Y. GE, Z. HAN, Z. WANG, K. DING* (SHANGHAI INSTITUTE OF ORGANIC CHEMISTRY, P. R. OF CHINA)

Ir-Catalyzed Double Asymmetric Hydrogenation of 3,6-Dialkylidene-2,5-diketopiperazines for Enantioselective Synthesis of Cyclic Dipeptides
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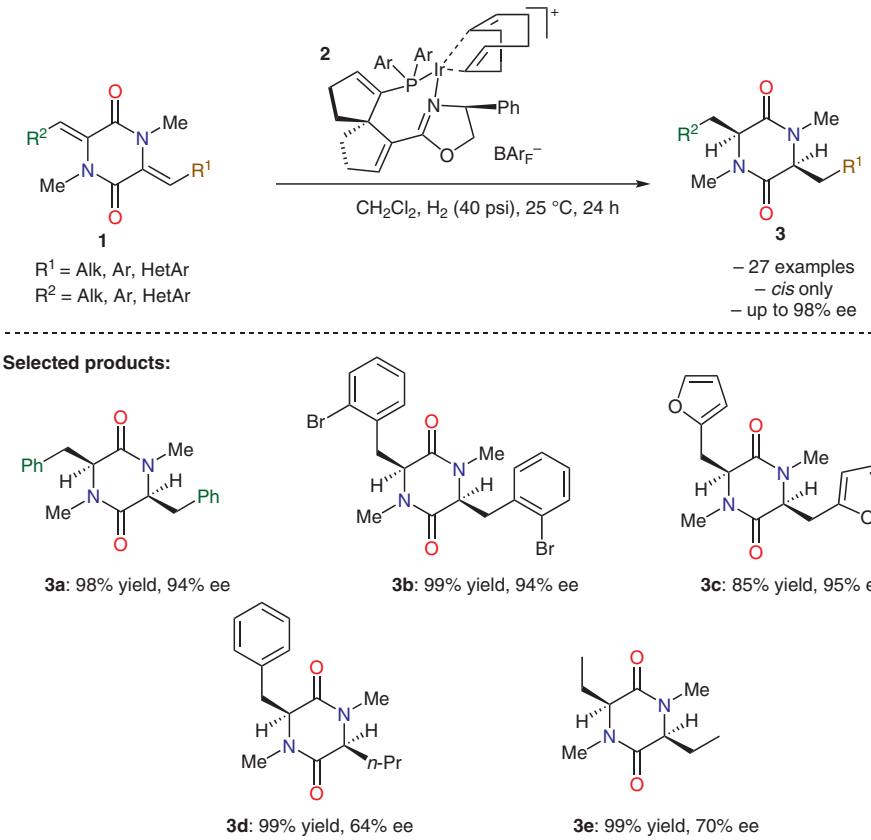
Enantioselective Synthesis of Cyclic Dipeptides by Iridium-Catalyzed Hydrogenation



Significance: The 2,5-dioxopiperazine motif, also known as a cyclic dipeptide, is found in compounds possessing biological activity, such as retosiban and fumitremorgin C (see first Review below). In addition, the motif has found utility in asymmetric synthesis as a chiral auxiliary or organocatalyst (see second Review below; C. Becker et al. *Eur. J. Org. Chem*. **2005**, 1497). The synthesis of the ring system is usually accomplished by careful cyclization of protected acyclic peptide precursors. Other methods exist, including asymmetric alkylation of 2,5-diketopiperazines and, to a limited degree, asymmetric reduction of compounds similar to **1** by cobalt catalysis in the total synthesis of an alkaloid (S. Takeuchi et al. *Heterocycles* **1990**, *31*, 2073).

Comment: In the current method, the asymmetric reduction of compounds **1** to give dioxopiperazines **3** in high yields with ee values of up to 98% and exclusive formation of the *cis* diastereomer. The optimal catalyst [SpinPHOX/Ir(I)] was identified by screening a series of ligands. The scope of the reduction is exemplified by products **3a–e**. A mechanism that rationalizes the high ee values observed is proposed in which two C=C double bonds of the substrate are hydrogenated successively while bound to the iridium center.

Reviews: 1. A. D. Borthwick *Chem. Rev*. **2012**, *112*, 3641–3716; 2. E. A. Colby Davie, S. M. Mennen, Y. Xu, S. J. Miller *Chem. Rev*. **2007**, *107*, 5759–5812.

SYNFACTS Contributors: Victor Snieckus, John I. Trujillo (Pfizer)
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Synthesis of Heterocycles

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