

SYNFACTS Highlights in Current Synthetic Organic Chemistry

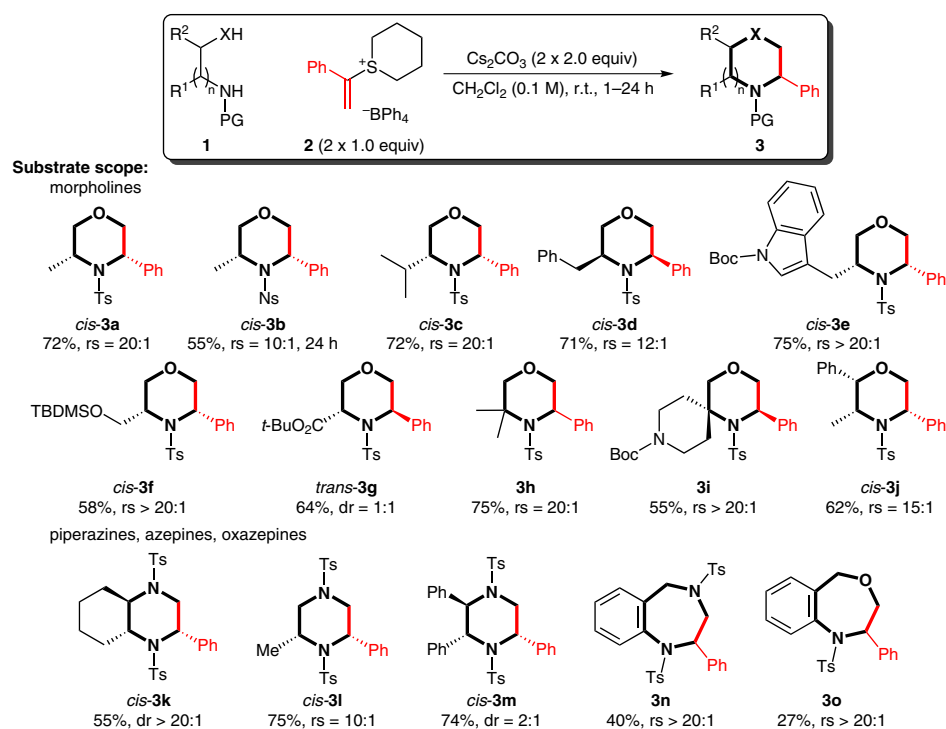
This electronic reprint is provided for non-commercial and personal use only: this reprint may be forwarded to individual colleagues or may be used on the author's homepage. This reprint is not provided for distribution in repositories, including social and scientific networks and platforms.

Publishing House and Copyright:

© 2015 by
Georg Thieme Verlag KG
Rüdigerstraße 14
70469 Stuttgart
ISSN 1861-1958

Any further use
only by permission
of the Publishing House

Synthesis of Six- and Seven-Membered Heterocycles



Significance: Reported is a highly regio- and diastereoselective synthesis of morpholines **3** from N-protected amino alcohols **1** (PG = protecting group) and the α -phenylvinylsulfonium salt **2**; the method can also be used to prepare piperazines, azepines, or oxazepines. Cs_2CO_3 was required for high diastereoselectivity, the optimum yields being obtained by batchwise addition of both the base and salt **2**. No desired product was formed when PG = Boc, Cbz, Troc, Bn, or COCF_3 , whereas PG = nosyl led to a lower yield and regioselectivity. A variety of R^1 groups were well tolerated, whereas $\text{R}^2 = \text{Me}$ led to diminished diastereoselectivity. The structure of *cis-3a* was confirmed by single-crystal X-ray analysis.

Comment: Given the importance of six- and seven-membered heterocycles in pharmaceutically relevant compounds, the development of synthetic routes to compounds of type **3** is desirable (R. Wijtman, M. K. S. Vink, H. E. Schoemaker, F. L. van Delft, R. H. Blaauw, F. P. T. Rutjes *Synthesis* **2004**, 641). The method described has advantages over previous methods and involves simple operations. In this regard, a comparable yield and selectivity were observed in a gram-scale synthesis of *cis-3a* (72%, rs = 20:1), without the need for anhydrous conditions. Furthermore, deprotection of *cis-3a* and *cis-3b* to the corresponding hydrochloride salts was demonstrated in high yields (86–92%). A plausible rationale for the observed selectivity is provided.