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# Regioselective Intramolecular Dipolar Cycloaddition of Azides and Unsymmetrical Alkynes

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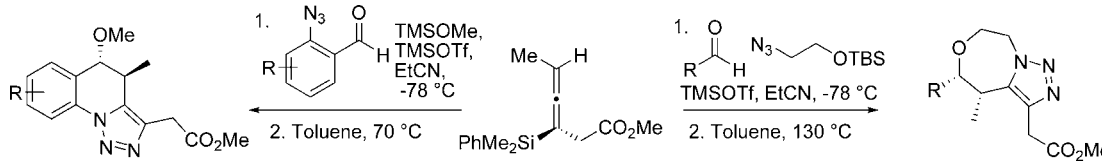
## ABSTRACT




**Enantioenriched allenylsilanes are used in three-component propargylation reactions with aldehydes and silyl ethers to form *syn*-homopropargylic ethers that contain an imbedded azide. These materials then undergo thermally induced intramolecular 1,3-dipolar cycloaddition reactions, resulting in unique fused ring systems containing 1,2,3-triazoles. The ability to modify all three components of the reaction allows for expedient access to compounds containing significant structural and stereochemical variation.**

Recent advancements in the Huisgen 1,3-dipolar cycloaddition reaction have led to a renewed interest in its application in the synthesis of 1,2,3-triazoles.[1] Small molecules containing a triazole functionality have been shown to exibit a range of biological functions, including antitumor, antibacterial, antiparasitic, and antiviral activity (Figure 1).[2]

Historically terminal and symmetrically substituted alkynes have been used predominantly in these reactions since unsymmetrical alkynes often result in diminished reaction rates and poor regioselectivity.[3] One solution to this problem is a tandem dipolar cycloaddition/cross coupling reaction, which can access fully substituted triazoles.[4] Another approach is an intramolecular cycloaddition, where the regioselectivity is determined by the

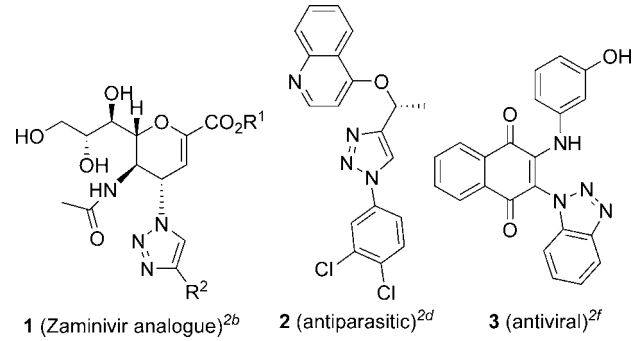



**Figure 1.** Representative examples of biologically active molecules containing 1,2,3-triazoles.

(1) (a) Huisgen, R. *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984. (b) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004–2021. (c) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596–2599. (d) Kelly, A. R.; Wei, J.; Kesavan, S.; Marié, J.-C.; Windmon, N.; Young, D. W.; Marcaurelle, L. A. *Org. Lett.* **2009**, *11*, 2257–2260. (e) Spiteric, C.; Moses, J. E. *Angew. Chem., Int. Ed.* **2009**, *48* (early view DOI, 10.1002/anie.200905322).

(2) (a) Lewis, W. G.; Green, L. G.; Grynszpan, F.; Radiæ, Z.; Carlier, P. R.; Taylor, P.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 1053–1057. (b) Tron, G. C.; Pirali, T.; Billington, R. A.; Canonico, P. L.; Sorba, G.; Genazzani, A. A. *Med. Res. Rev.* **2008**, *28*, 278–308. (c) Lee, T.; Cho, M.; Ko, S.-Y.; Youn, H.-J.; Baek, D. J.; Cho, W.-J.; Kang, C.-Y.; Kim, S. *J. Med. Chem.* **2007**, *50*, 585–589. (d) Maurya, S. K.; Gollapalli, D. R.; Kirubakaran, S.; Zhang, M.; Johnson, C. R.; Benjamin, N. N.; Hedstrom, L.; Cuny, G. D. *J. Med. Chem.* **2009**, *52*, 4623–4630. (e) Kolb, H. C.; Sharpless, K. B. *Drug Discovery Today* **2003**, *8*, 1128–1137. (f) Puig-Basagoiti, F.; Qing, M.; Dong, H.; Zhang, B.; Zou, G.; Yuan, Z.; Shi, P.-Y. *Antiviral Res.* **2009**, *83*, 71–79.

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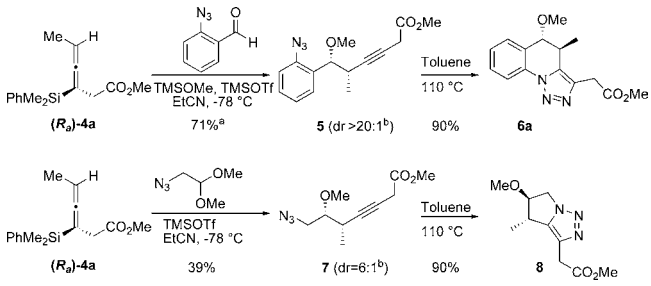
initial positions of the azide and alkyne in the starting material.[5] While both of these strategies have proven to be useful, methods for the formation of fully functionalized triazoles remain underdeveloped.

We have recently reported a three-component reaction of enantioenriched allenylsilanes with aldehydes and silyl ethers, resulting in highly functionalized *syn*-homopropargylic ethers.[6] In our continued interest in developing these allenes as chiral carbon nucleophiles,[7] we sought to further expand the use of the resulting homopropargylic ethers by incorporating a pendant azide moiety which will further react to provide heterocycles containing fused 1,2,3-triazoles. In this paper, we describe the development of a three-component propargylation/cycloaddition strategy to give access to densely functionalized fused triazole ring systems.

The propargylation of enantioenriched allenylsilane **(*R*$_a$)-4a** with 2-azidobenzaldehyde[8] and methoxytrimethylsilane (TMSOMe), promoted by TMSOTf, resulted in the formation of alkyne **5** in 71% yield as a single observed diastereomer (Scheme 1). Heating alkyne **5** in toluene at 110 °C promoted

**Scheme 1.** Two-Step Triazole Formation[a,b]




[a] Isolated yields after purification over silica gel. [b] Diastereomeric ratios determined by $^1$H NMR analysis on crude material.

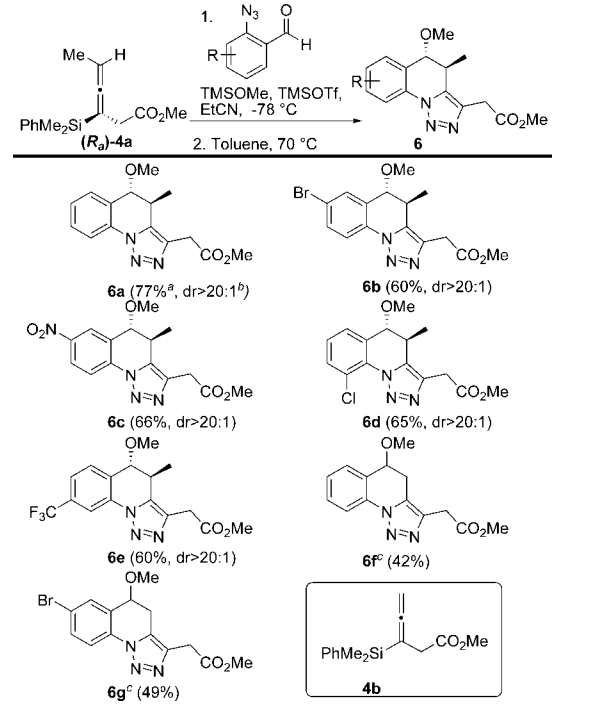
the desired dipolar cyclization reaction, resulting in the formation of triazole **6a** in 90% yield. As anticipated, a single regioisomer of the desired triazole was observed.

A similar experiment was conducted with 2-azidoacetaldehyde dimethylacetal (Scheme 1). Due to concerns with volatility and stability, the preformed acetal was used instead of the aldehyde. The propargylation reaction provided homopropargylic ether **7**, and heating this product in toluene gave desired triazole **8** in 90% isolated yield. This reaction sequence demonstrates that the methodology can be expanded to aliphatic systems using acetals with imbedded azides.

When this strategy was applied to more substituted azidobenzaldehydes, we observed that some of the triazole product was formed in the crude propargylation reaction mixture.[8] Attempts to purify these propargylation products proved difficult, as the triazole product would be observed in postchromatographic NMR spectra. This observation led to the development of a two-step sequence where the propargylation reaction was quenched, and the crude product was heated to 70 °C in toluene, to directly produce the desired triazole product.

This modified procedure gave the desired tricyclic system with an imbedded triazole **6** in good yield and high diastereoselectivity (Scheme 2). The reactions were tolerant

**Scheme 2.** One-Pot Propargylation/Cycloaddition[a,b]




[a] Isolated yields after purification over silica gel. [b] Diastereomeric ratios determined by $^1$H NMR analysis on crude material. [c] Reaction run using achiral allenylsilane **4b**.

to a range of functionality on the aromatic ring, including electron-donating and -withdrawing groups. When achiral allenylsilane **4b** was subjected to the same reaction conditions, products **6f** and **6g** were formed in moderate yield.

Further structural variation was achieved by using silyl ether reaction partners containing an azide functionality (Table 1). The silyl-protected 2-azidoethanol could be prepared from 2-bromoethanol in two steps using a known

(3) (a) Zhang, L.; Chen, X.; Xue, P.; Sun, H. H. Y.; Williams, I. D.; Sharpless, K. B.; Fokin, V. V.; Jia, G. *J. Am. Chem. Soc.* **2005**, *127*, 15998–15999. (b) Majireck, M. M.; Weinreb, S. M. *J. Org. Chem.* **2006**, *71*, 8680–8683.

(4) (a) Ackermann, L.; Potukuchi, H. K.; Landsberg, D.; Vicente, R. *Org. Lett.* **2008**, *10*, 3081–3084. (b) Chowdhury, C.; Mukherjee, S.; Das, B.; Achari, B. *J. Org. Chem.* **2009**, *74*, 3612–3615.

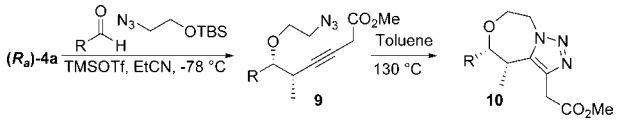
(5) (a) Pearson, W. H.; Bergmeier, S. C.; Chytra, J. A. *Synthesis* **1990**, 156–159. (b) Oliva, A. I.; Christmann, U.; Font, D.; Cuevas, F.; Ballester, P.; Buschmann, H.; Torrens, A.; Yenes, S.; Pericás, M. A. *Org. Lett.* **2008**, *10*, 1617–1619. (c) Balducci, E.; Bellucci, L.; Petricci, E.; Taddei, M.; Tafi, A. *J. Org. Chem.* **2008**, *74*, 1314–1321.

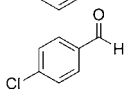
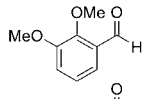
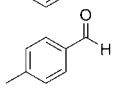
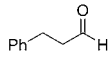
(6) Brawn, R. A.; Panek, J. S. *Org. Lett.* **2007**, *9*, 2689–2692.

(7) For a recent review on chiral organosilanes in diversity oriented synthesis, see: Shaw, J. *Nat. Prod. Rep.* **2009**, *26*, 11–26.

(8) For the synthesis of functionalized 2-azidobenzaldehydes, see: (a) Pelkey, E. T.; Gribble, G. W. *Tetrahedron Lett.* **1997**, *38*, 5603–5606. (b) Main, C. A.; Petersson, H. A.; Rahman, S. S.; Hartley, R. C. *Tetrahedron* **2008**, *64*, 901–914. (c) Cuevas, J. C.; De Mendoza, J.; Prados, P. *J. Org. Chem.* **1988**, *53*, 2055–2066.

**Table 1.** Propargylations with TBS 2-Azidoethanol




| entry | aldehyde (R) | product **9** (yield[a]; dr[b]) | product **10** (yield[a]) |
|---|---|---|---|
| 1 |  | **9a** (72%; 18:1) | **10a** (71%) |
| 2 |  | **9b** (89%; >20:1) | **10b** (75%) |
| 3 |  | **9c** (76%; 15:1) | **10c** (76%) |
| 4 |  | **9d** (87%; >20:1) | **10d** (74%) |
| 5 |  | **9e** (74%; >20:1) | **10e** (66%) |
| 6 |  | **9f** (76%; 15:1) | **10f** (74%) |
| 7 |  | **9g** (60%; >20:1) | **10g** (75%) |
| 8 |  | **9h** (37%; 5:1) | **10h** (57%) |
| 9 |  | **9i** (16%; >20:1) | **10i** (80%) |

[a] Isolated yields after purification over silica gel. [b] Diastereomeric ratios determined by $^1$H NMR analysis on crude material.

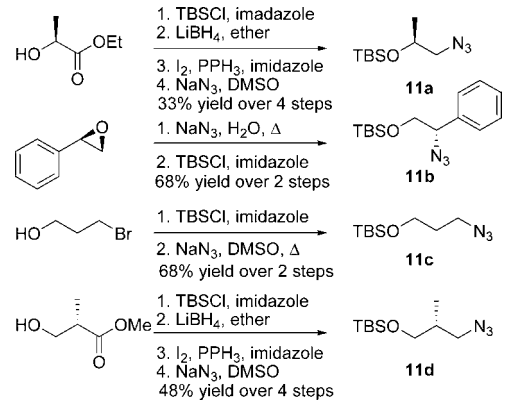
procedure.[9] The TBS ether was explored after the TMS version proved to be difficult to work with due to its inherent volatility.

The propargylation reaction of allenylsilane **($R_a$)-4** with aldehydes and silyl-protected 2-azidoethanol resulted in the formation of *syn*-homopropargylic ethers **9a**−**i**. High yields and selectivities were obtained for a variety of aromatic aldehydes (entries 1−6). The use of aliphatic aldehydes in this reaction sequence resulted in lower yields (entries 7−9) and lower selectivity for the unbranched system (entry 8).

For all of the examples studied, heating the reaction products to 130 °C in toluene gave the desired triazoles **10a**−**i** in good yield.[10] None of the triazole products were observed after the propargylation reaction, as the alkyne products were stable at room temperature, and as expected, the dipolar cyclizations proceeded with complete regioselectivity.

To expand the scope of this methodology, we synthesized four additional azidosilyl ethers (Scheme 3) which

**Scheme 3.** Silyl Ether Synthesis




would allow access to fused triazole systems with greater complexity.[11] Silyl ether **11a** was prepared in four steps from (*S*)-ethyl lactate and contains a chiral center on the carbon with the silyl ether. Silyl ether **11b**, derived from the epoxide opening of (*R*)-styrene oxide, has a chiral center on the carbon containing the azide. TBS-protected 3-azidopropanol **11c** was prepared from 3-bromopropanol using the same procedure as TBS-protected 2-azidoethanol. Finally, the 3-carbon silyl ether containing a chiral center at C2 (**11d**) was accessed using commercially available (*S*)-methyl-3-hydroxy-2-methylpropanpoate in four steps. These procedures are all general and relatively straightforward, allowing for the rapid incorporation of stereochemical variation into the synthesis of the desired fused triazole systems.

Propargylation reactions with **11a** proceeded in good yield, but with a significant loss of diastereoselctivity when the ($R_a$) enantiomer of allenylsilane **4a** was used (Scheme 4, **12a**+**b**). When the ($S_a$) enantiomer of the allenylsilane was used, the diasteroselectivity was substantially higher (Scheme 4, **12c**+**d**), exhibiting a "matched pair" of reaction partners in a double stereodifferentiating reaction. The cycloadditions proceeded with moderate to high yield, although the products of matched cases (**13c**+**d**) showed higher yields than the mismatched cases (**13a**+**b**).[12]

When the silyl ether's chiral center was located on the carbon bearing the azide, the diastereoselectivity of the reaction products was not effected by switching the enantiomer of the allene. Propargylations with silyl ether **11b** gave high yields and diastereoselectivities with both enantiomers (Scheme 4, **12e**−**h**). The cycloadditions also proceeded in similar yields for the different diastereomers (Scheme 4, **13e**−**h**), with moderate yields obtained in all cases.

Propargylations with the three-carbon silyl ether **11c** proceeded with good yield and excellent diastereoselectivity (Scheme 4, **12i**+**j**). While the reactions were

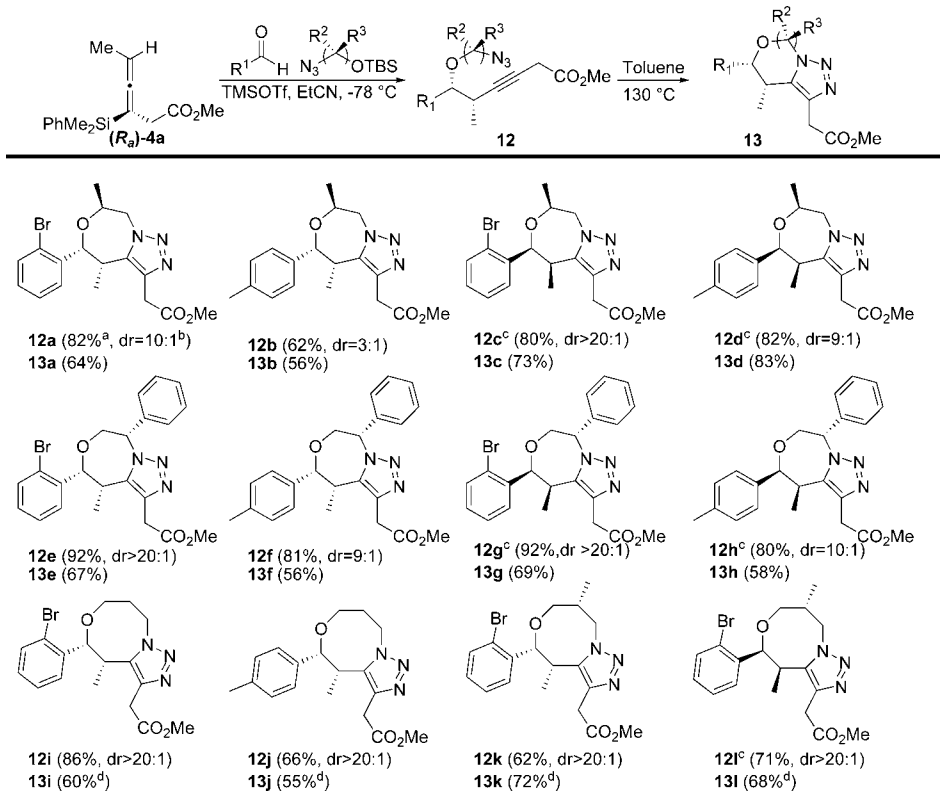
(9) Smith, R. H.; Mehl, A. F.; Shantz, D. L.; Chmurny, G. N.; Michejda, C. J. *J. Org. Chem.* **1988**, *53*, 1467–1471.

(10) All of the dipolar cycloaddition reactions were run in a sealed tube. No reactivity was observed using the copper(I) catalyst systems which have been previously reported.

(11) For the synthesis of these silyl ethers, see the Supporting Information.

(12) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed.* **1985**, *24*, 1.

**Scheme 4.** Propargylations and Dipolar Cycloadditions with Substituted Silyl Ethers[a,b]




[a] All yields refer to isolated products after purification over silica gel. [b] All diastereomeric ratios were determined by $^1$H NMR analysis on crude material. [c] The ($S_a$) enantiomer of the allenylsilane **1** was used for the propargylation reaction. [d] Cycloaddition reaction run in chlorobenzene at 150 °C.

sluggish in toluene, switching the solvent to chlorobenzene at 150 °C resulted in significantly higher yields for **13i**+**j**. Use of silyl ether **11d**, which contained a stereocenter at C2, had no effect on the selectivity, as the products were formed in good yields as a single observed diasteromer regardless of which enantiomer of allenylsilane **4a** was used (Scheme 4, **12k**+**l**).

In conclusion, we have reported a tandem propargylation/dipolar cycloaddition sequence to rapidly construct structurally and stereochemically diverse fused ring systems containing 1,2,3-triazoles. Continued exploration of these ring systems, along with preliminary biological evaluation, is currently in progress.

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**Supporting Information Available:** Experimental data 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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