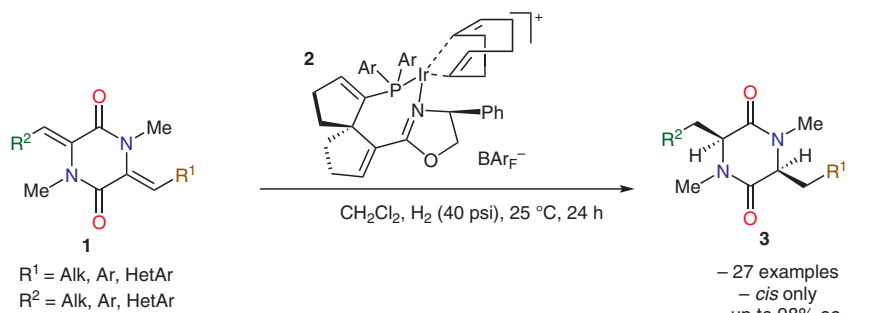


Y. GE, Z. HAN, Z. WANG, K. DING\* (SHANGHAI INSTITUTE OF ORGANIC CHEMISTRY, P. R. OF CHINA)

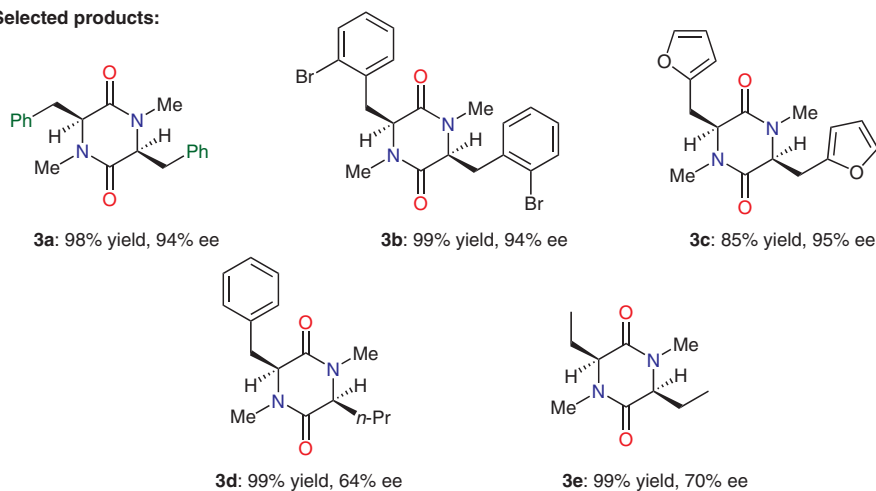
Ir-Catalyzed Double Asymmetric Hydrogenation of 3,6-Dialkylidene-2,5-diketopiperazines for Enantioselective Synthesis of Cyclic Dipeptides

*J. Am. Chem. Soc.* **2019**, *141*, 8981–8988.

## Enantioselective Synthesis of Cyclic Dipeptides by Iridium-Catalyzed Hydrogenation



### Selected products:



**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)  
Synfacts 2019, 15(10), 1105 Published online: 17.09.2019  
DOI: 10.1055/s-0039-1690979; Reg-No.: V11319SF

© 2019, Thieme. All rights reserved.  
Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

Category

Synthesis of Heterocycles

Key words

cyclic dipeptides

piperazinediones

iridium catalysis

asymmetric hydrogenation

asymmetric catalysis

Synfact  
of the  
Month

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.