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"Super Silyl" Group for Diastereoselective Sequential Reactions: Access to Complex Chiral Architecture in One Pot

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The *syn*-1,3-diol motif is a very common substructure for a multitude of important medicinal compounds and materials.[1] The majority of syntheses of molecules containing this motif require a multistep protocol for access to the stereodefined diol.[2] Our previous work utilizing the *tris*(trimethylsilyl)silyl (TTMSS),[3,4] also called "super silyl" group,[5] allowed controlled installation of either 1 or 2 equiv of the acetaldehyde moiety in one step with the capability of stereoselectively generating 1,3-*syn*-diols in high yield. Because our reaction worked with a variety of aldehyde substrates and generated isolable aldehydes, we imagined that many reactions would be suitable to follow the aldol reaction in one pot. With the increasing interest for environmentally and economically friendly reactions, one-pot reactions have emerged as an important means for saving bulk materials (especially solvents) and time.[6−8] Due to the extremely low catalyst loading (0.05 mol % of $HNTf_2$) used for the initial aldol reaction and high diastereoselectivity obtained, we anticipated that further acid-catalyzed reactions and/or basic reactions (i.e., alkyl metal species) would succeed in one pot.

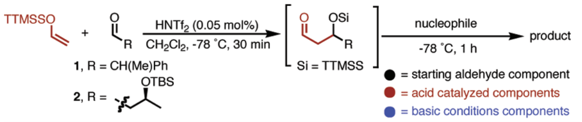
To gain insight into whether this sequential reaction employing different nucleophiles would proceed, we first tested pivalaldehyde as the starting material, added the acetaldehyde super silyl enol ether, and laterally added the super silyl enol ether of cyclohexanone (Scheme 1). We were pleased to find that the product was obtained in 70% yield with essentially complete diastereoselectivity without needed addition of more catalyst. Fortunately, the major diastereomer was crystalline, and the structure was directly determined from X-ray analysis. Pleased with the ability to sequentially follow the aldol reaction with other acid-catalyzed reactions, we were intrigued by the possibility of adding basic reagents (i.e., Grignard reagents). Using pivalaldehyde and the acetaldehyde super silyl enol ether again, followed by allyl magnesium bromide, we obtained the aldol-allylation product in 84% yield and 90/10 *syn*/*anti* selectivity (Scheme 1).[9] To our knowledge, this represents the first example of a homogeneous, sequential, one-pot, strong acid−strong base system that proceeds with high diastereoselectivity.

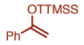
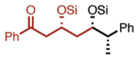
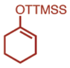
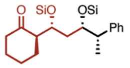
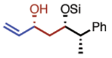
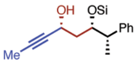
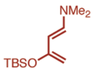
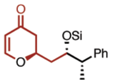
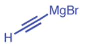
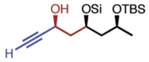
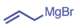
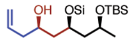
Satisfied with this initial result, we decided to examine different starting aldehydes. Given that many syntheses of natural products and biologically important molecules are done in enantiomerically enriched form, we decided to explore chiral starting aldehydes as substrates. The initial aldehyde used was 2-phenyl propanal, and gratifyingly, the sequential reactions proceeded with high selectivity, giving the products shown in Table 1 in good yield (entries 1−5). The first nucleophiles examined were the addition of the super silyl enol ether of acetophenone and cyclohexanone, which gave the *syn*-diol-ketones in near perfect selectivity (entries 1 and 2). The use of vinyl- and alkynyl-Grignard reagents gave products with high selectivity, generating synthetically useful allylic and propargylic alcohols (entries 3 and 4).[9] Another reaction was envisaged, in which a hetero-Diels−Alder reaction could be performed on the in situ formed aldehyde. Use of the aminosiloxy diene developed by Rawal generated the hetero-Diels−Alder adduct with extremely high selectivity (entry 5).[10] Entry 4 was also performed with enantioenriched (*S*)-2-phenyl propanal (98% ee), giving the product in 97% ee showing no considerable racemization during the acid-catalyzed aldol step.

Encouraged by the possibility of generating all-*syn*-triol motifs with our method, we utilized *β*-siloxy aldehyde **2** as a substrate (Table 1, entries 6−8). In this manner, ethynyl- and allyl magnesium bromide succeeded in giving products with high selectivity (entries 6 and 7).[9,11]

Intrigued by the results shown in Table 1, and the prevalence of the 1,3,5-triol substructure present in natural products, we endeav-

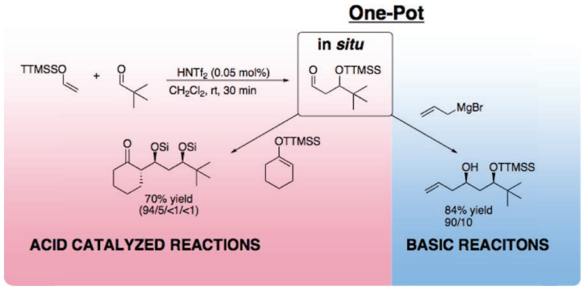
Table 1. Diastereoselective Sequential Reactions



entry	aldehyde	nucleophile	major product	% yield[e] (dr)[f]
1	**1**[b]			78 (94/5/<1/<1)
2	**1**[b]			80 (97/2/<1/<1)
3	**1**[b]			83 (85/14/<1/<1)
4	**1**[c]			79 (86[d]/13/<1/<1)
5	**1**[b]			63 (95/4//<1/<1)
6	**2**			71 (75/13/10/<5)
7	**2**			85 (74/18/<5/<5)

[a] Reactions performed on 0.5−2 mmol scale. [b] Racemic aldehyde used. [c] (*S*)-2-Phenyl propanal used (98.3% ee). [d] Major product 97.4% ee. [e] Isolated yield. [f] Determined by ^{1}H NMR of crude reaction mixture.

Scheme 1. Reaction Compatibility with Acidic and Basic Conditions



10.1021/ja0693542 CCC: $37.00

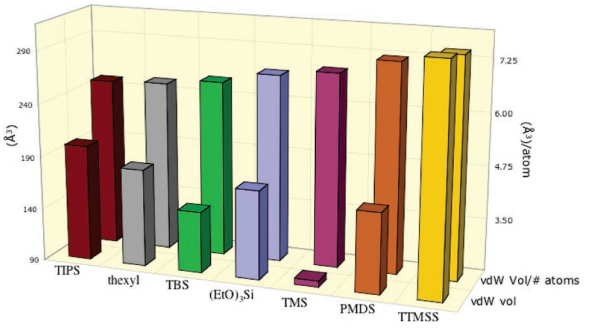
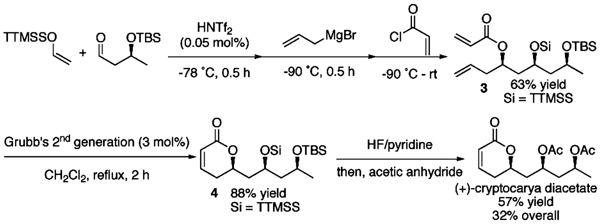


Figure 1. Van der Waals volume vs number of atoms of typical silyl protecting groups.

Scheme 2. Three-Step Synthesis of (+)Cryptocarya Diacetate



ored on the extremely concise synthesis of cryptocarya diacetate. This compound has been isolated from the bark of the South African plant, *Cryptocarya latifolia*, which has been used for medicinal purposes.[12] The aldol reaction was performed under standard conditions with 0.05 mol % $HNTf_2$; subsequent addition of 1.2 equiv of allyl magnesium bromide followed by acryloyl chloride provided dienyl compound **3** in 63% yield along with a 24% yield of an inseparable mixture of the other minor diastereomers (Scheme 2). Use of Grubb's second generation catalyst for ring-closing metathesis gave **4**, which was treated with HF/pyridine followed by addition of excess pyridine and acetic anhydride to give cryptocarya diacetate in 57% yield with a 32% overall yield for the three steps.

We attribute the high diastereoselectivity obtained by using super silyl-containing substrates and catalysts partly due to the steric influence of the group.[13] Along these lines, the van der Waals volumes of common silyl groups were calculated for the parent silanes (R_3SiH) using the method of Abraham (Figure 1, front row).[14] The volumes were also normalized by dividing by the number of atoms in the molecule to gain insight into how the steric size relates to atom economy (Figure 1, back row). To this point, TBS and pentamethyldisilane (PMDS) have the same number of atoms, but have the third lowest and second highest ratio, respectively, pointing to the value of having Si−Si bonds present to increase size without decreasing atom economy. The super silyl group having three Si−Si bonds has the highest van der Waals volume as well as the highest ratio, highlighting its overwhelming steric influence created by the Si−Si bonds. Interestingly, the TIPS group, which has the second highest van der Waals volume, has the worst volume-to-number of atoms ratio.

In summary, a very useful means to generate synthetically important molecules in a simple one-pot procedure has been developed. A sizable number of suitable nucleophiles were discovered to be efficacious for this sequential reaction including, but certainly not limited to, alkyl metal species, silyl enol ethers, as well as dienes for the hetero Diels−Alder reaction. The important factors for the described reactions are: *(1) extremely low catalyst loading for the initial aldol allows for acidic or basic reagents to be sequentially added without erosion of yields or selectivities, and (2) super silyl allows for extremely high diastereoselection in the initial aldol as well as the following sequential reaction, generating multiple stereocenters in one pot.* We believe this is an important method for efficiently generating polyol-containing compounds with very high selectivity and high yield. Furthermore, we have demonstrated the power of one-pot procedures for generating multifunctional compounds stereoselectively. Further applications utilizing the super silyl group are currently underway.

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Supporting Information Available: Experimental procedures, compound characterization; crystallographic data in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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