Direct Asymmetric Hydrogenation of \( N \)-Methyl and \( N \)-Alkyl Imines with an \( \text{Ir(III)} \)H Catalyst

Ernest Salomó,† Albert Gallen,‡ Giuseppe Sciortino,§,# Gregori Ujaque,§ Arnald Grabulosa,‡ Agustí Lledós,§,‡ Antoni Riera,§,‡,†,‡ and Xavier Verdaguer

†Institute for Research in Biomedicine (IRB Barcelona), Barcelona Institute of Science and Technology, Baldirí Reixac 10, 08028 Barcelona, Spain
‡Dept. Química Inorgànica i Orgànica, Universitat de Barcelona, Martí i Franquès 1, 08028 Barcelona, Spain
§Dept. de Química, Ed. C.n., Universitat Autònoma de Barcelona, Cerdanyola del Vallès, Barcelona 08193, Spain
#Dipt. di Chimica e Farmacia, Università di Sassari, via Vienna 2, 1-07017 Sassari, Italy

ABSTRACT: A novel cationic \( [\text{IrH(THF)}(P,N)-(\text{imine})][\text{BARF}] \) catalyst containing a \( P \)-stereogenic MaxPHOX ligand is described for the direct asymmetric hydrogenation of \( N \)-methyl and \( N \)-alkyl imines. This is the first catalytic system to attain high enantioselectivity (up to 94\% ee) in this type of transformation. The labile tetrahydrofuran ligand allows for effective activation and reactivity, even at low temperatures. Density functional theory calculations allowed the rationalization of the stereochemical course of the reaction.

Chiral \( N \)-methyl or \( N \)-alkyl amine is a frequent pharmacophore in pharmaceutical substances (Figure 1). Examples include sertraline (to treat depression),12 dextro-

methamphetamine (to treat ADHD and narcolepsy),2 rivastigmine (to treat Alzheimer’s and Parkinson’s diseases)3 and cinacalcet (to treat hyperparathyroidism).4 Because of the importance of this moiety, many efforts have been devoted to the asymmetric synthesis of optically pure \( N \)-methyl amines.5 An ideal methodology to obtain this class of compounds is the catalytic reduction of the corresponding imines. However, the high basicity and nucleophilicity of \( N \)-methyl amines often results in catalyst deactivation. The most successful approaches for the asymmetric reduction of \( N \)-methyl imines are Ti-catalyzed hydroisilylation, reported by Buchwald,6 and Brønsted acid-catalyzed reduction using Hantzsch ester in the presence of Boc\(_2\)O, reported by List.7 In both cases, the final amine product is protected with either a SiR\(_3\) or Boc group, thus circumventing the basicity issue associated with the free amine.

From an industrial perspective, the direct hydrogenation of imines is a much more desirable process;1 however, in contrast to the good results obtained with \( N \)-aryl ketimines,8,9 the hydrogenation of \( N \)-methyl ketimines has not yet been achieved with useful levels of enantioselectivity. Pfaltz and co-workers reported the hydrogenation of the \( N \)-methyl imine of acetophenone with \( \text{Ir-PHOX} \) catalysts, achieving only 58\% ee (Scheme 1).10 The conversion was complete, but harsh pressures of hydrogen (100 bar) and high catalyst loadings (4 mol \%) were required. We hypothesize that this difference between \( N \)-aryl and \( N \)-alkyl ketimines is due to the aforementioned basicity of this class of compounds. Here we report a novel type of \( \text{Ir(III)} \) precatalyst that can be used directly in hydrogenation reactions and that has allowed the direct hydrogenation of \( N \)-methyl and \( N \)-alkyl imines in mild conditions and with high levels of selectivity (Scheme 1).

We have recently reported that cationic \( \text{Ir(I)} \)-MaxPHOX catalysts are highly active and selective in the hydrogenation of \( N \)-aryl imines.12 Here we tested whether these catalysts are...