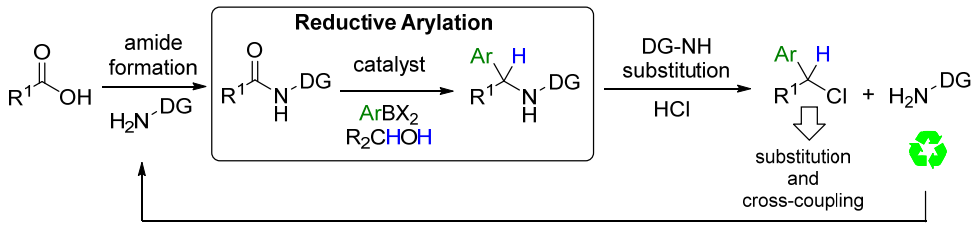
RUTHENIUM-CATALYZED REDUCTIVE ARYLATION OF *N*-(2-PYRIDINYL)AMIDES WITH ISOPROPANOL AND ARYLBORONATE ESTERS

Evelien Renders[a], Thomas O. Ronson[a], Ben F. Van Steijvoort[a], Xubin Wang[a], Clarence C. D. Wybon[a], Hana Prokopcová[b], Lieven Meerpoel[b], and Bert U. W. Maes[a]

[a]Organic Synthesis, Department of Chemistry, University of Antwerp, Groenenborgerlaan 171, B-2020 Antwerpen (Belgium)
[b]Janssen Research & Development, Janssen Pharmaceutica NV, Turnhoutseweg 30, B-2340 Beerse (Belgium)

Amides are ubiquitous and easily accessible functional groups, making them versatile and convenient substrates for the synthesis of amines. The catalytic reduction of amides into α-unbranched alkanamines has already received significant attention [1]. However, only a small number of strategies have been reported for the reductive functionalization of amides into α-branched alkanamines. This reaction has a huge synthetic potential considering the carbonyl is replaced by both a carbon–carbon and a carbon–hydrogen bond. A number of pioneering reports have described such a reaction on secondary and tertiary amides. However, these reactions have some drawbacks, as they involve strongly nucleophilic and basic organometallic reactants (Li and Mg) in combination with air- and moisture-sensitive metal hydrides or silanes as reducing agents. Moreover, the amide sometimes also has to be pre-activated *in situ* (e.g. Tf_2O). Amongst these reports on reductive functionalization, there are conspicuously few which describe the use of aryl nucleophiles, despite the fact that this gives rise to synthetically useful benzylamines [2]. Our group developed a novel method for the reductive arylation of amides based on a stable arylboron reactant and an alcohol, used both as reductant and solvent [3]. The method utilizes a Ru catalyst along with a Pyridine directing group (DG) on the amide nitrogen to allow reaction with the unreactive carbonyl. The DG can be easily introduced via e.g. reaction of carboxylic acid with $PyNH_2$. The PyNH moiety in the *N*-Py 1-arylalkanamine product can be readily substituted with HCl giving 1-aryl-1-chloroalkane, concomitantly generating recyclable $PyNH_2$.



[1] (a) A. M. Smith, R. Whyman, *Chem. Rev.* **2014**, *114*, 5477. (b) A. Volkov, F. Tinnis, T. Slagbrand, P. Trillo, H. Adolfsson, *Chem. Soc. Rev.* **2016**, *45*, 6685.

[2] (a) Y. C. Hwang, M. Chu, F. W. Fowler, *J. Org. Chem.* **1985**, *50*, 3885. (b) K.-J. Xiao, A. E. Wang, P.-Q. Huang, *Angew. Chem. Int. Ed.* **2012**, *51*, 8314. (c) L.-G. Xie, D. J. Dixon, *Chem. Sci.* **2017**, *8*, 7492.

[3] T. O. Ronson, E. Renders, B; F. Van Steijvoort, X. Wang, C. C. D. Wybon, H. Prokopcová, L. Meerpoel, B. U. W. Maes, *Angew. Chem. Int. Ed.* **2019**, *58*, 482.