Asymmetric transfer hydrogenation of 1-aryl-3,4-dihydroisoquinolines using and iridium-amide complex

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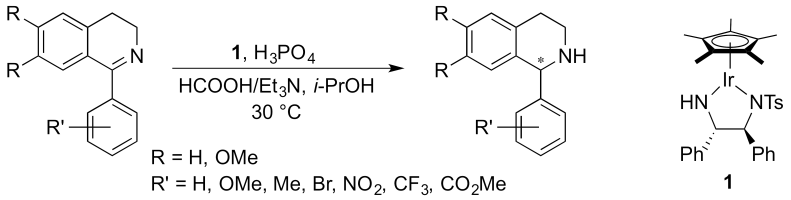
Optically pure chiral compounds are abundant among active pharmaceutical ingredients, agrochemicals, and fragrances. Efficient methods allowing the direct synthesis of single enantiomers are thus highly sought-after. The Noyori-Ikariya asymmetric transfer hydrogenation (ATH) of imines, catalysed by complexes of the [MCl(arene)(diamine)] (where M = Ru, Rh, Ir) type, belongs to a group of popular and well-established methods for the preparation of optically enriched amines [1]. However, this catalytic system still has certain limitations, one of which is the poor reactivity of 1-aryl-3,4-dihydroisoquinolines (1-Ar-DHIQs) as precursors of the chiral 1-aryl-1,2,3,4-tetrahydroisoquinoline motif present in naturally-occurring alkaloids (Cryptostylines) and drugs (*e.g.*, Solifenacin and Gantacurium). The currently used protocols are based on iridium-phosphine complexes that are oxygen sensitive and often are not readily available [2–4].

Herein, we report a simple alternative method for the ATH of 1-Ar-DHIQs. The method employs the Cp*Ir(TsDPEN) (where Cp* = pentamethylcyclopentadienyl and TsDPEN = $HNCHPhCHPhNTs^{2-}$) catalytic complex (**1**) that is stable and readily available, propan-2-ol and HCOOH/triethylamine mixture as the solvent and hydrogen donor, and anhydrous phosphoric acid as an additive. In total, 12 examples of substrates were hydrogenated in high yields and good to high enantioselectivity, showing tolerance for a broad spectrum of functional groups and a clear structure-reactivity pattern. Interestingly, when a 1-alkyl-DHIQ (6,7-dimethoxy-1-methyl-DHIQ) was studied for comparison, the chiral product's *ee* was decreasing in the course of the reaction and and surprisingly, in the absence of phosphoric acid, the effect was even more pronounced as we observed a reversal of enantioselectivity at high conversions. No such decrease of *ee* was detected with 1-Ar-DHIQs, which do require the presence of the acid for hydrogenation to take place.



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[1] R. Noyori, S. Hashiguchi, Accounts of Chemical Research, **1997**, 30, 97.
[2] M. Ružič, A. Pečavar, D. Prudič, D. Kralj, C. Scriban, A. Zanotti-Gerosa, Organic Process Research & Development, **2012**, 16, 1293.
[3] M. Chang, W. Li, X. Zhang, Angewandte Chemie International Edition, **2011**, 50, 10679.
[4] F. Berhal, Z. Wu, Z. Zhang, T. Ayad, V. Ratovelomanana-Vidal, Organic Letters, **2012**, 14, 3308.