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Super Silyl Group for a Sequential Diastereoselective Aldol–Polyhalomethyllithium Addition Reaction

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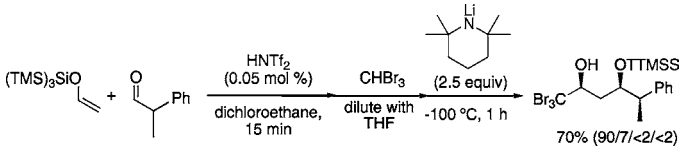
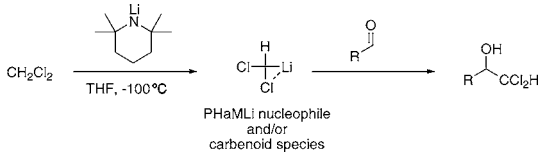
ABSTRACT



The super silyl group governs high diastereoselectivity and yields for a sequential aldol–polyhalomethyllithium addition reaction. This unique silyl group is necessary to obtain the diastereoselectivities associated with this sequential reaction, capable of generating two new stereocenters. α-Polyhalomethylcarbinols are generated with the simple and inexpensive dihalomethanes and trihalomethanes.

Halogens have a long-standing importance in chemistry and have received considerable attention due to their abundance and distinct reactivity. Polyhalomethanes (PHaMs) are small, inexpensive molecules that are able to create a variety of functional groups as electrophiles (halogens as leaving group) and nucleophiles (after metal−halogen exchange). Currently, fluoro and chloro compounds are receiving considerable attention due to their special reactivity in biological settings as well as crop management.[1] They have often conferred resumed anticancer and antibacterial activity on otherwise drug-resistant strains of bacteria. While the importance of these halogens is obvious, stereo controlled introduction of the polyhalomethyl group is still of importance and not widely achievable.[2] One of the most straightforward pathways to generate these useful derivatives would be the nuceloephilic addition of the polyhalomethyllithiums (PHaMLis) to aldehydes (Scheme 1).

Scheme 1. Generation of PhaMLi and Addition of an Aldehyde



The potential difficulties with this approach would be a lack of control in the stereochemistry of the addition as well as dealing with the instability of such species.[3] We have

(1) (a) Naumann, K. *J. Prakt. Chem.* **1999**, *341*, 417. (b) Isanbor, C.; O'Hagan, D. *J. Fluorine Chem.* **2006**, *127*, 303. (c) Kirk K. L. *J. Fluorine Chem.* **2006**, *127*, 1013. (d) Lézé, M.-P.; Le Borgne, M.; Pinson, P.; Palusczak, A.; Duflos, M.; Le Baut, G.; Hartmann, R. W. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1134.

(2) For one example of modest diastereoselectivity, see: Mukaiyama, T.; Yamaguchi, M.; Kato, J.-I. *Chem. Lett.* **1981**, *10*, 1505. Select examples of nonstereocontrolled reactions: (a) Taguchi, H.; Yamamoto, H.; Nozaki, H. *J. Am. Chem. Soc.* **1974**, *96*, 3010. (b) Villieras, J.; Perriot, P.; Normant, J. F. *Synthesis* **1979**, 968. (c) Benner, J. P.; Gill, G. B.; Parrott, S. J.; Wallace, B. *J. Chem. Soc. Perkin Trans. 1* **1984**, 331. (d) Teager, D. S.; Ward, H. D.; Marray, Jr. R. K. *J. Org. Chem.* **1993**, *58*, 5493. (e) Hu, D.-M.; Tu, M.-H. *J. Fluorine Chem.* **1994**, *67*, 9. (f) Concellón, J. M.; Bernad, P. L.; Pérez-Andrés, J. A. *Tetrahedron Lett.* **1998**, *39*, 1409.

(3) (a) Köbrich, G. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 41. (b) Hoeg, D. F.; Lusk, D. I. *J. Am. Chem. Soc.* **1964**, *86*, 928. (c) Kirmse, W. *Carbene Chemistry*, 2nd ed.; Academic Press: New York, 1971.

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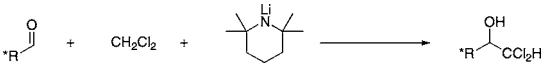
recently reported a one-pot stereoselective cascade and sequential aldol reactions (SA reactions) based on a super silyl/super Brønsted acid system.[4] Since the requisite acid catalyst is present at only 0.05 mol % and the reaction proceeds in a non-protic solvent, we envisioned being able to couple the reaction with sequential C−C bond formation using PhaMLis (Scheme 2). One-pot, sequential, and multicomponent reactions are garnering significant attention due to their many economic advantages.[5] To this end, this reaction sequence is amenable to these conditions. We now wish to report the acetaldehyde super silyl enol ether's use in conjunction with PhaMLis generated in situ by deprotonation of polyhalomethyls with the bulky lithium amide LiTMP (TMP = 2,2,6,6-tetramethylpiperidine). The entire process proceeds smoothly with high stereoselectivities due to the efficient stereocontrol exhibited by the super silyl group.

Scheme 2. In Situ Generation of PhaMLi

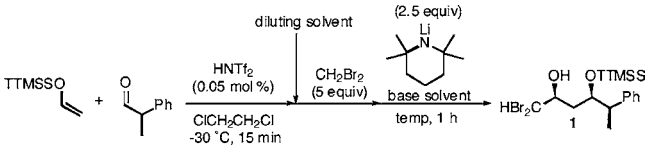


It should be noted that PHaMLi species are rather unstable even at low temperature.[2,3] However, if a solution of aldehyde in the presence of excess PHaMs is treated with the lithium amide, the kinetically generated lithium carbenoid specie reacts with the aldehyde before side reactions and decomposition occur.[3a]

Using our standard aldol reaction of the super silyl enol ether and 2-phenylpropionaldehyde,[4b] we screened a variety of solvents and temperatures for the diastereoselective sequential addition of the dibromomethyllithium to generate the α-dibromomethylcarbinol **1** (Table 1). Dichloromethane could not be used due to competitive deprotonation of the dichloromethane molecule, so dichloroethane was used (high Felkin selectivity still observed for initial aldol).[6] After completion of the aldol reaction (15 min at −30 °C), the solution was diluted with another solvent and cooled to the indicated temperature. It was found that temperatures at or below −78 °C were necessary for good selectivities and yields likely due to high reactivity and stability issues of the carbenoid species (entries 1−3). Diethyl ether and toluene gave similar results, while THF gave slightly better results at −78 °C (compare entry 3 to entries 4−6). Cooling to −100 °C and comparing THF and 2-Me-THF showed a somewhat surprisingly large difference in selectivity between the solvents. Clearly, THF was the superior choice, and these conditions were taken forward.

Naturally, the scope of the reaction was next investigated using a variety of aldehydes as well as different PhaMLi's, which all generated the *syn*-diols.[7] Dichloromethyllithium gave the lowest diastereoselectivities, producing **2** and **3** with moderate selectivity. It is particularly noteworthy that the initial aldol reaction in entry 2 (Table 2) highly discriminates an ethyl group from a methyl group,[8] showcasing the power

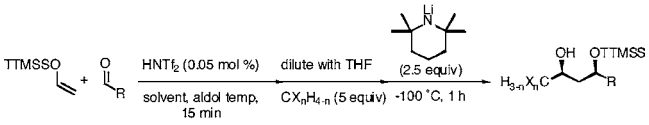
Table 1. Solvent/Temperature Screening for Sequential Aldol−PhaMLi Addition Reaction

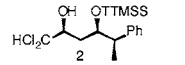
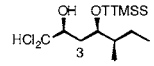
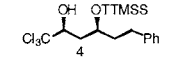
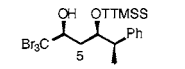
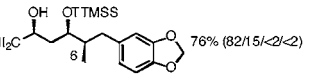
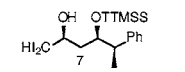


entry[a]	diluting solvent	base solvent	T (°C)	% yield[b]	dr[c]
1	none	THF	−30	trace	nd
2	THF	THF	−30	<10	60/30/5/5
3	THF	THF	−78	68	80/10/5/5
4	Et_2O	Et_2O	−78	65	70/20/5/5
5	toluene	THF	−78	50	70/20/5/5
6	toluene	Et_2O	−78	35	66/24/5/5
7	THF	THF	−100	72	85/5/5/5
8	2-Me-THF	2-Me-THF	−100	70	73/17/5/5

[a] General reaction protocol: 1 mmol of silyl enol ether and 1 mmol of aldehyde in the indicated solvent were cooled to the indicated temperature, and a solution $HNTf_2$ was added dropwise. After 15 min, the polyhalomethane and THF were added, and the solution was cooled to −100 °C. Lithium amide was then added dropwise and the solution stirred for 1 h at −100 °C. [b] Isolated yield. [c] Determined by ^1H NMR.

Table 2. Sequential One-Pot Aldol−PhaMLi Addition Reaction



entry[a]	CXnH4-n	solvent	aldol temp (°C)	product	yield[b] (dr)[c]
1	CH_2Cl_2	CH_2Cl_2	-78	 2	70% (80/10/5/5)
2	CH_2Cl_2	CH_2Cl_2	-78	 3	72% (70/18/10/2)
3	$CHCl_3$	$CHCl_3$	-30	 4	70% (90/10)
4	$CHBr_3$	1,2-dichloroethane	-30	 5	70% (90/7/<2/<2)
5	CH_2I_2	1,2-dichloroethane	-30	 6	76% (82/15/<2/<2)
6	CH_2I_2	1,2-dichloroethane	-30	 7	76% (82/15/<2/<2)

[a] General reaction protocol: 1 mmol of silyl enol ether and 1 mmol of aldehyde in the indicated solvent were cooled to the indicated temperature, and a solution $HNTf_2$ was added dropwise. After 15 min, the polyhalomethane and THF were added, and the solution was cooled to −100 °C. Lithium amide was then added dropwise and the solution stirred for 1 h at −100 °C. [b] Isolated yield. [c] Determined by ^1H NMR.

(4) (a) Boxer, M. B.; Yamamoto, H. *Org. Lett.* **2005**, *7*, 3127. (b) Boxer, M. B.; Yamamoto, H. *J. Am. Chem. Soc.* **2006**, *128*, 48. (c) Boxer, M. B.; Yamamoto, H. *Nat. Protocols* **2006**, *1*, 2434−2438. (d) Boxer, M. B.; Yamamoto, H. *J. Am. Chem. Soc.* **2007**, *129*, 2762.

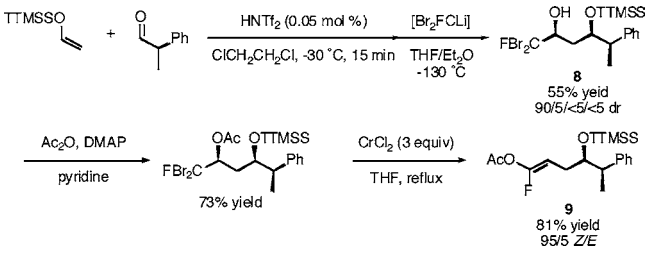
(5) (a) Hall, N. *Science* **1994**, *266*, 32. (b) Tietze, L. F.; Beifuss, U. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 131.

(6) Felkin selectivity is 90/10, which is similar to when dichloromethane is used (see ref 4b).

of the super silyl aldol reaction. After proceeding under high Felkin control, the sequential PHaMLi addition is also quite selective. The bigger chloroform derived anion shows a significant increase in diastereoselectivitiy generating **4** in a 90/10 syn/anti ratio (entry 3). The best selectivity was obtained with the largest tribromomethyllithium anion, giving **5** in high yield with high syn selectivity (entry 4). Diiodomethane is also successfully deprotonated under these conditions and adds with high selectivity to give α-diiodomethylcarbinols **6** and **7** in good yield. Use of iodoform under a variety of conditions and temperatures did not yield any desired α-triiodocarbinol presumably due to solubility problems of iodoform at lower temperatures.

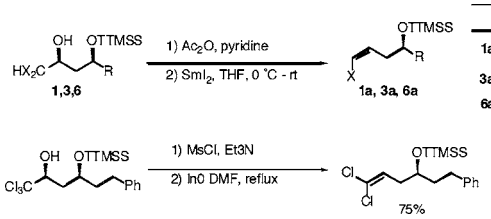
A mixed α-polyhalomethylcarbinol was also synthesized using the method of Kuroboshi.[9] The aldol reaction was performed under standard conditions, and after dilution with THF/Et_2O (2/1) and addition of $CFBr_3$ the solution was cooled to −130 °C. Br_2FCLi was prepared in situ by lithium bromine exchange with *n*-BuLi. The α-dibromofluorocarbinol **8** was produced in moderate yield with good selectivity (Scheme 3). This product could be converted to the (*Z*)-α-haloenol ester **9** by use of $CrCl_2$ in refluxing THF.[10]

Scheme 3. Synthesis of a Mixed α-Halomethylcarbinol and Its Conversion to the (*Z*)-α-Haloenol Ester



We next decided to endeavor on a few useful transformations of some of the aforementioned products. The utility of vinyl halides is widely known in synthetic chemistry,[11] and the conversion to these compounds was done with a simple two-step one-purification sequence. The α-dihalocarbinol adducts were converted to the acetate and treated with SmI_2 in THF at room temperature for a clean conversion to the *Z*-vinyl halides (Scheme 4).[12] The yields and selectivities

Scheme 4. Transformations to Vinyl Halides

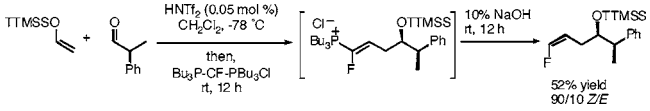


	X	% yield (*Z/E*)
1a	Br	73 (95/5)
3a	Cl	59 (85/15)
6a	I	75 (>95/5)

for the bromo and iodo derivatives were near perfect, while the chloro compound was less reactive and gave a lower selectivity as well. The α-trichlorocarbinol adduct was transformed to the vinylidene dichloride by conversion to the mesylate and subsequent treatment with In metal in refluxing DMF.[13]

In order to access the vinyl fluoride (not accessible via aforementioned route due to the difficulty in generating difluoromethyllithium), a survey of the literature uncovered a report using $CFCl_3$ and Bu_3P to generate a unique species capable of Wittig-type olefinatin to generate *Z*-vinyl fluorides.[14] This sequential reaction sequence succeeded in which the aldol reaction was followed by addition to the in situ prepared $Bu_3P{-}CF{-}PBu_3Cl$. After the mixture was stirred for 12 h, 10% NaOH was added and stirring continued for 12 h. This NaOH-induced hydrolysis of the vinyl phosphonium moiety generated the *Z*-vinyl fluoride in moderate yield with very high selectivity (Scheme 5).

Scheme 5. One-Pot Synthesis of *Z*-Vinyl Fluoride



In conclusion, we have described a sequential reaction protocol capable of generating α-polyhalomethylcarbinols in good yield with high selectivity. Clean and easy conversion to the vinyl halides is also achieved with high diastereoselectivity. The use of the super silyl group goverened aldol reaction is a key for obtaining the high selectivities. Further utility of this unique silyl group is being investigated.

Acknowledgment. M.B.B. thanks Novartis Pharmaceuticals for the ACS Division of Organic Chemistry Fellowship.

Supporting Information Available: Experimental procedures, compound characterization, and spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

OL702825P

(7) Relative stereochemistry determined by conversion to the acetonides: Rychnovsky, S. D.; Rogers, B.; Yang, G. *J. Org. Chem.* **1993**, *58*, 3511.

(8) Aldol proceeds with 86/14 Felkin selectivity. See the Supporting Information for conversion to known compounds.

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(12) Concellón, J. M.; Rodríguez-Solla, H.; Huerta, M.; Pérez-Andrés, J. A. *Eur. J. Org. Chem.* **2002**, 1839.

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