S. ZHUO, T. ZHU, L. ZHOU, C. MOU, H. CHAI, Y. LU, L. PAN*, Z. JIN, Y. R. CHI* (NANYANG TECHNOLOGICAL UNIVERSITY, SINGAPORE; GUIYANG COLLEGE OF TRADITIONAL CHINESE MEDICINE AND GUIZHOU UNIVERSITY, GUIYANG, P. R. OF CHINA)

Access to All-Carbon Spirocycles through a Carbene and Thiourea Cocatalytic Desymmetrization Cascade Reaction
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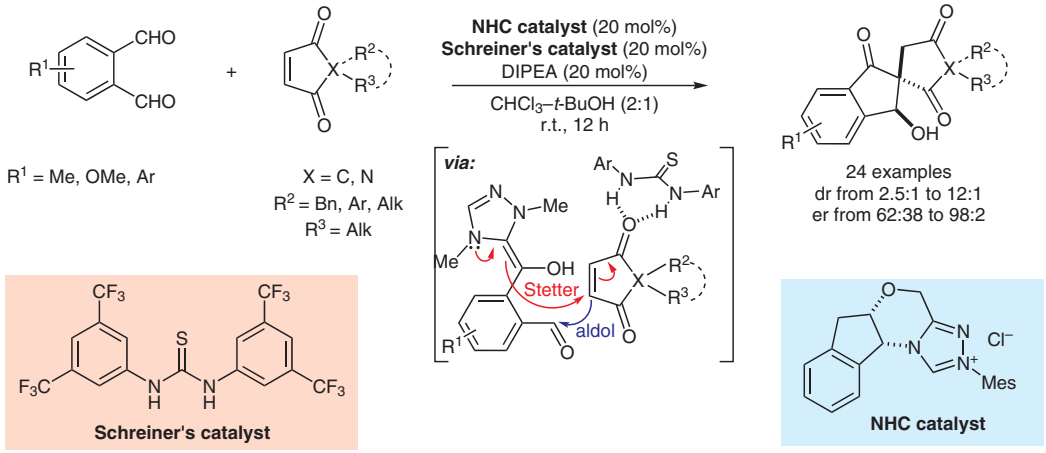
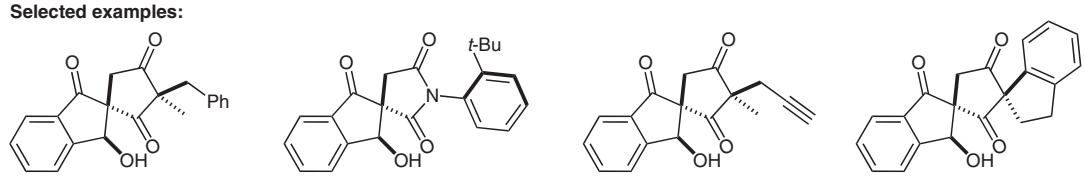
Asymmetric Synthesis of All-Carbon Spirocycles by a Stetter/Aldol Cascade



Selected examples:



63% yield
dr = 9:1
er = 96:4

56% yield
dr = 2.5:1
er = 94:6

44% yield
dr = 4:1
er = 62:38

37% yield
dr = 4:1
er = 81:19

Significance: Pan, Chi, and co-workers report an asymmetric carbene- and thiourea-cocatalyzed desymmetrizing cascade reaction to form all-carbon spirocycles in a single step. The process initiates with an intermolecular Stetter reaction catalyzed by an NHC catalyst, followed by an intramolecular aldol reaction; the latter of which is suggested to be promoted by the substrate's hydrogen-bonding network with the thiourea cocatalyst. The authors demonstrate the utility of the resulting enantioenriched spirocycles by further functionalizing the products to give polycyclic molecules as well as chiral phosphite ligands.

Comment: Biaryl-based chiral ligands and organocatalysts have long dominated asymmetric methods that utilize axially chiral scaffolds. However, a unique feature of spirocycles in relation to biaryl systems is that they are configurational more stable and therefore theoretically, at least, more practical (see: V. B. Birman, A. L. Rheingold, K.-C. Lam *Tetrahedron: Asymmetry* **1999**, *10*, 125). Therefore, the limited use of spirocycles in asymmetric catalysis has likely not been a consequence of their lack of efficiency, but rather the insufficient practicality and modularity of their synthesis. While many approaches depend on a chiral resolution of the corresponding racemate, the authors herein report a novel and straightforward approach to the synthesis of enantioenriched spirocyclic molecules, including those bearing up to two spirocyclic centers.

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Category

Organo- and Biocatalysis

Key words

spirocycles
carbene catalysis
thiourea catalysis
desymmetrization
Stetter/aldol cascade
cascade reaction