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Communication

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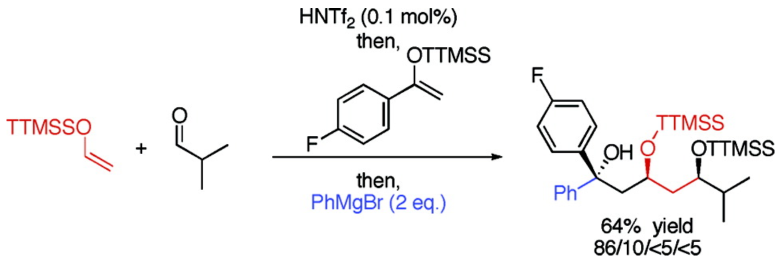

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Ketone Super Silyl Enol Ethers in Sequential Reactions: Diastereoselective Generation of Tertiary Carbinols in One Pot

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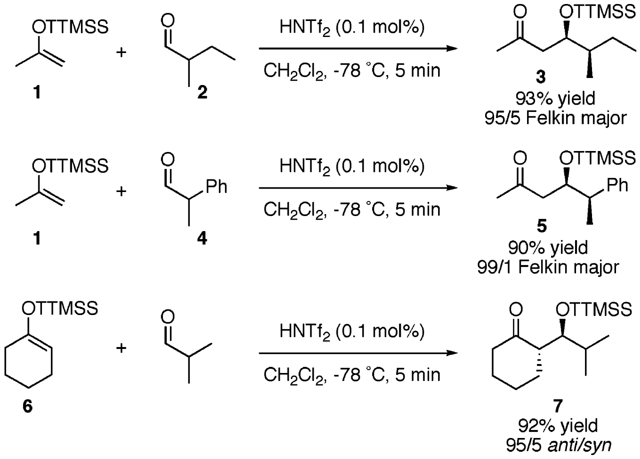
Generation of tertiary carbinols in a diastereoselective manner remains an important synthetic task in organic chemistry.[1] While the design of catalytic enantioselective reactions is garnering the majority of recent attention, broadly applicable, catalytic, diastereoselective reactions remain a significant objective. This is particularly true for compounds with nearby stereocenters where frequent use of expensive external chiral sources is not ideal. Continuing our research efforts with the *tris*(trimethylsilyl)silyl (TTMSS or super silyl group) and its sequential aldol (SA) reactions,[2] which were shown to proceed with unprecedented reactivity and diastereoselectivity, we initially explored the use of ketone derived silyl enol ethers for the simple aldol reaction. Starting with the acetone-derived super silyl enol ether **1**, we looked at the diastereoselective aldol reaction with chiral aldehydes **2** and **4** (Scheme 1). The reaction proceeded giving ketones **3** and **5** in high yield with high Felkin selectivity even in the case of 2-methylbutyraldehyde, showcasing this enol ether's ability to differentiate methyl and ethyl groups.[3] The super silyl enol ether of cyclohexanone (**6**) was reacted with *iso*-butyraldehyde giving **7** in high yield with unprecedented high anti selectivity for this type of Mukaiyama aldol reaction. This is in stark contrast to the TBS- and TMS-enol ethers of cyclohexanone, which have been reported to give little to no selectivity in aldol reactions with a variety of catalysts.[4]

Pleased with these initial aldol results, we wondered if these reagents could be used for SA-reactions such as subsequent addition of organometallics, that is, Grignards, in a one-pot SA-Grignard protocol to generate tertiary carbinols. While a plethora of literature reports and in-depth studies exist regarding the diastereoselectivity of additions to β-oxygenated aldehydes,[5] significantly fewer reports can be found for the corresponding simple β-oxygenated ketones (aside from hydrogenation/reduction reactions).[6] The majority of these reports involve a β-hydroxy ketone and are proposed to undergo cyclic, six-membered transition states involving a Lewis acid catalyst or the metal from the organometallic species. While there is a report concerning syn selectivity for the methyl and butyl addition to β-TBSoxy protected ketones,[6c] sparse examples exist for this type of diastereoselective reaction. This may be due to two main factors: (1) ketones are typically less selective and less reactive than aldehydes in many stereoselective reactions, and (2) stereoselectivity induced by β-chirality is often lower than that induced by α-chirality. We hoped that the superior diastereoselectivity imposed by the super silyl group would also allow for a successful sequential reactions of in situ formed β-super siloxy ketones.

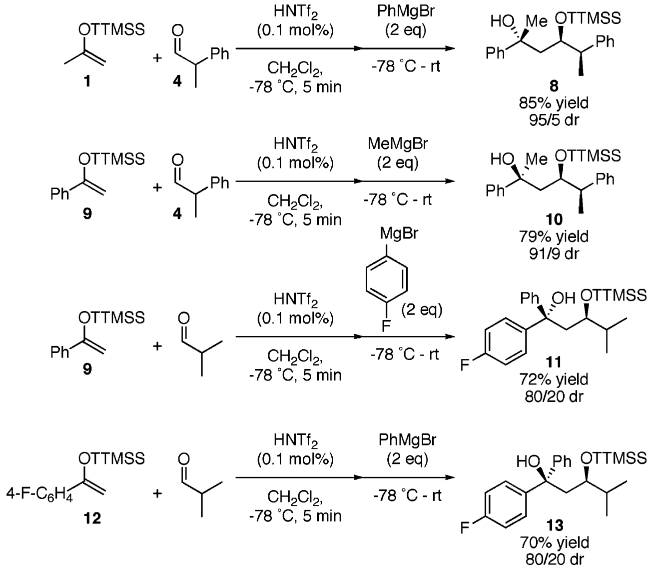
Using a simple one-pot SA-reaction protocol, **1** underwent the aldol reaction with **4** initiated by 0.1 mol % of $HNTf_2$, and phenyl magnesium bromide was subsequently added dropwise at −78 °C (Scheme 2). The product **8** was formed with good yield and excellent diastereoselectivity giving the *anti* product as the major diastereomer.[7,8] This observed sense of stereoinduction results from nucleophilic attack on the *opposite* π-face of the carbonyl to our previously reported SA-Grignard reactions utilizing the acetaldehyde super silyl enol ether.[2c] The proposed reason for this distinction was investigated with DFT calculations and will be discussed subsequently.

Scheme 1. Highly Diastereoselective Mukaiyama Aldol Reactions



*TTMSS − TMS_3Si-

Scheme 2. SA-Grignard Reaction to Generate Distinct Diastereomers



Realizing that by simple substrate choice distinct diastereomers could be generated, **10** was formed with high selectivity by simply

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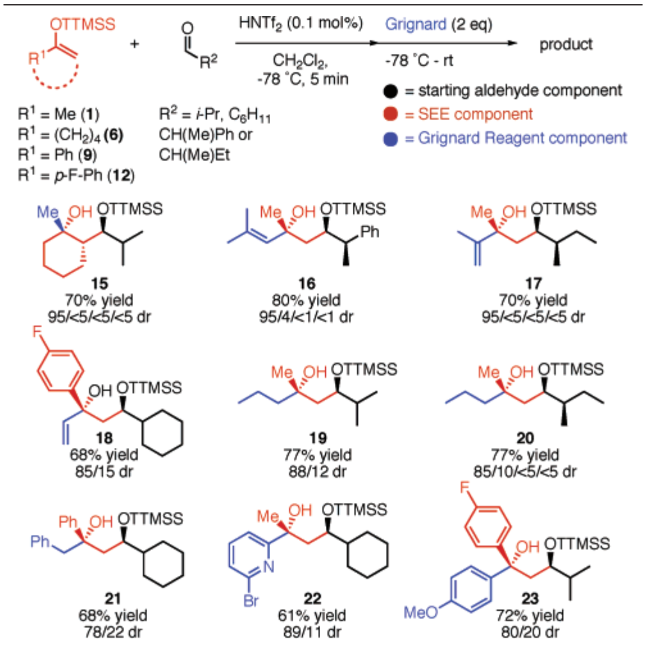
Table 1. SA−Grignard Reaction

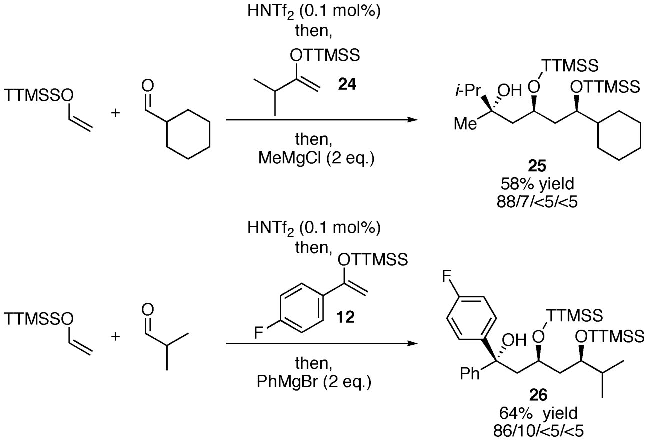


switching to the super silyl enol ether of acetophenone (**9**) and sequentially adding methyl Grignard (Scheme 2). Intrigued by the possibility of accessing stereodefined isomers with similarly sized substituents at the quaternary carbon, we used **9** and added *p*-F-phenyl Grignard obtaining the expected anti isomer **11** in good yield and selectivity (Scheme 2).[7] Using the super silyl enol ether of 4′-F-acetophenone (**12**) and adding phenyl Grignard did indeed give the expected diastereomer **13** in similar yield and selectivity. These examples clearly indicate the control of the transition state exhibited by the super siloxy substituent in these open-chain β-super siloxy ketones as well as the ability to generate the desired diastereomers by the simple choice of silyl enol ether and Grignard.

The generality of this one-pot reaction was shown by the success of a variety of super silyl enol ethers, aldehydes, and Grignard reagents (Table 1). The cyclohexanone super silyl enol ether **6** was used, followed by the addition of the methyl Grignard to give **15**, containing three contiguous stereocenters with the selectivity of the Grignard addition dictated by the stereocenter at the α-position of the ketone.[7] Use of vinyl Grignards worked well giving products **16**, **17**, and **18** with good diastereoselectivity.[7] The use of the propyl Grignard succeeded in this reaction giving products **19** and **20**. Importantly, formation of **17** and **20** showcases the super silyl groups powerful control of diastereoselection by first differentiating methyl and ethyl groups to give large excess of the Felkin isomer and by second stereoselectively controlling the Grignard addition via its presence in the β-position. Use of benzylmagesium chloride gave the lowest selectivity producing **21** with a moderate 78/22 ratio.[9] A variety of aryl Grignards worked very well in this reaction producing bisaryl tertiary carbinols **22** and **23** with good selectivity. Product **22**, containing the valuable pyridine moiety was generated by *in situ* preparation of the heteroaryl Grignard formed by Knochel's powerful *i*PrMgCl 2,6-dibromopyridine exchange reaction.[10]

Owing to our past success with the sequential aldol−aldol (SA−A) reaction,[2a] we decided to combine this method with our SA−Grignard reaction for a 4-component SA−A−Grignard protocol (Scheme 3). The aldol reaction of the acetaldehyde silyl enol ether was followed by a second aldol reaction with **24**, and subsequent addition of methyl Grignard to give the 4-component product **25** in moderate yield with high diastereoselectivity. The same protocol was used with **12** as the second silyl enol ether and phenylmagnesium bromide was finally added to give **26** in moderate yield and selectivity.

Scheme 3. 4-Component SA−A−Grignard Reactions



DFT calculations at the B3LYP/6-311+G(d,p)//B3LYP/6-31G(d) level were done to address the aforementioned diastereoselectivities.[11] Where we had previously observed syn selectivity (SA-Grignard reaction with β-super siloxy aldehydes), we are now seeing anti selectivity (SA-Grignard reaction with β-super siloxy ketones). The calculations assigned a reactant weak complex (RWC) as the relative zero point. The transition state (TS) energy was then calculated as well as the product energy. The vinyl Grignard dimer was used in the calculations due to classic experiments[12] as well as in new calculations showing its likelihood as the reactive species.[13] This was done for both syn and anti reaction courses. The calculations showed that the vinyl Grignard addition to the β-super siloxy aldehyde favored the syn pathway by 0.3 kcal/mol in the TS leading to the experimentally observed syn isomer (Figure 1). Calculations for the β-super siloxy methyl ketone showed a preference for the observed anti isomer formation by 2.6 kcal/mol in the TS (Figure 2). The major reasons for the dissimilarity in TS energies for the latter is the presence of significant steric repulsion between the ketone's methyl group and β-isopropyl group in the syn TS. The anti TS does not suffer from this interaction and is

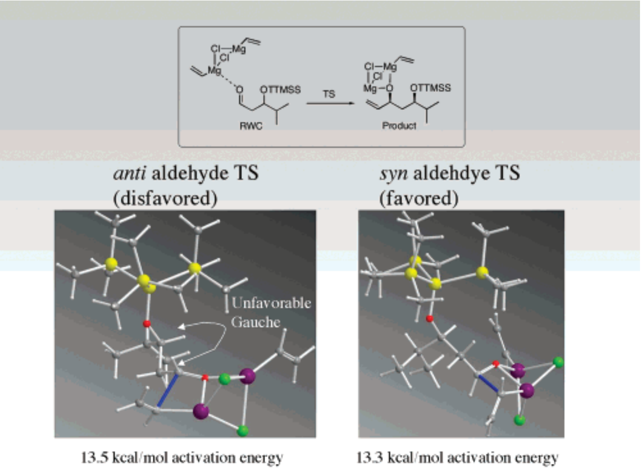


Figure 1. Structures of optimized transition states (TS). Calculated energies (kcal/mol) determined via stationary-point calculations of reactant weak complex (RWC), TS and product in vinyl Grignard addition to β-super siloxy aldehyde. Yellow = Si, gray = C, white = H, red = O, green = Cl, purple = Mg; blue bond indicates forming C−C bond in TS.

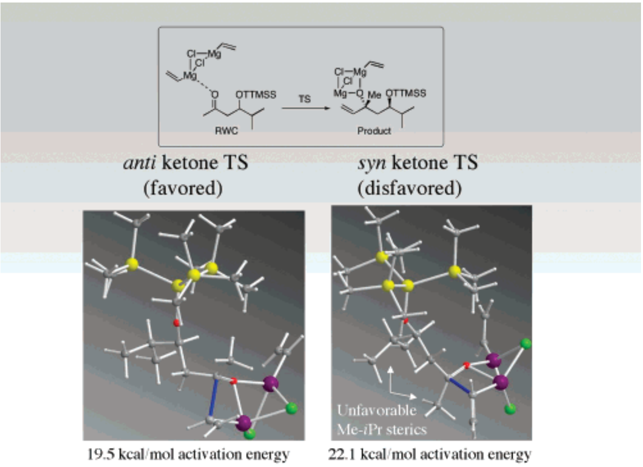


Figure 2. Structures of optimized transition states (TS). Calculated energies (kcal/mol) determined via stationary point calculations of reactant weak complex (RWC), TS and product in vinyl Grignard addition to β-super siloxy ketone. Yellow = Si, gray = C, white = H, red = O, green = Cl, purple = Mg; blue bond indicates forming C−C bond in TS.

thus largely favored. Both the ketone and aldehyde TSs indicate a conformational preference that minimizes destabilizing electrostatic β-C−O and C═O dipole interactions.[14] The aldehyde, in which the methyl group is replaced with a hydrogen, results in the oxygen being the larger atom (hydrogen vs oxygen in aldehyde and methyl vs oxygen in ketone) and preferably passes through the TS leading to the syn isomer. This calculated TS is in accord with our previously predicted TS for the similarly acid-catalyzed SA−A reaction.[2a] A key feature that can be realized from these calculations is that the super silyl group creates a large umbrella-like structure under which the rest of the molecule aligns. This umbrella restricts the conformational freedom of the remaining portion of the molecule. The stereochemical outcome is then largely determined by the carbonyl and its substituent's (methyl for ketone and hydrogen for aldehyde in this study) interaction with the medium β-group (*i*sopropyl in this study). This is in contrast to typical open-chain ketones and aldehydes which have much more freedom of rotation due to a lack of the umbrella effect. This umbrella effect is why we believe we see such high selectivities for these β-super siloxy carbonyl addition reactions.

In conclusion, we have shown the utility of ketone super silyl enol ethers for SA reactions. These silyl enol ethers were shown to succeed in simple Mukaiyama aldol reactions with high selectivity as well as SA-Grignard reactions and 4-component SA-A-Grignard reactions. With the growing demand for one-pot reactions capable of generating relatively complex molecular architecture, we believe the super silyl group is emerging as a key piece for diastereoselective one-pot SA-reactions.

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Supporting Information Available: Complete ref 11, experimental procedures, computational methods, compound characterization and crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) The term anti concerns the relationship between the two alcohol groups when the final *incoming* nucleophile and alkyl chain *containing* the β-supersiloxy moiety are placed in the same plane. This is done as it is a consistent method with our (and others) previous work with aldehydes (ref. 2) and conveys the opposite selectivity generated between these β-supersiloxy carbonyl compounds.
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