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Preparation and Use of Enantioenriched Allenylsilanes for the Stereoselective Synthesis of Homopropargylic Ethers

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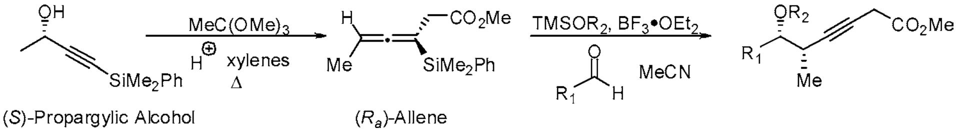
ABSTRACT



A convenient procedure for the synthesis of highly enantioenriched allenylsilanes by Johnson orthoester Claisen rearrangement of 1-silyl propargylic alcohols is described. Allenylsilanes are then used as carbon nucleophiles in three-component, Lewis acid mediated additions to in situ generated oxonium ions, resulting in enantioenriched homopropargylic ethers.

In recent years, allenes have emerged as an important functional group and have been used in a variety of organic transformations, including ionic additions,[1] cycloadditions,[2] cyclizations,[3] and sp^2-sp^2 and sp^2-sp cross-coupling processes.[4] Despite these important contributions, the chemistry of allenes remains underdeveloped. One important class of allenes that has proven to be useful is enantioenriched allenylstannanes, which have been used as carbon nucleophiles for the diastereo- and enantioselective synthesis of homopropargylic alcohols.[5]

As a complement to allenylstannane chemistry, an efficient synthesis of highly enantioenriched allenylsilanes is a desirable synthetic objective and a potentially useful contribution to the field. Like allenylstannanes, the related silanes can be used to synthesize homopropargylic alcohols.[6] These reagents share the ability to convert axial chirality into central chirality in the resulting product, by addition to carbon−heteroatom π-bonds. Chiral allenylsilanes have been prepared using Fleming's S_N2' displacement strategy;[7] the majority of the reports have used racemic reagents. The lack of general synthetic pathways to highly enantioenriched allenylsilanes may have hindered their development, and a convenient

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[1] Ma, S. In *Modern Allene Chemistry*; Krause, N., Hashmi, A. S. K., Eds.; Wiley-VCH: Weinheim, Germany, 2004; pp 595−699.

[2] Murakami, M.; Matsuda, T. In *Modern Allene Chemistry*; Krause, N., Hashmi, A. S. K., Eds.; Wiley-VCH: Weinheim, Germany, 2004, pp 727−815. (b) Mandai, T. In *Modern Allene Chemistry*; Krause, N., Hashmi, A. S. K., Eds.; Wiley-VCH: Weinheim, Germany, 2004; pp 925−972.

[3] (a) Tius, M. A. In *Modern Allene Chemistry*; Krause, N., Hashmi, A. S. K., Eds.; Wiley-VCH: Weinheim, Germany, 2004; pp 817−845. (b) Hashmi, A. S. K. *Angew. Chem., Int. Ed.* **2000**, *39*, 3590−3593. (c) Zimmer, R.; Reissig, H.-U. In *Modern Allene Chemistry*; Krause, N., Hashmi, A. S. K., Eds.; Wiley-VCH: Weinheim, Germany, 2004; pp 877−923.

[4] Zimmer, R.; Reissig, H.-U. In *Modern Allene Chemistry*; Krause, N., Hashmi, A. S. K., Eds.; Wiley-VCH: Weinheim, Germany, 2004; pp 847−876.

[5] (a) Marshall, J. A.; Wang, X.-J. *J. Org. Chem.* **1990**, *55*, 6246−6248. (b) Marshall, J. A.; Wang, X.-J. *J. Org. Chem.* **1992**, *57*, 1242−1252. (c) Marshall, J. A.; Perkins, J. *J. Org. Chem.* **1994**, *59*, 3509−3511. (d) Marshall, J. A.; Perkins, J. F.; Wolf, M. A. *J. Org. Chem.* **1995**, *60*, 5556−5559. (e) Marshall, J. A.; Palovich, M. R. *J. Org. Chem.* **1997**, *62*, 6001−6005.

[6] (a) Danheiser, R. L.; Carini, D. J. *J. Org. Chem.* **1980**, *45*, 3925−3927. (b) Danheiser, R. L.; Carini, D. J.; Kwasigroch, C. A. *J. Org. Chem.* **1986**, *51*, 3870−3878. (c) Marshall, J. A.; Maxson, K. *J. Org. Chem.* **2000**, *65*, 630−633.

[7] (a) Fleming, I.; Terrett, N. K. *J. Organomet. Chem.* **1984**, *264*, 99−118. (b) Fleming, I.; Newton, T. W. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1805−1808.

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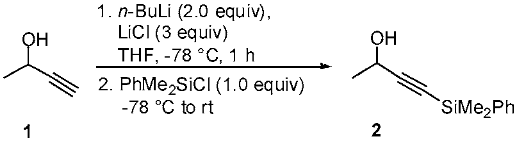
stereoselective route to the synthesis of chiral allenylsilanes remains a desirable objective.

In that regard, a convenient, straightforward pathway has been developed for the preparation of highly enantioenriched allenylsilanes. We began the synthesis with commercially available 3-butyn-2-ol (**1**), which was deprotonated using *n*-butyllithium (2 equiv) to generate a dianion. C-Silylation with phenyldimethylchlorosilane resulted in alkyne **2**, in high yield (86.3% after purification, >35 g scale). Selective C-silylation was observed, and the addition of lithium chloride resulted in nearly exclusive C-silylation. Trace amounts of bis-silylated product (<10%) were observed (^{1}H NMR analysis) in the absence of LiCl.[8]

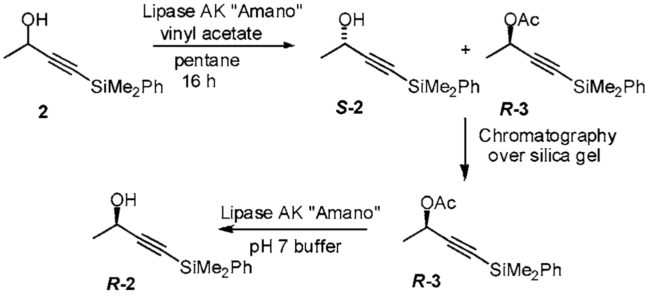
Scheme 1. Silylation of 3-Butyn-2-ol



Racemic propargylic alcohol **2** was subjected to a kinetic resolution using Amano lipase AK.[9] The advantages of employing a biocatalytic resolution are several fold: the procedure is operationally simple; both enantiomers are obtained in high ee; the reagents are readily available and inexpensive; and the enzyme can be recycled for multiple uses without losing catalytic efficiency. The resolution afforded the enantioenriched propargylic alcohol (*S*)-**2** (49% yield, >95% ee) and acetate (*R*)-**3** (48% yield) after purification over silica gel. Acetate (*R*)-**2** was hydrolyzed when re-exposed to the lipase in pH 7 aqueous buffer to afford propargylic alcohol (*R*)-**3** (77% yield, >99% ee) after purification over silica gel.[10]

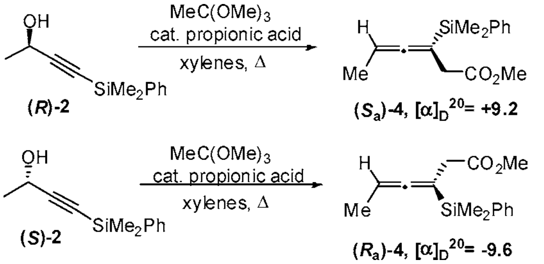
The individual propargylic alcohols (*S*)-**2** and (*R*)-**2** were then subjected to an orthoester Claisen rearrangement[9b,11] to afford the enantioenriched allenylsilanes (R_a)-**4** and (S_a)-**4**.[12] The (S_a)-allene is obtained in 81% yield and 98% ee, and the complementary (R_a)-allene is obtained in 79% yield and 98% ee.[12]

Scheme 2. Lipase Resolution



The ee's of the allenes have been determined by HPLC and, as anticipated, are nearly identical to the ee's of the starting propargylic alcohols.[13] The optimal conditions for the Claisen rearrangement were found using refluxing xylenes, while the use of toluene or other lower boiling hydrocarbon solvents resulted in low conversion. The absolute configuration of the allenylsilane is based on the concerted nature of the sigmatropic rearrangement using a pseudo-chair transition state, and accordingly, (*R*)-**2** afforded (S_a)-**4** and (*S*)-**2** afforded (R_a)-**4**.[14]

Scheme 3. Johnson Orthoester Claisen Rearrangement



Having established a reliable protocol for the production of enantioenriched allenylsilanes, we used the silanes in three-component, Lewis acid catalyzed S$_E$2′ reactions to form homopropargylic ethers.[15] By examining a series of Lewis acids that were likely to effect this reaction, we found that BF$_3$•OEt$_2$ was the most efficient catalyst. A solution of aldehyde and TMSOMe was exposed to BF$_3$•OEt$_2$, followed by addition of a solution of the allenylsilane. After performing a solvent screen, it was found that the optimal solvent for the reaction was acetonitrile (Table 1).[16]

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[8] Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1624−1654.

[9] (a) Sparks, M. A.; Panek, J. S. *Tetrahedron Lett.* **1991**, *32*, 4085−4088. (b) For assignment of absolute configuration, see: Panek, J. S.; Clark, T. D. *J. Org. Chem.* **1992**, *57*, 4323−4326 and references found therein. (c) Lipase AK available from Amano Enzyme Inc.

[10] HPLC analyses were performed using a ChiralCel OD-H column, isocratic 1% isopropanol/hexane eluent at 1mL/min flow rate.

[11] (a) Johnson, W. S.; Werthemann, L.; Bartlett, W. R.; Brocksom, T. J.; Li, T.-T.; Faulkner, D. J.; Petersen, M. R. *J. Am. Chem. Soc.* **1970**, *92*, 741−743. (b) Mori, K.; Nukanda, T.; Ebata, T. *Tetrahedron* **1981**, *37*, 1343−1347.

[12] For other examples of orthoester Claisen rearrangements to access allenes, see: (a) Allenylstannanes: Marshall, J. A.; Wang, X.-j. *J. Org. Chem.* **1991**, *56*, 3211−3213. (b) Racemic allenylsilanes: Yun, S.-J.; Chung, K. H.; Yu, B.-C. *J. Korean Chem. Soc.* **2004**, *48*, 439−442.

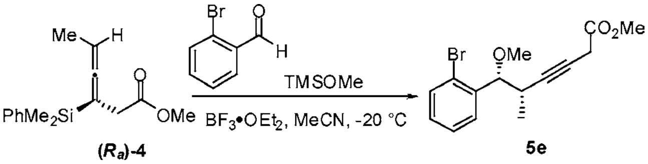
[13] Ziegler, F. E. *Acc. Chem Res.* **1977**, *10*, 227−232. HPLC analyses were performed after conversion of the methyl ester to a carboxylic acid (LiOH in H$_2$O/MeOH) using a ChiralPak AD column, isocratic 1% isopropanol/hexane eluent at 1mL/min flow rate.

[14] See Supporting Information for a detailed description.

[15] Panek, J. S.; Yang, M.; Xu, F. *J. Org. Chem.* **1992**, *57*, 5790−5792.

[16] No product was observed in THF, diethyl ether, or DMF; −20 °C was found to be the best temperature for the reaction, as lower temperatures resulted in an incomplete reaction, with recovered staring materials.

Table 1. Solvent Screen



(R_a)-4

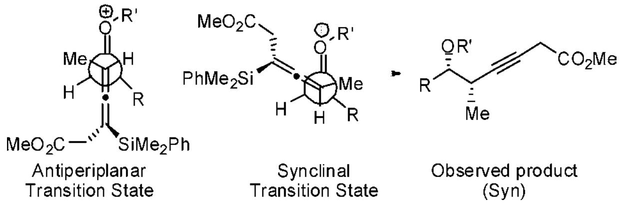
5e

solvent	temp	yield[a]	dr[b]
MeCN	−20 °C	78%	>20:1
MeNO$_2$	−20 °C	49%	>20:1
DCM	−20 °C	11%	>20:1
Toluene	−20 °C	<5%	>20:1
MeCN	−45 °C	44%	>20:1

[a] Isolated yield after chromatographic purification over silica gel. [b] Diastereomeric ratios (dr) were determined by ^{1}H NMR analysis.

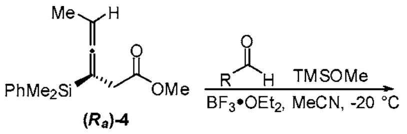
The observed *syn* stereochemistry can be explained by either an antiperiplanar or a synclinal transition state (Scheme 4), where the (R_a)-allenylsilane adds to the *Re* face of the oxonium ion. While either transition state will result in the observed stereochemistry, the antiperiplanar transition state, where the interaction between the R group on the oxonium ion and the methyl on the allene is minimized, may be the best illustration of this reaction.

Scheme 4. Transition State Models



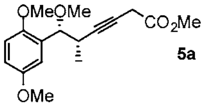
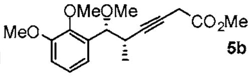
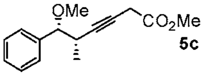
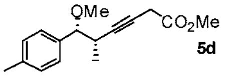
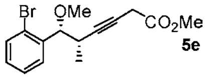
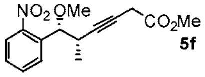
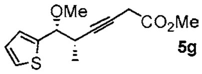
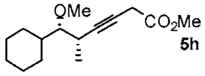
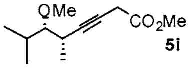
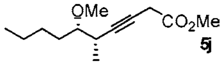
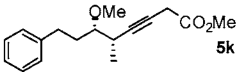
Aromatic aldehydes afforded the highest yields and selectivities in the three-component reactions using TMSOMe as the oxonium ion precursor (Table 2, entries 1−6), with yields as high as 78%, and a single diastereomer observed for many of the systems. Branched aliphatic aldehydes (entries 8 and 9) also gave the homopropargylic ethers in high selectivity, albeit in moderate yield. Straight chain aliphatic systems typically gave low yields and selectivities (entries 10 and 11). Thiophenecarboxaldehyde (entry 7), a heteroaromatic system, showed reactivity and good yield (54%), but the diastereoselectivity was low (2.7:1).

Table 2. Three-Component Reactions with TMSOMe



(R_a)-4

5

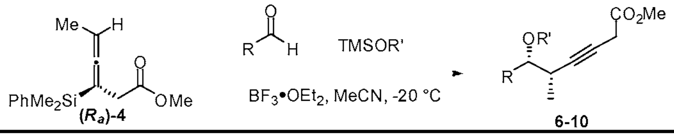
entry	aldehyde	yield[a]	dr[b]	product
1	2,5-Dimethoxybenzaldehyde	69%	>20:1	 5a
2	2,3-Dimethoxybenzaldehyde	61%	10:1	 5b
3	Benzaldehyde	54%	6:1	 5c
4	p-Tolualdehyde	49%	>20:1	 5d
5	2-Bromobenzaldehyde	78%	>20:1	 5e
6	2-Nitrobenzaldehyde	54%	>20:1	 5f
7	2-Thiophenecarboxaldehyde	54%	2.7:1	 5g
8	Cyclohexanecarboxaldehyde	45%	>20:1	 5h
9	Isobutyraldehyde	42%	>20:1	 5i
10	Valeraldehyde	43%	1.8:1	 5j
11	Hydrocinnamaldehyde	43%	2.1:1	 5k

[a] Isolated yields reported as a diastereomeric mixture after purification over silica gel. [b] Diastereomeric ratios (dr) were determined by ^{1}H NMR analysis.

More complex trimethylsilyl ethers were also effective in generating oxonium ions for these reactions (Table 3). These include primary allylic and benzylic ethers (entries 1−6) and select secondary ethers (entries 7−10). The latter cases are illustrative of examples of double stereodifferentiation, where the magnitude of diastereoselectivity is either enhanced (matched cases) or attenuated (mismatched cases). In general, the yields for these reactions were similar to those using TMSOMe, but the diastereoselectivities tended to be slightly lower.

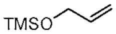
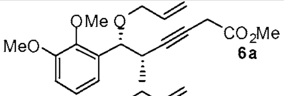
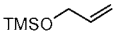
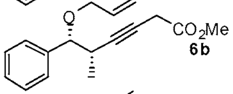
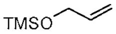
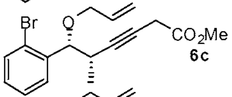
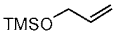
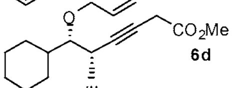
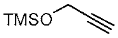
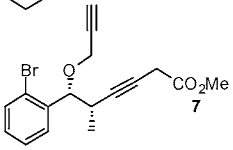
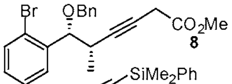
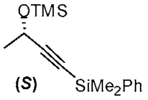
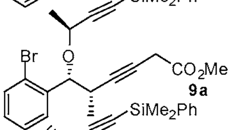
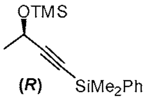
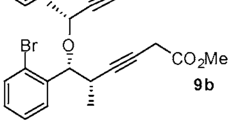
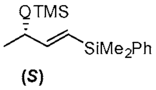
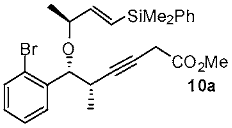
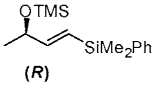
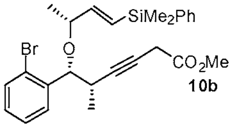
In conclusion, an efficient procedure for the preparation of highly enantioenriched allenylsilanes (>97% ee) with high yields on a multigram scale is reported. The allenylsilanes were used as carbon nucleophiles in three-component, Lewis acid catalyzed additions to in situ generated oxonium ions for the asymmetric synthesis of a range of structurally diverse homopropargylic ethers. The use of these reagents in complex molecule synthesis will be reported at a later time.

Table 3. Three-Component Reactions with Other TMS Ethers



(R_a)-4

6-10

entry	aldehyde	TMS ether	yield[a]	dr[b]	product
1	2, 3-Dimethoxybenzaldehyde		77%	10:1	 **6a**
2	Benzaldehyde		46%	6:1	 **6b**
3	2-Bromobenzaldehyde		78%	>20:1	 **6c**
4	Cyclohexanecarboxaldehyde		34%	>20:1	 **6d**
5	2-Bromobenzaldehyde		56%	12:1	 **7**
6	2-Bromobenzaldehyde	TMSOBn	60%	>20:1	 **8**
7	2-Bromobenzaldehyde		69%	>20:1	 **9a**
8	2-Bromobenzaldehyde		56%	5:1	 **9b**
9	2-Bromobenzaldehyde		64%	15:1	 **10a**
10	2-Bromobenzaldehyde		49%	10:1	 **10b**

[a] Isolated yields reported as a diastereomeric mixture after purification over silica gel. [b] Diastereomeric ratios (dr) were determined by ^{1}H NMR analysis.

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Supporting Information Available: Experimental details and selected spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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