether through a synclinical open transition state (**TS1** or **TS2**, Scheme 4),[22] where *gauche* interactions between the $OSiMe_2Ph$ moiety and the substituents on the oxocarbenium reaction partner are minimized, compared to the more sterically encumbered **TS3**.

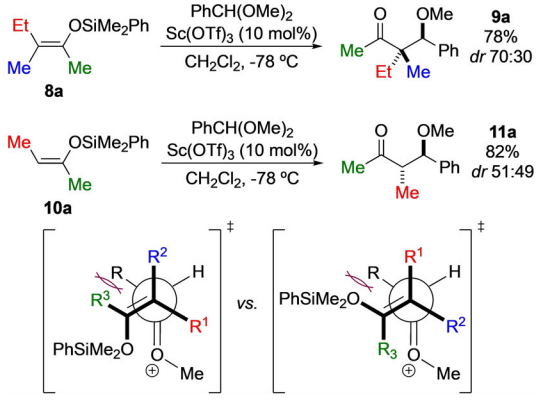
Overall, this transformation is unique in that stereoselectivity depends on the steric differentiation between H and $OSiMe_2Ph$, rather than the steric nature of R^1 and R^2, culminating in a completely stereoselective transformation, unexpected for an aldol reaction proceeding through an open transition state.

To test our stereochemical model, we subjected disubstituted ketone-derived enolates to the reaction. The additional substituent (R^3) present in such enolates is expected to clash with the oxocarbenium R group, leading to decreased diastereoselectivity. Indeed, disubstituted ketone-derived silyl enol ether (*Z*)-**8a** or mono-substituted silyl enol ether (*Z*)-**10a** furnished aldol products **9a** and **11a** in excellent yields, but with low to nil diastereoselectivity, in line with our mechanistic interpretation (Scheme 5).

In summary, reliable access to either stereoisomer of disubstituted aldehyde-derived silyl enol ethers enabled the exploration of their Sc-catalyzed Mukaiyama-aldol reaction. This method affords synthetically valuable aldol products in excellent yields and diastereomeric ratios, while the unique stereochemical features observed pose intriguing mechanistic questions and point to a non-classical open transition state.



Scheme 4. Mechanistic hypothesis.



Scheme 5. Sc(OTf)$_3$-catalyzed Mukaiyama-aldol reaction of ketone-derived enolates.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: acetals · enolates · Mukaiyama-aldol reaction · scandium · selectivity

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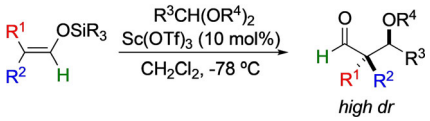
P.-Y. Wang, I. Massad, I. Marek* ——— ■■■■–■■■■

Stereoselective $Sc(OTf)_3$-Catalyzed Aldol Reactions of Disubstituted Silyl Enol Ethers of Aldehydes with Acetals



Facile and modular access to stereodefined disubstituted aldehyde-derived silyl enol ethers allowed their successful application in a stereoselective aldol reaction affording the products with excellent yields and diastereomeric ratios. The counter-intuitive stereochemical behavior of this Mukaiyama-aldol reaction are accounted for by a non-classical open transition state.