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Catalytic Enantio- and Diastereoselective Domino Halocyclization and Spiroketalization
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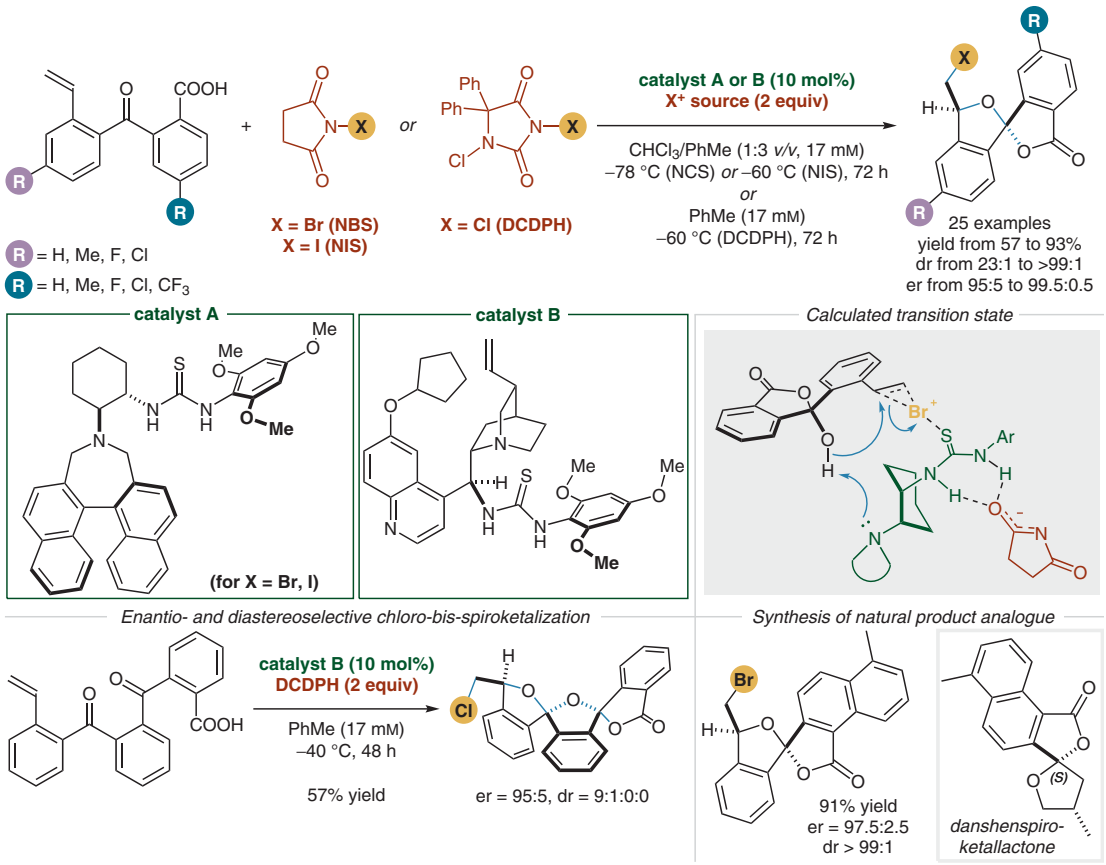
Bifunctional Thiourea Organocatalyst Enables a Halocyclization and Spiroketalization Cascade



Significance: Tse, Yeung, and co-workers report an enantio- and diastereoselective domino halocyclization and spiroketalization of styryl keto acids. In the presence of an electron-rich bifunctional thiourea organocatalyst and the appropriate electrophilic halogen source, the corresponding spirocyclic products are obtained in good to excellent yields and with excellent diastereo- and enantioselectivities. The method can be extended toward an enantio- and diastereoselective chloro-dispiroketalization. Additionally, the authors demonstrate its applicability in the synthesis of structural analogues of danshenspiroketallactone, a naturally occurring monobenzannulated 5,5-spiroketal.

Comment: The reported method expands the toolbox of catalytic asymmetric electrophilic halocyclizations, which previously focused on polyenes as substrates to provide fused-ring systems (R. C. Samanta, H. Yamamoto *J. Am. Chem. Soc.* **2017**, *139*, 1460). Mechanistic studies suggest that the transformation involves a dynamic kinetic resolution of the hemiketal form of the starting material, followed by activation of the halogen and asymmetric halocyclization. Intriguingly, an electron-rich thiourea catalyst is required for high enantioselectivities as opposed to its commonly used electron-deficient congeners. The authors propose that electron-donating substituents lead to an enhanced interaction between the halogen source and the sulfur atom of the thiourea.

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Organo- and Biocatalysis

Key words
halocyclization
spirocyclization
hydrogen-bond donor catalysis
dynamic kinetic resolution
cascade reaction

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