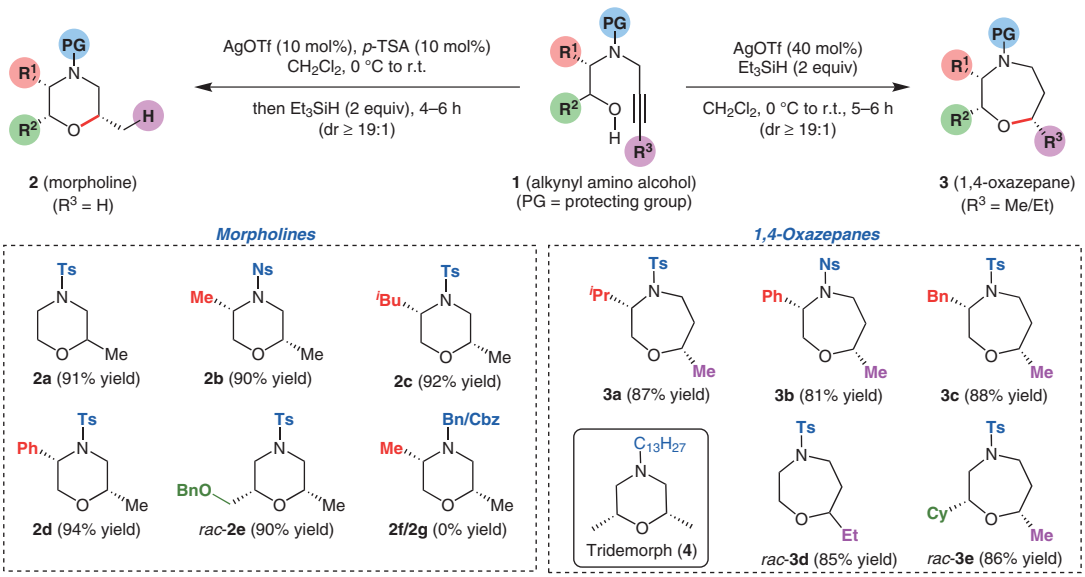
S. J. GHARPURE*, D. KALITA, S. SOMANI, J. PAL (INDIAN INSTITUTE OF TECHNOLOGY BOMBAY, MUMBAI, INDIA)

Deciphering Substitution Effects on Reductive Hydroalkoxylation of Alkynyl Aminols for Stereoselective Synthesis of Morpholines and 1,4-Oxazepanes: Total Synthesis of Tridemorph and Fenpropimorph
Org. Biomol. Chem. **2024**, *22*, 5529–5533, DOI: 10.1039/D4OB00855C.

Substituent-Directed Cycloisomerization Reduction Cascade for Synthesizing Oxacycles



Significance: Pharmaceutical research widely uses morpholines and oxazepanes as building blocks for the fine-tuning or enhancement of pharmacological properties of the intended drug molecules. Many methods are available for the synthesis of these 1,4-heterocycles; however, *intra*molecular cyclization to form these oxacycles through hydroalkoxylation of alkynes is not completely explored (e.g., S. V. Ley and co-workers *Angew. Chem. Int. Ed.* **2008**, *47*, 209). Here, oxacycles are formed not only in diastereoselective fashion but also with complete control over the regioselectivity, which was governed by using terminal or internal alkynes. The *intra*molecular hydroalkoxylation–cycloisomerization reduction cascade was further utilized in the synthesis of agrochemicals, namely tridemorph (**4**) and fenpropimorph.

Comment: *N*-Sulfonylated alkynyl amino alcohols **1** furnished the desired morpholines **2a–e**, while the benzyl- or Cbz-protected alkynols (**1f,g**) failed to afford any products (**2f,g**). The optimized reaction conditions using catalytic amounts of Ag(OTf) provided the products in excellent yield and with exquisite diastereoselectivity (dr ≥ 19:1). Likewise, 1,4-oxazepanes **3a–e** were prepared in good yields and with high diastereoselectivity (dr ≥ 19:1) with internally placed alkynes. Mechanistically, morpholines **2** were formed through 6-*exo*-dig hydroalkoxylation–cyclization of terminal alkynes followed by reduction with Et_3SiH, whereas 1,4-oxazepanes **3** were formed via hydration of internal alkynes following a 7-*endo*-dig cyclization pathway and then reduction with Et_3SiH. Overall, this heterocyclomerization protocol could be a good addition to the toolbox for the stereoselective construction of desirable O/N/S-heterocycles in drug discovery research.

SYNFACTS Contributors: Mark A. Reed, Prashant S. Deore (Paraza Pharma)
Synfacts 2024, 20(10), 1019 Published online: 13.09.2024
DOI: 10.1055/s-0043-1775347; **Reg-No.:** V11324SF

Category
Synthesis of Heterocycles

Key words
hydroalkoxylation
cycloisomerization
morpholines
1,4-oxazepanes

Synfact of the Month