Electrochemical Nickel-Catalysed Aryl-Halide Amination

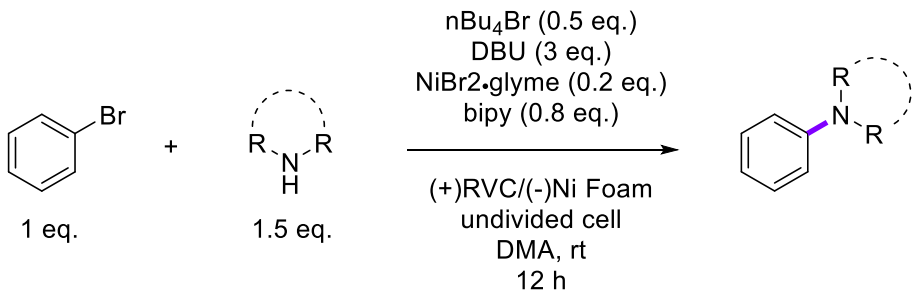
Authors: Ryan Nouch, Èric Ferrer Mallofré & Chloe Donnart.
Charnwood Molecular, BioCity, Pennyfoot Street, Nottingham, NG1 1GF

The amination of aryl-halides is one of the most widespread and commonplace transformations in modern medicinal chemistry.[1] Common methodologies used to effect this transformation include (i) palladium-catalysed cross coupling (e.g., Buchwald–Hartwig amination); (ii) copper-catalysed cross-coupling (e.g., Ullmann amination); (iii) sequential borylation and cross-coupling (Miyaura borylation followed by a Chan-Lam coupling) and (iv) S_NAr reactions.[2] These reactions can often be selective and high-yielding, but can possess some drawbacks. They may require high temperatures or strong bases, be extremely substrate specific or need a large amount of optimization to achieve useful conversions.

Recently, Phil Baran and co-workers developed an electrochemical protocol to achieve this transformation.[3] This could be performed under mild conditions, requiring no strong base or elevated temperatures. In the publication a pre-formed nickel catalyst was used. This was synthesized in a simple, single step. However, near-comparable yields could also be achieved using a commercial nickel pre-catalyst and simple ligand.

This mild and effective system was attractive to us, at Charnwood Molecular. Using our IKA ElectraSyn 2.0 Pro system (see Figure 1), we applied the conditions developed by Baran and co-workers to a diverse range of compounds typical of those found in small molecule drug discovery programs (see Scheme 1 for a summary of the general conditions used to support his work).

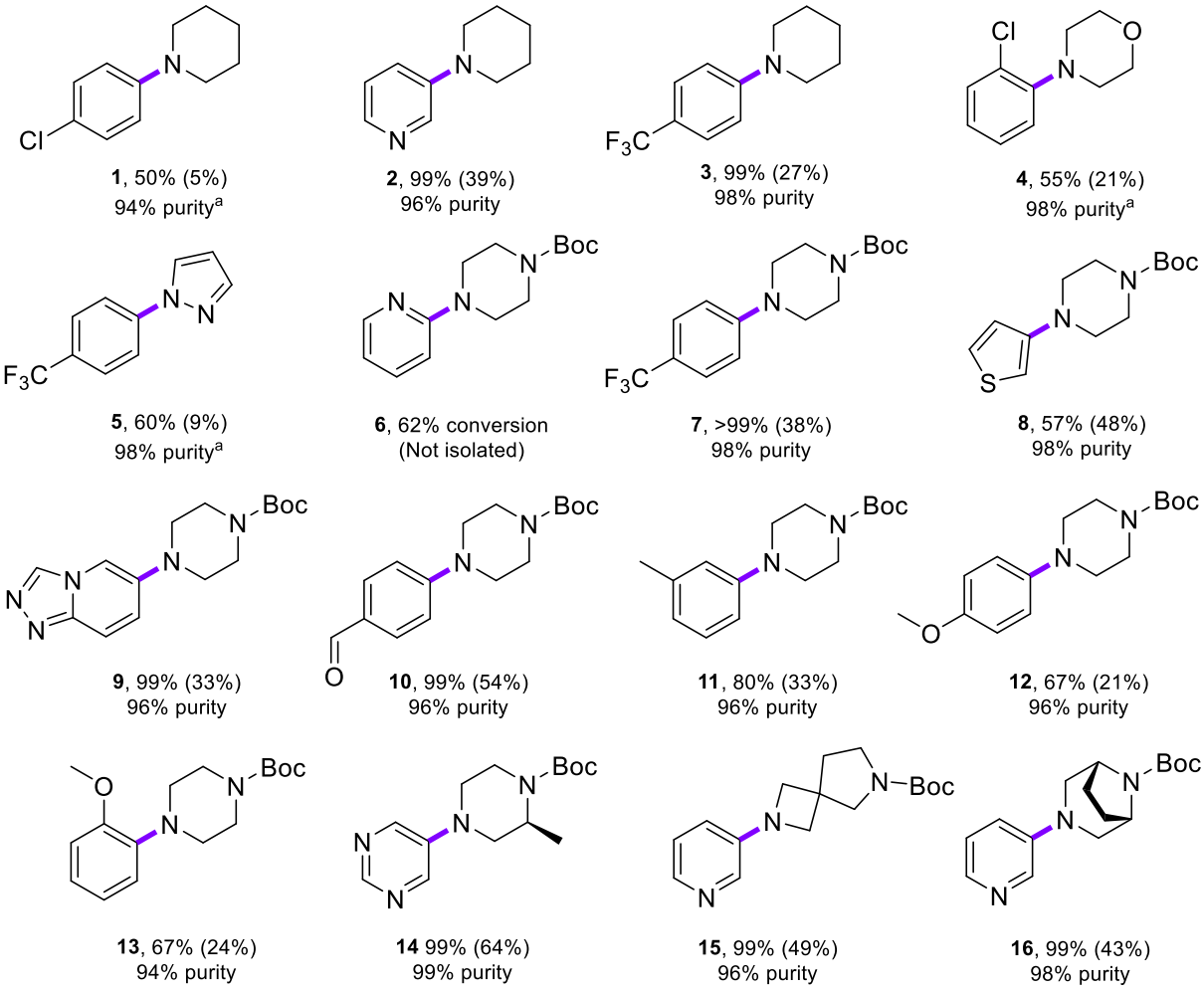
Figure 1: The IKA ElectraSyn 2.0.[1]



Scheme 1: General reaction conditions used in this work.

We endeavoured to demonstrate the utility of this chemistry in two ways. Firstly, we aimed to show that this chemistry could be applied to an electronically diverse set of aryl halides. Secondly, we wanted to demonstrate the potential of this chemistry in synthesizing 'drug-like' moieties as well as molecules possessing reactive handles for further derivatization. The diverse set of compounds synthesized by our chemists using our IKA ElectroSyn 2.0 system are summarized in Table 1. Electron poor aryl-halides (3, 7, 10) and electron rich aryl-halides (12, 13) were both well tolerated, as well as a variety of aromatic heterocycles (2, 6, 8, 9, 15).

Table 1: Synthesized compounds showing their conversion (isolated yield). [a]Using the alternative conditions: amine (3.0 eq.), Ar-Br (1.0 eq.), LiBr (4.0 eq.), $NiBr_2$·glyme (0.2 eq.), bipy (0.8 eq.), DMA, rt, 3 h



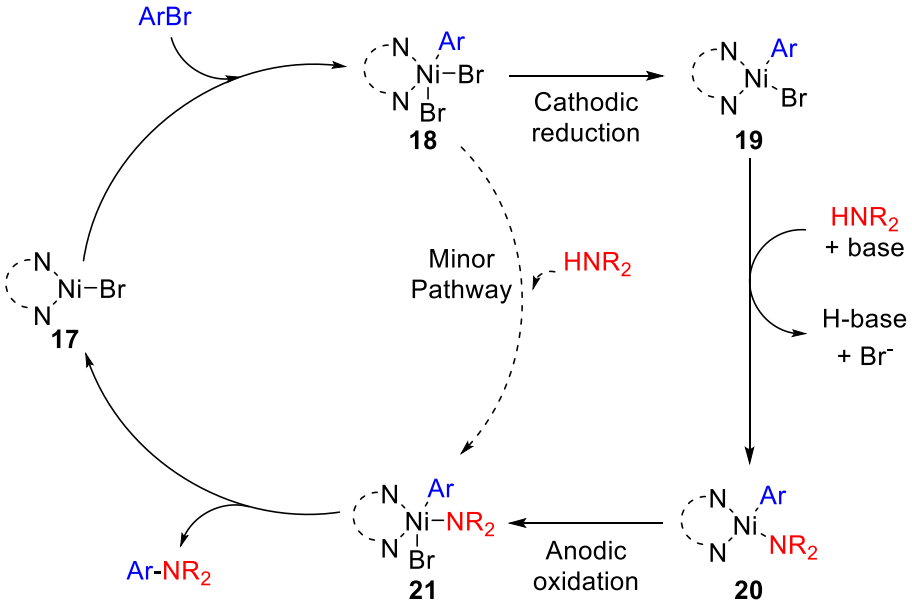
Notably, these conditions showed complete chemoselectivity for an aryl-bromide over an aryl-chloride functionality (e.g., 4), as well as tolerating an unprotected aldehyde group (e.g., 10) and a Boc-protected secondary amine (e.g., 6– 16). The mild nature and functional group tolerance of these reaction conditions represent significant advantages over existing chemistries, providing handles for further functionalization using cross coupling, reductive amination and amidation chemistries, as well as eliminating the need for additional and inefficient protection/deprotection cycles and functional group interconversion steps.

The synthesis of the pyrazole-containing compound 5 represents an extremely challenging transformation, which would typically be accomplished via a two stage process involving (i) the

initial formation of an aryl hydrazine, followed by (ii) the cyclization to the hydrazine with 1,1,3,3-tetramethoxypropane to form the pyrazole. The good conversion observed for this target demonstrates the robust nature of this methodology. Although some of the compounds listed in the table afforded lower isolated yields than we were expecting, based on their apparent conversions by UPLC-MS (e.g. , **1**, **5** or **6**), we believe that these differences could be addressed following a period of optimisation.

Lastly, we investigated the introduction of spirocyclic and carbon-bridged aliphatic nitrogen containing heterocycle (**15**, **16**). Systems of this type have become increasingly popular in medicinal chemistry projects in recent years, where they have been used as rigidified piperazine isosteres.[5] Recent publications from Degorce have also highlighted the lipophilicity-lowering effects of adding a signal carbon to bridged piperazines[6] or introducing an extra carbon to a piperazine or morpholine ring to afford the corresponding azaspiro system,[7] further expanding the overall utility and popularity of these systems. Pleasingly, both of the amines performed well under these conditions, affording the corresponding products in good yields and high purity.

Baran and co-workers proposed a mechanism for this transformation which is summarized in Scheme 2. Oxidative addition of the aryl-halide into Ni^{I} species **17** affords Ni^{III} complex **18**. This is then electrochemically reduced to Ni^{II} species **19** which undergoes a ligand exchange to form amido-Ni^{II} complex **20**. This is electrochemically oxidized to Ni^{III} complex **21** which can then undergo a reductive elimination to release the coupled product and reform Ni^{I} species **17**.



Scheme 2: Proposed mechanism for Phil Baran's electrochemically driven, Ni-catalysed aryl amination reaction.[4]

In summary, a facile alternative to traditional methods of aryl halide amination is now available at Charnwood Molecular. The versatility and functional group tolerance permitted by this technique, as well as open access to IKA's ElectraSyn 2.0 Pro system, means that we now have access to a new range of reactions and products for our clients drug discovery projects.

References

(1) D. G. Brown, J. Boström, *J. Med. Chem.* **2016**, *59*, 4443–4458.
(2) C. Fischer, B. Koenig, *Beilstein J. Org. Chem.* **2011**, *7*, 59–74.
(3) Y. Kawamata *et al*, *J. Am. Chem. Soc.* **2019**, *141*, 6392–6402.

(4) Image obtained from: https://www.ika.com/en/Products-Lab-Eq/Electrochemistry-Kit-csp-516/ElectraSyn-20-Package-cpdt-20008980/ on 21/10/2020
(5) S. Hanessian *et al*, *Bio. & Med. Chem. Lett.* **2018**, *28*, 2627–2630
(6) S. Degorce *et al*. *J. Med. Chem.* **2018**, *61*, 8934–8943
(7) S. Degorce *et al*. *ACS Med. Chem. Lett.* **2019**, *10*, 1198–1204

Charnwood Molecular Ltd
The Heritage Building
7 Beaumont Court
Prince William Road
Loughborough
LE11 5DA

+44 (0) 1509 232007 info@charnwood-molecular.com www.charnwood-molecular.com