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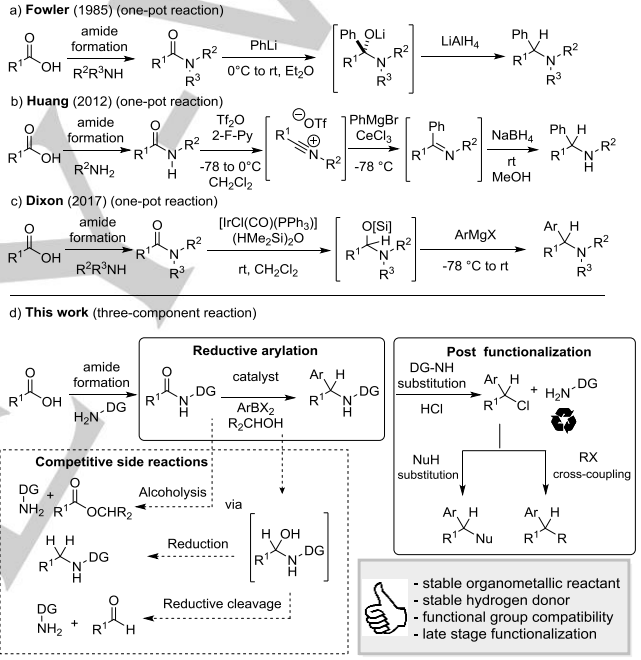
Ruthenium-Catalyzed Reductive Arylation of *N*-(2-Pyridinyl)amides with Isopropanol and Arylboronate Esters

Thomas O. Ronson,[a][χ] Evelien Renders,[a][χ] 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]*

Abstract: *A new three-component reductive arylation of amides with stable reactants (iPrOH and arylboronate esters), making use of a 2-pyridinyl (Py) directing group, is described. The N-Py-amide substrates are readily prepared from carboxylic acids and $PyNH_2$, and the resulting N-Py-1-arylalkanamine reaction products easily transformed into the corresponding chlorides by substitution of the HN-Py group with HCl. The 1-aryl-1-chloroalkane products allow substitution and cross-coupling reactions; thereby, a general protocol for the transformation of carboxylic acids into a variety of functionalities is obtained. The Py-NH_2 by-product can be recycled.*

Amides are ubiquitous and easily accessible functional groups,[1] making them versatile and convenient substrates for the synthesis of amines. The catalytic reduction of amides into α-unbranched alkanamines, involving a variety of homogeneous transition metal catalysts in combination with silanes and, more recently, molecular hydrogen as reductants, has received significant attention.[2–3] Less frequently studied is the reductive functionalization of amides into α-branched alkanamines, despite the fact that this reaction has a huge synthetic potential since the carbonyl is replaced by both a carbon–carbon and a carbon–hydrogen bond. In this way, a variety of α-branched alkanamines are accessible from a single amide substrate. 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.[4-6] These reactants typically require a low reaction temperature to control their reactivity and show a limited chemoselectivity and functional group compatibility. Moreover, the amide sometimes also has to be pre-activated *in situ* with Tf_2O,[7] generating a more reactive nitrilium salt to allow the nucleophilic addition.[4b-c] 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 benzylic amines. An early study by Fowler employed ArLi followed by addition of $LiAlH_4$ to give a 1-phenylalkanamine and is limited to tertiary amides, primarily lactams (Scheme 1, a).[4a] Huang subsequently extended this reaction to secondary amides using a convenient, general one-pot method involving pre-activation of the amide using Tf_2O, followed by reaction with PhMgBr/$CeCl_3$ and finally reduction with $NaBH_4$ (Scheme 1, b).[4b] Addition of $CeCl_3$ transforms the Grignards into organocerium derivatives, maintaining a high nucleophilicity but with attenuated basicity. Finally, Dixon recently described an elegant alternative method whereby a tertiary amide is partially reduced into an *O*-silyl hemiaminal with tetramethyldisiloxane (TMDS) and a catalytic amount of Vaska's complex, followed by addition of ArMgX at low temperature (Scheme 1, c).[4d]



Scheme 1: Approaches for the reductive arylation of amides and further transformations.

To our knowledge, there are no reports on reductive functionalization of amides based on (transfer) hydrogenation and a stable organometallic reactant, such as $ArBX_2$.[8] An alcohol is an attractive hydrogen transfer agent as it is cheap and can also be used as a solvent.[9] Moreover, alcohols are recognized as green solvents.[10] Arylboron derivatives are air- and moisture-stable, easily accessible, feature an excellent functional group tolerance, and are compatible with alcohols and therefore suitable for our purpose. In order to overcome the inertness of the amide carbonyl for nucleophilic attack with these milder reactants, we envisaged the use of a recyclable directing group (DG) on the amide nitrogen. Use of a DG to activate bonds intramolecularly is a strategy commonly employed in the field of transition-metal-catalyzed C–H functionalization,[11] yet rarely explored to activate the carbonyl of amides. Recently, our group provided the first example making use of a nicotinate DG

[a] Dr. T. O. Ronson, E. Renders, B. F. Van Steijvoort, Dr. X. Wang, C. C. D. Wybon, Prof. Dr. B. U. W. Maes
Organic Synthesis, Department of Chemistry
University of Antwerp
Groenenborgerlaan 171, 2020 Antwerp (Belgium)
E-mail: bert.maes@uantwerpen.be
[b] Dr. H. Prokopcová, Dr. L. Meerpoel
Janssen, Pharmaceutical Companies of Johnson & Johnson
Turnhoutseweg 30, 2340 Beerse (Belgium)
[χ] These two authors made equal contribution to this paper.

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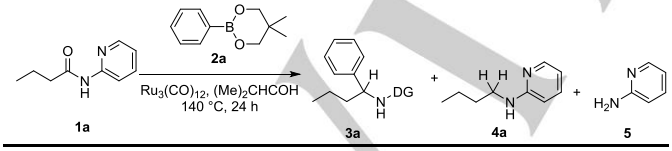
10.1002/anie.201810947

allowing for amide activation in an alcoholysis reaction.[12] In fact, amide esterification involving C-N cleavage is an undesired reaction in this work. The three-component reaction targeted here allows the overall transformation of a carboxylic acid into an *N*-DG 1-arylalkanamine (Scheme 1, d). Considering that both reduction and collapse of the hemiaminal intermediate and direct cleavage of the amide will be competitive reactions,[13] this is a challenging goal. We reasoned that the DG present in the *N*-DG 1-arylalkanamine products could be used to our advantage as the DG-NH moiety can act as a leaving group by reaction with e.g. HCl, giving 1-aryl-1-chloroalkanes and DG-NH_2, and enabling recovery. These secondary benzyl chlorides give access to a variety of other functionalities via substitution or cross-coupling reactions, allowing us to go beyond the 1-arylalkanamine products of the classical approaches (Scheme 1).[14]

Preliminary experiments revealed that with $Ru_3(CO)_{12}$ catalyst in *i*PrOH at 140 °C, *N*-Py-butyramide (**1a**) could be reductively arylated with PhBnep (**2a**), leading to 58% of the desired *N*-Py 1-phenylbutanamine **3a** (Table 1, entry 1). Besides this, PyNHBu (**4a**) (20%) and $PyNH_2$ (**5**) (5%), resulting from competitive reduction and cleavage of the amide, respectively, were also observed. An excess of **2a** is beneficial to suppress these competitive reactions, however too large an excess will hamper conversion (entries 1-3). A wide range of other catalysts, ligands, additives, and solvents were found to be ineffective, and substituted Py or other DGs led to less or none of the desired reaction product. $PhB(OH)_2$ and PhBpin gave none or a lower amount, respectively, of **3a** (see SI, Tables S1-S8). An optimization of the initial reaction conditions was carried out to maximize the selectivity for **3a** (Table 1). Decreasing the concentration increased the amount of **3a** (73%) versus **4a** (20%), while an increase in concentration gave a lower conversion and selectivity (entries 1, 4, 5). An increase in the catalyst loading further increased the selectivity. These conditions led to the formation of 94% of the desired product **3a**, only 6% of side product **4a**, and none of **5** (entry 6). Further decrease in concentration led to a poorer selectivity (entries 6, 7) and increase in catalyst loading gave a similar result (entries 6, 8). As expected, omitting the aryl donor from the reaction led solely to the reduction product **4a** in very good yield (Entry 10), again underlining the competition between reductive functionalization and reduction under these conditions.

Table 1: Selected optimization data of the reductive arylation of **1a** with **2a** and *i*PrOH.[a]

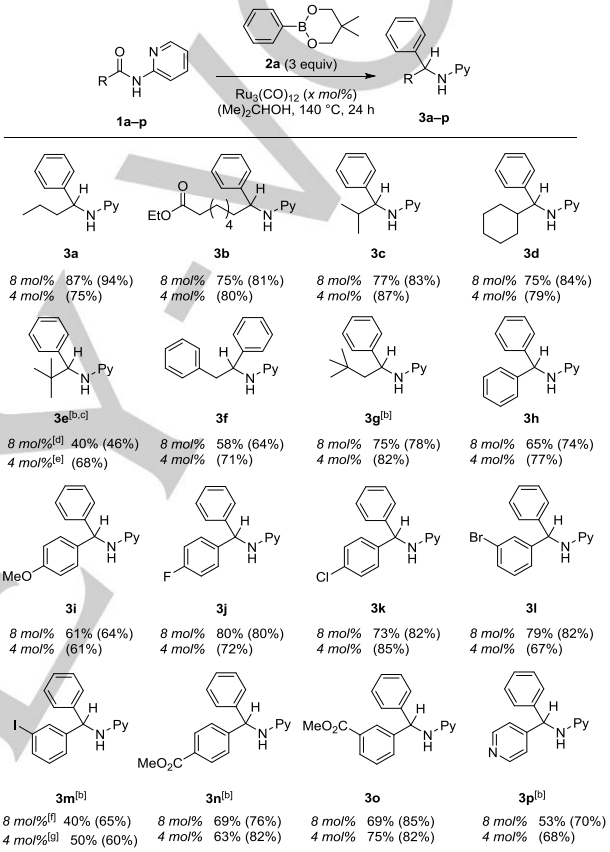


Entry	Cat. Loading (mol%)	**2a** (Equiv)	Conc. (M)	^{1}H NMR Yield (%)[b]			
				1a	**3a**	**4a**	**5**
1	4	3	1	3	58	20	5
2	4	1.5	1	12	30	32	12
3	4	5	1	31	29	2	13
4	4	3	2	40	28	2	10
5	4	3	0.5	0	73	20	1
6	8	3	0.5	**0**	**94 (87[c])**	**6**	**0**
7	8	3	0.25	0	81	15	0
8	10	3	0.5	0	89	7	3
9	8	5	0.5	0	92	0	0
10	8	0	0.5	0	0	88	9

[a] Conditions: **1a** (0.5 mmol), **2a** (0–2.5 mmol), $Ru_3(CO)_{12}$ (0.02–0.05 mmol), *i*PrOH (0.25–2 mL), Ar, 140 °C, 24 h. [b] ^{1}H NMR yield using 1,3,5-trimethoxybenzene (TMB) as internal standard. [c] Isolated yield.

With the optimized conditions in hand, we set out to establish the substrate scope of the reaction (Scheme 2). The required *N*-Py-amide substrates could be readily prepared from a range of different starting materials; from RCOOH and $PyNH_2$ with an activating agent,[15] as well as from $RCONH_2$ and PyX via *N*-arylation,[16] and from *N*-PyNHCOH and alkenes via hydroamidation (see SI, section 6.1).[17]

Scheme 2: Amide substrate scope (**1**) with **2a** and *i*PrOH. [a]



[a] Conditions: **1** (0.5 mmol), **2a** (1.5 mmol), $Ru_3(CO)_{12}$ (x mol%), *i*PrOH (1 mL), Ar, 140 °C, 24 h, Isolated yield (^{1}H NMR yield with TMB as internal standard in parentheses). [b] **2a** (2.5 mmol**)**. [c] *i*PrOH (0.5 mL). [d] 33% amine **4e** according to crude ^{1}H NMR. [e] 17% amine **4e** according to crude ^{1}H NMR. [f] 12% hydrodeiodinated product (**3h**) isolated. [g] 9% hydrodeiodinated product (**3h**) isolated.

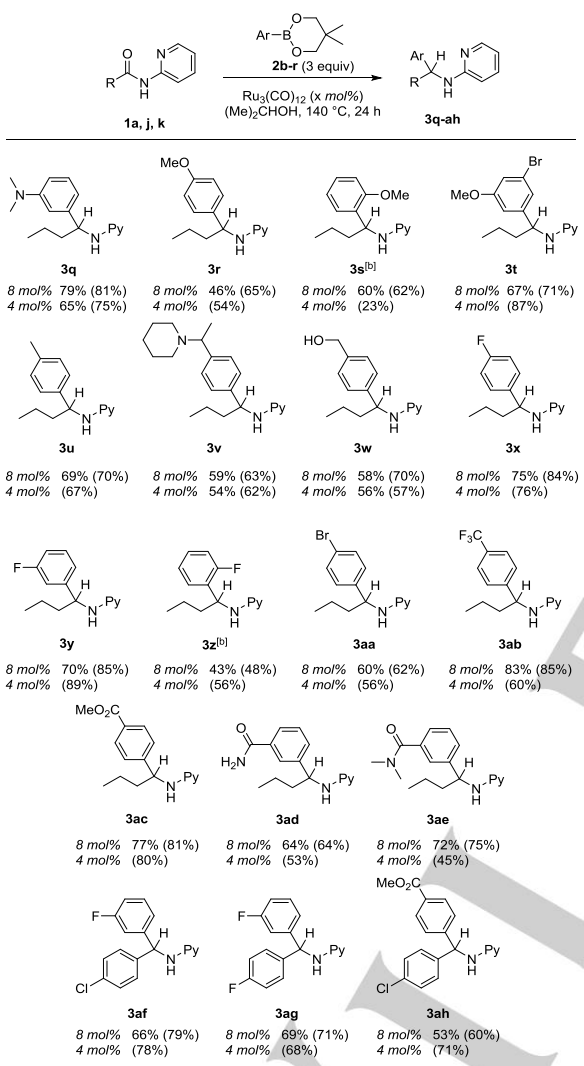
Besides simple unbranched (**1a–b**) amides, α-substituted (acyclic and cyclic) (**1c**–**f**) and β-substituted (**1g**) alkanamides, and benzamides (**1h**-**o**), as well as heteroaromatic amides (**1p**) were tolerated in the reductive arylation reaction with **2a**, giving the corresponding benzylic amine products **3** in generally good to excellent isolated yields (Scheme 2). Sterically hindered substrates, such as pivalamide (**1e**) and 3,3-dimethylbutanamide (**1g**), could also be employed but required a larger excess of **2a**. In the former, and most challenging, case the formation of reduced amide side product **4e** could not be suppressed.

The scope with respect to aryl donor **2** was then evaluated (Scheme 3). Those bearing strong and weak electron-releasing

10.1002/anie.201810947

groups (**3q**-**w**) were tolerated. Electron-withdrawing substituents, such as fluoro, bromo, trifluoromethyl, or methyl ester (**3x, 3aa**-**ac**) in the *para* position, worked efficiently. These substituents are also tolerated in other positions, as illustrated for an amide (**3ad**, **3ae**) and fluoro (**3y**, **3z**), although the yield for the *ortho* regioisomer **3z** was lower. A combination of an electron-withdrawing and -donating substituent (**3t**) also gave good results, as did substrates featuring a benzylic heteroatom (**3v**-**w**). On benzamides (**3af**-**3ah**) similar results to those on alkanamides were obtained (**3y**, **3ac**).

Scheme 3: Aryl reactant scope (**2**) with **1a**, **j**, **k** and *i*PrOH. [a]

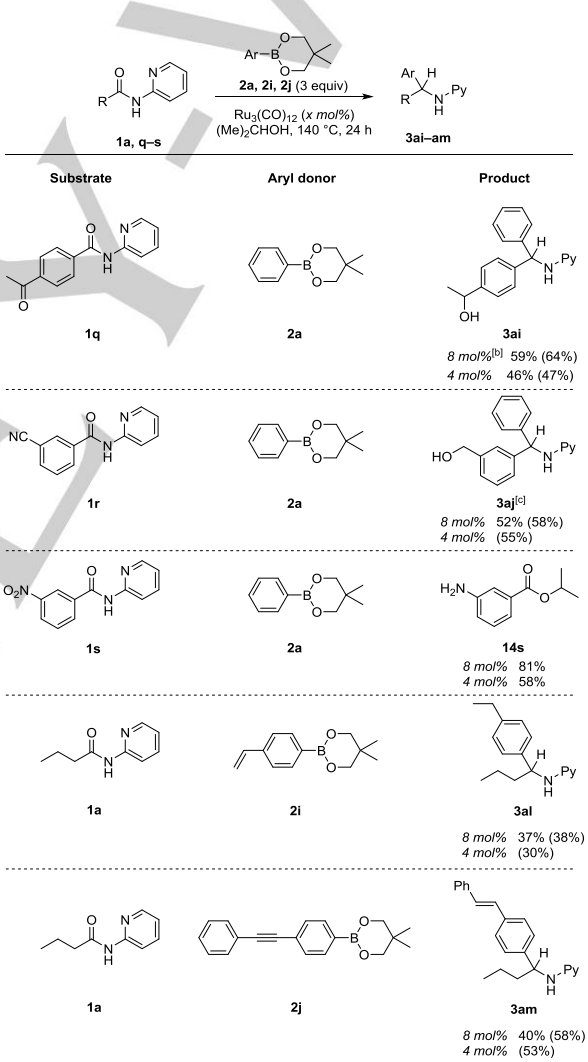


[a] Conditions: **1a**, **j**, **k** (0.5 mmol), **2b-r** (1.5 mmol), $Ru_3(CO)_{12}$ (x mol%), *i*PrOH (1 mL), Ar, 140 °C, 24 h, Isolated yield (^{1}H NMR yield with TMB as internal standard in parentheses). [b] **2g** (2.5 mmol).

The functional groups present in **1** and **2** show interesting features (Scheme 2-3). Reaction with an amide in the presence of an ester (**3b**, **3n**, **3o**, **3ac**, **3ah**) is an uncommon chemoselectivity,[18] considering the latter is easier to reduce. Also two amides can be discriminated, due to the presence of the directing group (**3ad**, **3ae**). Interestingly, ketone (**3ai**), cyano (**3aj**), nitro (**14s**), alkene (**3al**), and alkyne (**3am**) were additionally reduced (Scheme 4).[19] Good yields were generally achieved, considering two catalytic reactions (auto tandem catalysis), reductive arylation and reduction, are involved. Interestingly, a terminal alkene was reduced to an ethyl (**3al**) while a phenylethynyl chemoselectively transformed into an (*E*)-styryl (**3am**). The enhanced stability of the alkene in the latter case is presumably due to more extensive conjugation and sterics. Only a nitro substituent changed the selectivity of the tandem reaction towards the ester product (**14s**) involving alcoholysis/reductive cleavage instead of reductive arylation. Halogen, ether, alcohol, amine, ester and amide remained unaffected in the reductive arylation reaction (Scheme 2-3).

For all examples reported (Schemes 2-4), we also performed the reaction with a 4 mol% loading. Although for the model reaction of **1a** with **2a** 8 mol% catalyst resulted in a significantly higher yield of **3a** and less **4a**, pleasingly generally similar or higher yields can be obtained at lower loading (4 mol%) with only a few exceptions (**3a**, **3s**, **3ab**, **3ae, 3ai**).

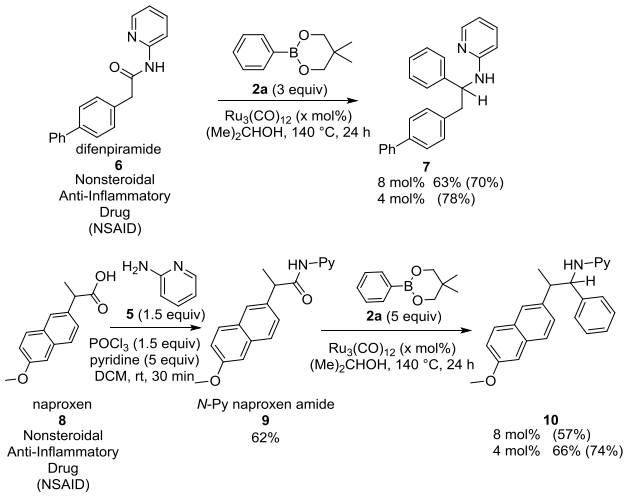
Scheme 4: Auto tandem catalysis with substrate **1a**, **q-s**, aryl donor **2a, i, j** and *i*PrOH. [a]



[a] Conditions: **1a**, **q-s** (0.5 mmol), **2a, i, j** (1.5 mmol), $Ru_3(CO)_{12}$ (x mol%), *i*PrOH (1 mL), Ar, 140 °C, 24 h, Isolated yield (^{1}H NMR yield with TMB as internal standard in parentheses [b] 7% reductively phenylated ketone (**3ai'**) isolated. [c] Benzylic alcohol formation via hydrolysis of imine intermediate and further reduction.

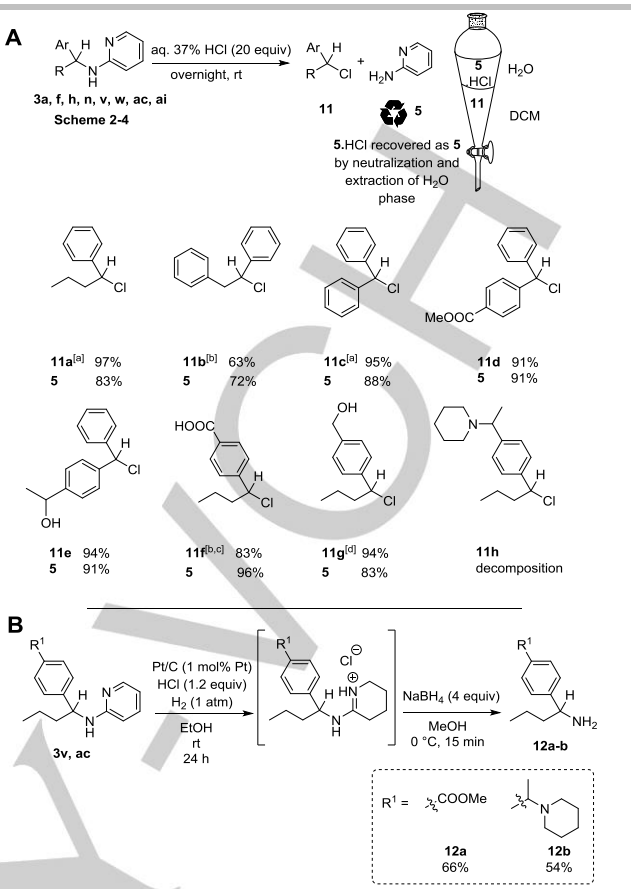
10.1002/anie.201810947

The developed methodology was also applied to the derivatization of active pharmaceutical ingredients (APIs) (Scheme 5). This strategy is consistent with the selective optimization of side activities (SOSA) approach, wherein existing APIs are taken as a starting point for new drug development.[20] Difenpiramide (**6**), containing an *N*-Py amide moiety, gave 63% of the corresponding 1-phenylalkanamine **7**. *N*-Py naproxen amide (**9**), obtained from naproxen (**8**), yielded 66% of the target compound **10**.



Scheme 5: Derivatization of APIs. Isolated yield (^{1}H NMR yield with TMB as internal standard in parentheses). Py = 2-Pyridinyl.

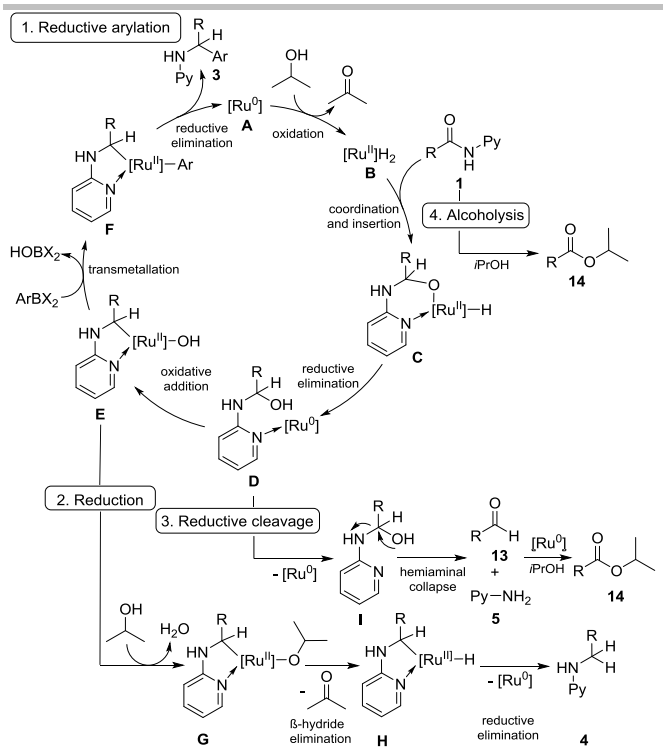
Finally, a protocol for the substitution of the PyNH moiety was developed on model product *N*-Py 1-phenylbutanamine (**3a**) derived from an aliphatic amide (Scheme 6, A). Reaction of **3a** in aq. HCl at room temperature gave 97% 1-chloro-1-phenylbutane (**11a**) by simple extraction, along with 83% of the $PyNH_2$ by-product (recovered from the aqueous phase) used to activate a carboxylic acid. To the best of our knowledge, such substitutions are unknown. Interestingly, this protocol can be generally applied as further exemplified by transformaton of **3f**, **3h**, **3n**, **3w**, and **3ai** into **11**. An ester (**3n**) was tolerated under the standard reaction conditions, however for **3ac** a higher temperature was used, resulting in hydrolysis. In some cases decomposition was observed (**3v**). In these cases (**3ac** and **3v**), our previously developed one-pot Py removal protocol can be applied yielding the corresponding benzylamines **12** (Scheme 6, B).[21] The secondary benzyl chloride products can be transformed via S_N with nucleophiles (see SI, Section 4) or cross-coupling reactions following literature procedures.[14] For **11b** the reported asymmetric reductive cross-coupling reactions with various RX (alkenyl, aryl, acyl) are of specific interest as no organometallic reactants are required.[14a,b,e]



Scheme 6: Substitution of the PyNH (A). Py removal (B). [a] 5 equiv aq. 37% HCl. [b] 40 °C. [c] 72h, starting from methyl ester. [d] 80 °C.

A plausible mechanism for the formation of **3** from **1** is presented in Scheme 7 (See SI, Section 3). The first step is the oxidative addition of *i*PrOH to Ru^0 (**A**), followed by β-hydride elimination resulting in a $Ru^{II}H_2$ (**B**).[22] Insertion of an amide carbonyl **1** into **B** forms **C**. Hemiaminal **D** is formed via reductive elimination in complex **C**. Oxidative addition of the hemiaminal gives a $Ru^{II}OH$ (**E**).[23] Transmetallation of the hydroxide group with arylboron compounds transforms **E** into $Ru^{II}Ar$ complex **F**.[24] Reductive elimination delivers target compound **3**. Undesired reduction to amine **4** takes place via alcoholysis of **E** with *i*PrOH, followed by β-hydride elimination in $Ru^{II}O$*i*Pr (**G**) and reductive elimination in **H**. Amide cleavage can be rationalized via decomplexation of **D** followed by hemiaminal collapse in **I** delivering side products $PyNH_2$ (**5**) and aldehyde (**13**). The latter can react further to the isopropyl ester **14** under Ru-catalysis.[19] Alternatively, **14** can be obtained via direct alcoholysis.

10.1002/anie.201810947



Scheme 7: Proposed reaction mechanism for the desired reductive functionalization (1.), competitive reduction (2.), competitive reductive cleavage (3.) and competitive alcoholysis (4.) of *N*-Py amides (**1**).

In conclusion, we have 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. The method utilizes a Ru catalyst along with a Py DG on the amide nitrogen to allow reaction with the unreactive carbonyl. The DG can be easily introduced via e.g. reaction of carboxylic acids with $PyNH_2$. The PyNH moiety in the resulting *N*-Py 1-arylalkanamine product can be readily substituted with HCl, concomitantly generating recyclable $PyNH_2$. The 1-aryl-1-chloroalkane products can be further transformed via substitution or cross-coupling reactions. This allows access to a wide structural variation of functionalities from a single carboxylic acid.

Acknowledgements

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Keywords: Ruthenium, amide, directed, three-component reaction

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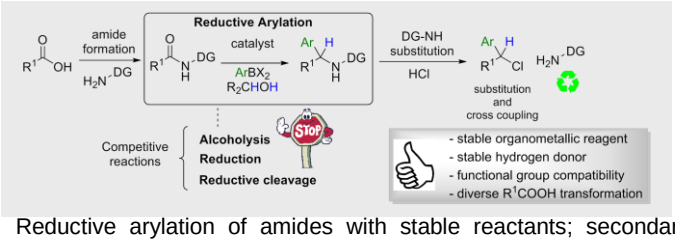

Reductive arylation of amides with stable reactants; secondary alcohol as the reductant and arylboronate ester as the aryl donor.

*Thomas O. Ronson, Evelien Renders, Ben F. Van Steijvoort, Xubin Wang, Clarence Wybon, Hana Prokopcová, Lieven Meerpoel, and Bert U. W. Maes**

Page No. – Page No.

Ruthenium-Catalyzed Reductive Arylation of *N*-(2-Pyridinyl)amides with Isopropanol and Arylboronate Esters