IKA ElectraSyn 2.0 Pro

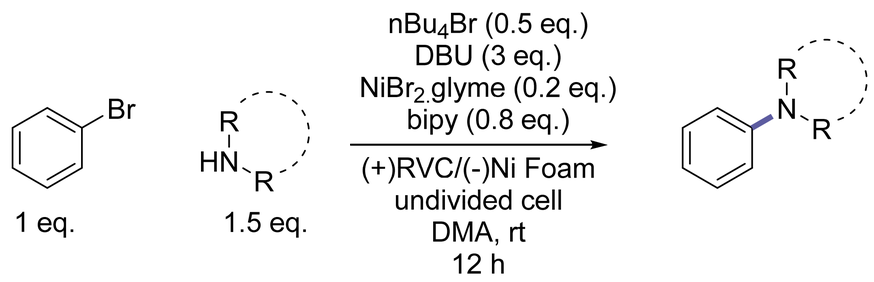
Electrochemical Nickel-Catalysed Aryl-Halide Amination

Authors: Ryan Nouch, Èric Ferrer Mallofré, Chloe Donnart and Jenny Stockwell

charnwood molecular
for the discovery

Abstract

The amination of aryl-halides is one of the most widespread and commonplace transformations in modern medicinal chemistry.[1] Attracted by the mild conditions and potential substrate scope, we investigated the electrochemical nickel-catalysed aryl-halide amination conditions developed by Baran's group.[2] Using our IKA ElectraSyn 2.0 Pro system, we applied the conditions to a diverse range of compounds relevant to small molecule drug discovery programs.



Background and Aims

There are multiple common methodologies used to effect the amination of aryl halides[3] including:

- Palladium-catalysed cross coupling (e.g. Buchwald–Hartwig amination)
- Copper–catalysed cross-coupling (e.g. Ullmann amination)
- Sequential borylation and cross-coupling (Miyaura borylation followed by a Chan-Lam coupling)
- S_NAr reactions.

These reactions can often be selective and high-yielding, but can possess some drawbacks such as:

- Require high temperatures
- Require strong bases
- Extremely substrate specific/need a large amount of optimization.

Recently, Phil Baran and co-workers developed an electrochemical protocol to achieve this transformation using a nickel catalyst. The advantage of this approach is it does not require high temperatures or strong bases.

Our plan was to replicate the conditions with our own IKA ElectraSyn 2.0 Pro to synthesis a diverse range of compounds relevant to small molecule drug discovery programs in order to explore the scope, utility and inhouse reproducibility of this transformation.

Scope

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.

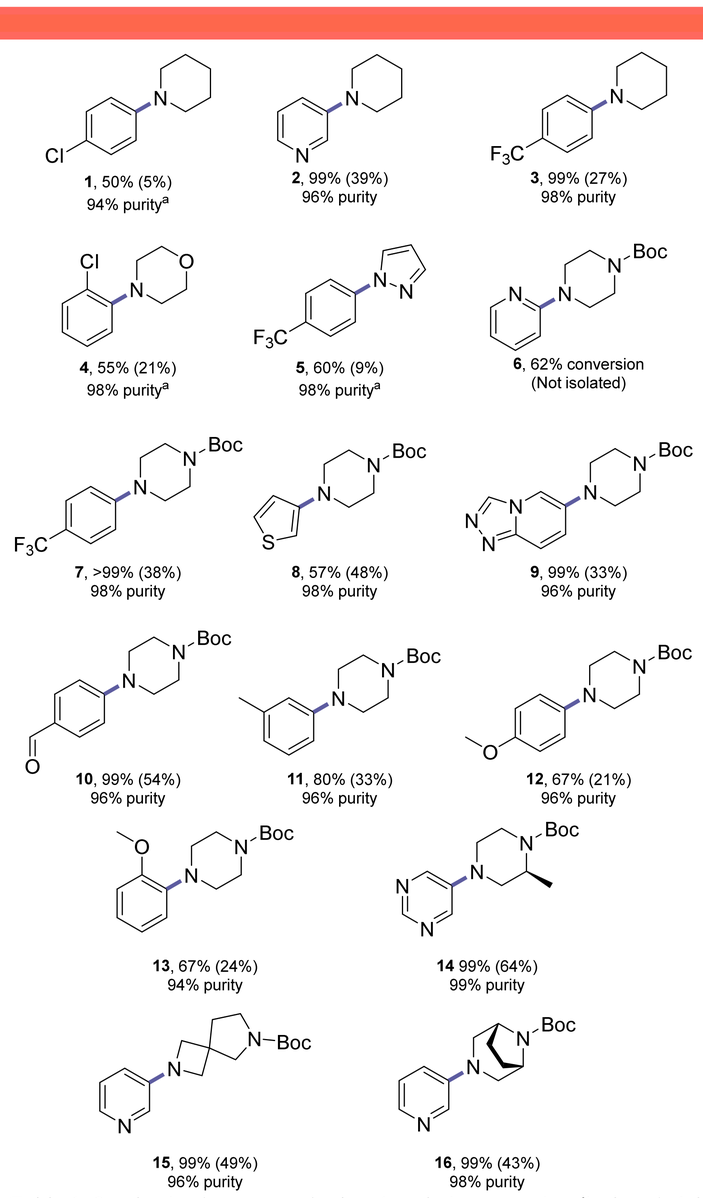
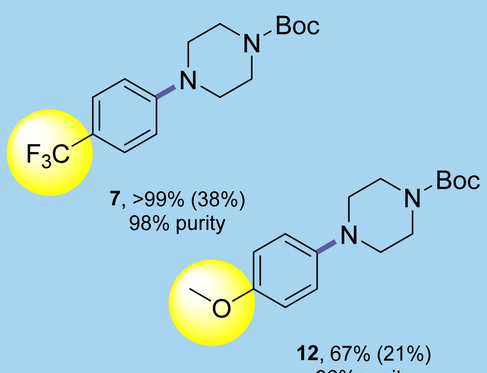


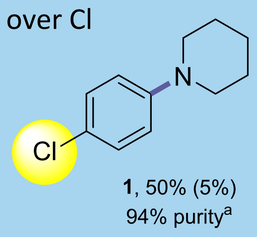
Table 1: Synthesized compounds showing their conversion (isolated yield). [a]Using the alternative conditions: amine (3.0 eq.), Ar-Br (1.0 eq.), LiBr (4.0 eq.), $NiBr_2$·glyme (0.2 eq.), bipy (0.8 eq.), DMA, rt, 3 h

Key Observations

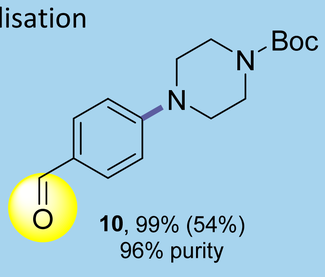
Tolerant of electron withdrawing and electron donating functional groups



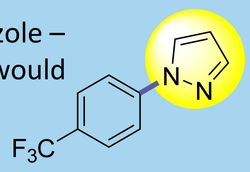
Chemoselective for Br over Cl



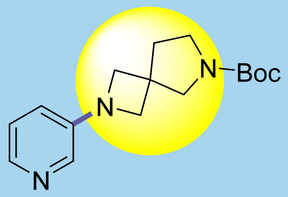
Mild conditions mean reactive functional groups can be tolerated without protection. This allows inclusion of synthetic handles for further functionalisation



Possible to directly *N*-functionalise a pyrazole – a group that using alternative conditions would have to be introduced in 2 steps



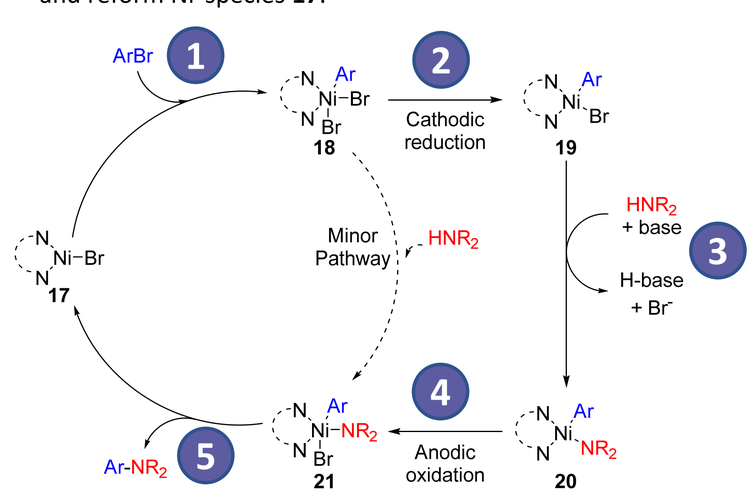
Can be used to incorporate interesting spirocyclic and bridge aliphatic heterocycles[4,5,6]



Mechanism

Baran and co-workers proposed a mechanism for this transformation which is summarized below.[2]

1. Oxidative addition of the aryl-halide into Ni^{I} species **17** affords Ni^{III} complex **18**.
2. **18** is electrochemically reduced to Ni^{II} species **19**
3. **19** undergoes a ligand exchange to form amido-Ni^{II} complex **20**.
4. **20** is electrochemically oxidized to Ni^{III} complex **21**
5. **21** undergoes a reductive elimination to release the coupled product and reform Ni^{I} species **17**.



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] Y. Kawamata et al, J. Am. Chem. Soc. 2019, 141, 6392–6402, [3] C. Fischer, B. Koenig, Beilstein J. Org. Chem. 2011, 7, 59–74, [4] S. Hanessian et al, Bio. & Med. Chem. Lett. 2018, 28, 2627–2630, [5] S. Degorce et al. J. Med. Chem. 2018, 61, 8934–8943, [6] S. Degorce et al. ACS Med. Chem. Lett. 2019, 10, 1198–1204, Image of the IKA ElectraSyn 2.0 Pro obtained from: https://www.ika.com/en/Products-Lab-Eq/Electrochemistry-Kit-csp-516/ElectraSyn-20-pro-Package-cpdt-40003261/ on 21/02/2022