COMMUNICATION

Expedient Access to Cyanated *N*-Heterocycles *via* Direct Flow-Electrochemical C(sp^2)-H Activation

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Abstract: Nitriles are recurring motifs in bioactive molecules and versatile functional groups in synthetic chemistry. Despite recent progress, direct introduction of a nitrile moiety in heteroarenes remains challenging. Recent developments in electrochemical reactions pave the way to more practical cyanation protocols. However, currently available methods typically require hazardous cyanide sources, expensive mediators, and often suffer from narrow substrate scope and laborious reaction set-up. To address the limitations of current synthetic methods, we report here an effective, sustainable, and scalable procedure for the direct C(sp^2)-H cyanation of aromatic *N*-heterocycles with a user-friendly flow-electrochemical set-up. Furthermore, high substrate and functional group tolerance is demonstrated, allowing for late-stage functionalization of drug-like scaffolds such as natural products and pharmaceuticals.

Nitriles are versatile functional groups in organic chemistry, and common structural motifs in natural products and agrochemicals. Furthermore, nitriles are ubiquitous in medicinal chemistry and drug discovery. Indeed, the ability of nitriles to isosterically replace other functional groups, as well as their ability to modulate pharmacokinetic and metabolic properties[1–3] make them highly desirable in pharmaceutical and agrochemical research, especially when incorporated in (hetero)aromatic scaffolds as displayed in Figure 1.[4–8] Expedient cyanation of *N*-heteroarenes is, therefore, highly desired by the medicinal chemistry community.

Cyanations of nitrogen-containing aromatic compounds are traditionally performed using transition-metal catalysts based on Pd, Cu, Rh or Zn, and usually requires the tedious incorporation/removal of directing groups. This can result in lengthy syntheses, reduced yields, and low atom economy.[8–20] Although numerous cyanation approaches have been reported in the last decade, there is still strong need for efficient, practical, versatile, and sustainable C(sp^2)-H cyanation of *N*-heteroarenes.[21,22] Moreover, in drug discovery, nitrile groups have the potential to impact the physicochemical properties of drug molecules, and can function as bioisosteres of carbonyl, hydroxyl, carboxyl, and halogen groups.[1,23] Lastly, nitrile-containing molecules are versatile synthetic intermediates capable of acting as nucleophiles (*e.g.*, Ritter reaction), electrophiles (*e.g.*, hydrolysis and Grignard addition), and partners in concerted pericyclic reactions (*e.g.*, cycloadditions).[24]

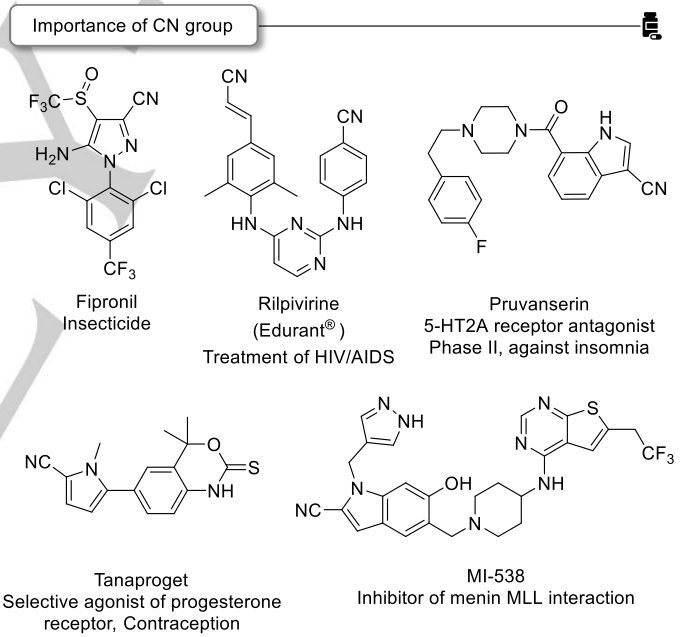
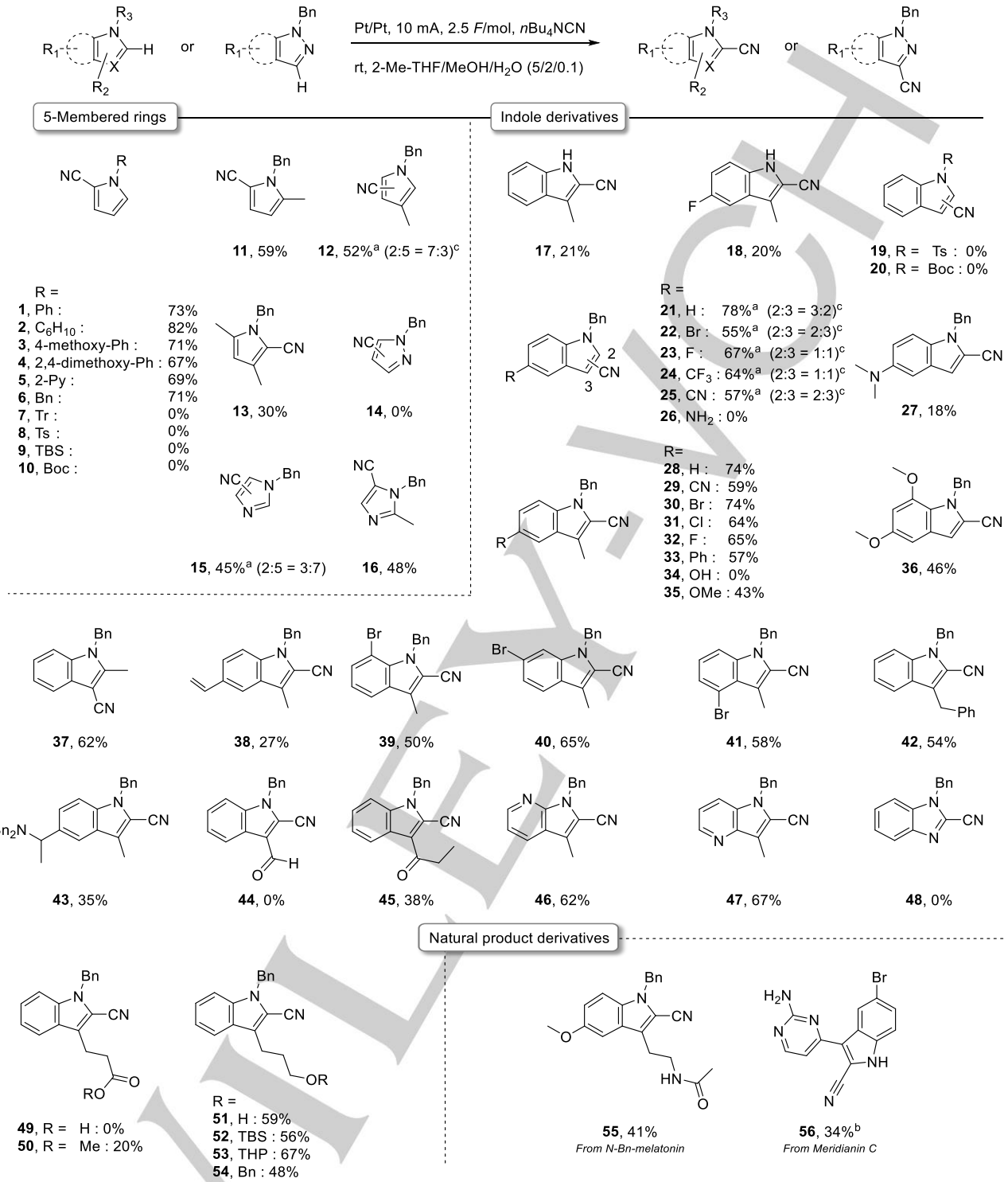


Figure 1. Nitrile-containing *N*-heteroaromatic scaffolds in selected pharmaceuticals and agrochemicals.

C(sp^2)-H functionalization of heteroaromatics by the generation of radical cations with "green" methodologies such as electrosynthesis has recently re-emerged as a powerful cyanation tool.[25–34] The first arene electrocyanations were described by Koyama and Parker back in 1965.[35,36] In 1977, Yoshida and co-workers described the first regiospecific anodic cyanation of pyrroles and indoles using sodium cyanide.[37,38] This method, and the few others that were reported around that time, were not general nor practical,[39–41] and it wasn't until Goossen reported a more general approach in 2018 that interest in electrochemical cyanations resurged.[42]



[a] Total yield from separated and isolated regioisomers, named **a** and **b** in experimental section

[b] 8 *F*/mol instead of 2.5 *F*/mol

[c] Explanation of notation: 2-CN and 3-CN or 5-CN isomer obtained in "x:x" ratio

Scheme 1. Scope of the C(sp^2)-H cyanation of *N*-heteroaromatic cycles at constant current in an undivided cell.

Although effective and straightforward, Goossen's methodology requires large excess of sodium cyanide and lacks selectivity when it comes to the varying electron density of the arene substrates. Moreover, pyrroles and indoles, which are privileged scaffolds for drug discovery, are incompatible with these reaction conditions because, according to the authors, "they underwent

oxidative degradation".[42] Following a similar strategy, Sun and co-workers recently showed that imidazo[1,2-a]pyridine derivatives are also amenable to electrochemical cyanation.[43]

In the realm of mediated electrochemical approaches, Wang and co-workers recently disclosed a site-selective cyanation of indoles using trimethylsilyl cyanide together with a tris(aryl)amine mediator.[44] Like many other mediated approaches, this method is mild and selective, but requires a mediator and a volatile cyanide source (TMSCN), limiting its potential implementation in industrial processes.[45,46] A direct electrocyanation, which employs a readily-available and non-volatile cyanide source, would be more suited for that purpose.

Thus, we focused our attention on the direct electrochemical C(sp^2)-H cyanation of *N*-heteroarenes. If successful, such methodology would introduce a versatile synthetic handle—the nitrile group—into complex molecules, paving the way for late-stage property modulation of drug candidates. For the latter application, we sought compatibility of our methodology with unprotected *N*-heterocycles, alleviating the need for additional protection/deprotection steps. To the best of our knowledge, the direct electrocyanation of unprotected nitrogen aromatics is not described in the literature. Following an initial proof-of-concept in batch, our main focus was running cyanation in flow. Flow-electrocyanation appears compelling to us given the speed and practicality of flow conditions, as well as its telescoping and scaling potential. Herein, we report the details of the development of the batch- and flow-electrocyanation reactions and elaborate on its scope and limitations. The types of *N*-heteroarenes amenable to our reaction conditions include indoles, pyrroles, imidazoles, and pyrazoles.

We started our investigation by evaluating different cyanide sources for the electrocyanation of 1*H*-pyrrole derivatives, the simplest 5-membered *N*-heterocycles, as model substrates (see Supporting Information). As *N*-substituent, we selected the relatively inert phenyl group. From a drug discovery perspective, a pyrrole ring is a compelling model system to cyanate given its electron-rich nature which is often associated with reactive metabolite formation.[47] Indeed, pyrroles could find broader application in drug discovery when substituted with electron-withdrawing groups. Because of the aforementioned limitations,[44-46] TMSCN was not considered as a suitable cyanating reagent. Instead, our initial attempts were performed using the non-volatile and more stable sodium cyanide and *n*Bu_4NCN (tetrabutylammonium cyanide) as reagents in less excess as compared to previous methods. Both cyanide salts have excellent solubility in protic solvents, and *n*Bu_4NCN is also highly soluble in non-protic organic solvents which makes them ideal for our reaction conditions. Moreover, we hypothesized that they would avoid the need for any additional wasteful supporting electrolyte, thus facilitating the purification. Yoshida and Yin, for example, demonstrated the dual function of sodium cyanide as electrolyte and reagent in the electrochemical cyanation of *N*-substituted pyrroles and indoles.[37,48]

After an extensive screening of reaction conditions, *n*Bu_4NCN in a 5:2:0.1 mixture of 2-methyltetrahydrofuran, methanol and water with Pt electrodes in an undivided cell were found to be optimal[49] (see Supporting Information for the full optimization table). As shown in Scheme 1, these electrolysis conditions led to the successful electrochemical cyanation of 1-phenyl-1*H*-pyrrole **1** (73%) as well as 1-cyclohexane-1*H*-pyrrole **2** (82%), 1-(4-methoxyphenyl)-1*H*-pyrrole **3** (71%), 1-(2,4-methoxyphenyl)- 1*H*-pyrrole **4** (67%) and 2-(1*H*-pyrrol-1-yl)pyridine **5** (69%). Much to our delight, an excellent yield was observed for 1-benzyl-1*H*-pyrrole **6**, while bulky or more electron-withdrawing groups such as tosyl, trityl, *tert*-butylsilyl, or Boc were not tolerated in this batch set-up. The scope and limitation of our new methodology were then explored by studying the substrate and functional group tolerance on *N*-H or deprotectable *N*-benzyl heteroaromatic cycles. Bn-protected imidazoles were successfully cyanated to afford the corresponding imidazole carbonitriles (**15, 16**). This approach also allowed for the functionalization of position 2 of 1-benzyl-1*H*-indoles with regioselectivity for benzyl-protected 3-methyl indoles (**28** to **35**, up to 74% yield). If the positions, 2 and 3 were both available, moderate to good α-selectivity was observed (**21** to **27**, **36**). For example, predominant α-functionalization of the *N*-benzyl indole **21** was observed, while a complete selectivity was obtained for 1-benzyl-5,7-dimethoxy-1*H*-indole **27** and 1-benzyl-2-methyl-1*H*-indole **36**. Substituents on the indole phenyl moiety did not appear to have a profound influence on the reaction yield. For instance, 4-, 5-, 6- and 7-bromo substituted indoles **41**, **30**, **40** and **39** all gave yields in the 50-74% range.

Overall, this methodology tolerates numerous functional groups such as halogens (Br, Cl, F), trifluoromethyls, nitriles, ethers, aromatic cycles, alkyls alcohols, esters, amides, tertiary amines, allyls, and ketones, as well as various protecting groups, including the sensitive *tert*-butyldimethylsilyl. Remarkably, conversion was also observed for unprotected *N*-H free indoles **17** and **18** (21% and 20% yield, respectively) which is, to the best of our knowledge, unprecedented and broadens the scope for late-stage functionalization.

The methodology was successfully extended to aza-indoles affording the corresponding cyanated compounds **46** (62%) and **47** (67%). As a proof of concept, we also performed the late-stage cyanations of *N*-benzylmelatonin and Meridianin C[50] to afford **55** to **56** in good yields. This opens the possibility to rapidly functionalize and fine-tune the properties of complex drug molecules and natural products.

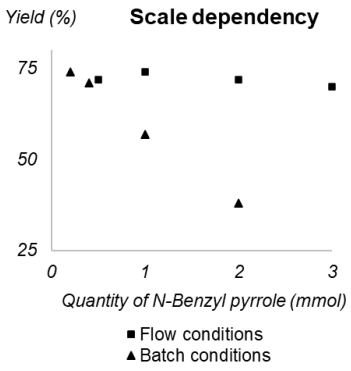


Figure 2. Isolated yield vs quantity of *N*-benzyl pyrrole **6** as starting material. Comparison between batch (triangles) and flow (squares) conditions.

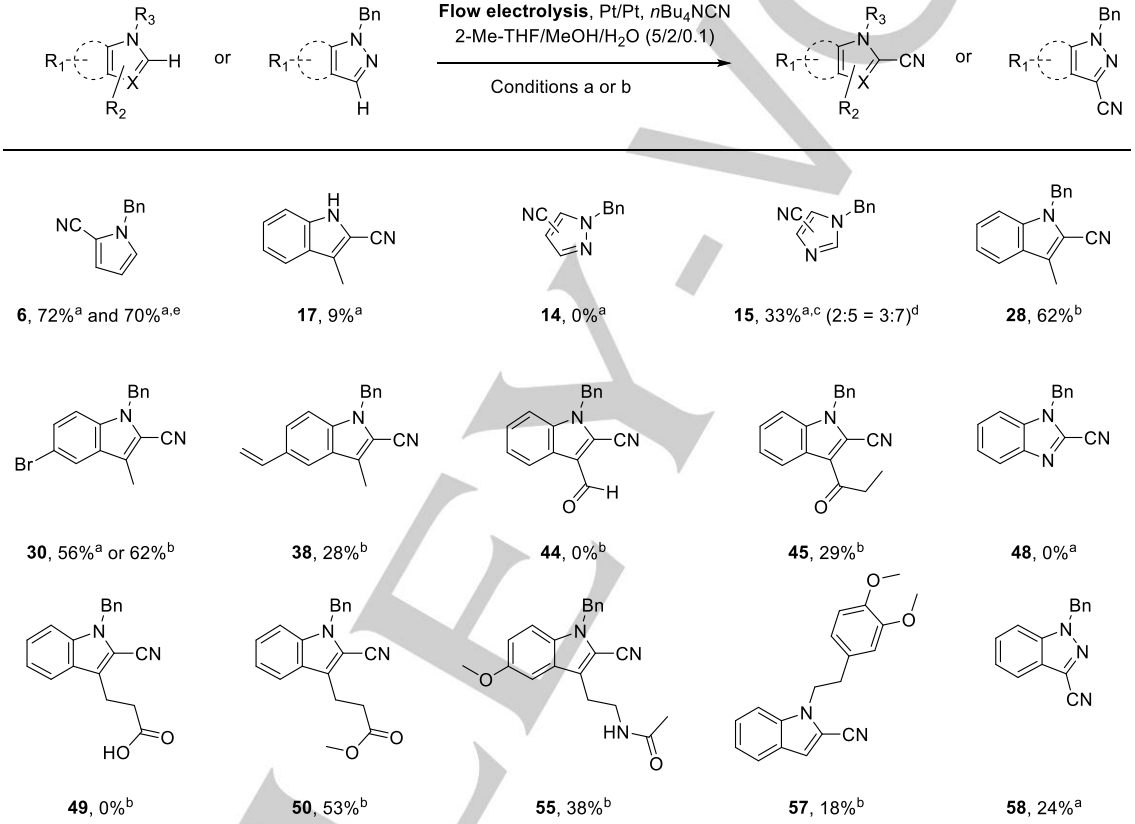
When performing the cyanation of 1-benzyl-1*H*-pyrrole **6** on a larger batch scale, a drastic and quasi-linear yield decrease was observed beyond 0.4 mmol (Figure 2). An explanation for this scale effect could be the instability of the nitrile-product during the electrolysis. We hence decided to transpose our new reaction to

flow electrosynthesis since the flow conditions would avoid the possible overoxidation of the product. Indeed, the use of a constant current of 30 mA or 50 mA, a concentration of 0.05 M in the substrate, a flow rate of 0.2 mL/min (residency time (t_r) = 3 min) or 0.12 mL/min (residency time (t_r) = 5 min) and a minimal quantity of cyanide source (1.4 equiv), allowed to isolate **6** with yields up to 72% on various scales (including on a 2.4 g scale, see SI), demonstrating the scalability of this route.

Aside from developing a scalable procedure, this new flow methodology enhanced the functional group compatibility of the reaction since the indole-ester **50** was isolated in a yield (53%) significantly higher than in batch (20%, Scheme 2).

Similarly, the compound **57** containing a 3,4-dimethoxyphenyl, a group known to be easily oxidizable and, therefore, unstable when subjected to electrolysis,[51,52] could still be selectively functionalized at the position 2 of the indole, yet with a moderate yield of 18%. The reaction was also successfully performed on a 1-benzyl-1*H*-indazole to afford **58** in 24% yield.

The flow conditions also provided melatonin derivative **55** with 38% yield. Compounds **17**, **14**, **15**, **21**, **30**, **38** and **45** were obtained with yields comparable to the batch conditions. Unfortunately, indole-3-carbaldehyde **44**, benzimidazole **48** and carboxylic acid **49** did not get cyanated under our optimized flow conditions, with only starting material or unidentified degradation products being observed.



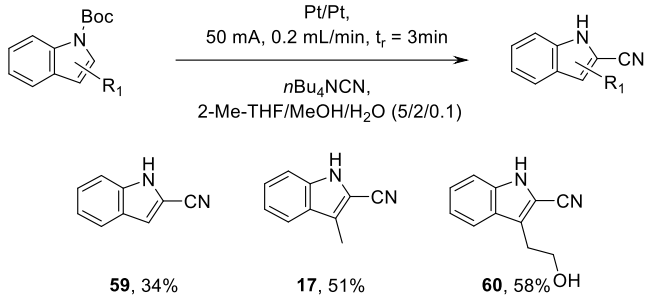
[a] 50 mA, 0.2 mL/min, t_r = 3 min
[b] 30 mA, 0.12 mL/min, t_r = 5 min
[c] Total yield from separated and isolated regioisomers
[d] Explanation of notation: 2-CN and 5-CN isomer obtained in 3:7 ratio
[e] Reaction performed on a 2.4 g scale

Scheme 2. Scope of the C(sp^2)-H cyanation of *N*-heteroaromatic cycles under flow-electrochemical conditions.

Interestingly, our flow conditions allowed for a tandem cyanation/deprotection of *N*-Boc-indoles providing **17**, **59** and **60** (Scheme 3). Those unprecedented results are worthy alternatives to the approach described in Scheme 2 using unprotected indoles. Moreover, increased yields in cyanated *N*-H indoles can now be obtained as testified by the formation of **17** with 51% yield from the corresponding *N*-Boc indole compared to 9% from the *N*-H indole. This yield difference suggests that the CN insertion occurs before or concomitantly to the Boc deprotection. Therefore, this practical methodology allows for rapid access to cyanated *N*-H free indoles, in good yields, without the need for an additional deprotection step.

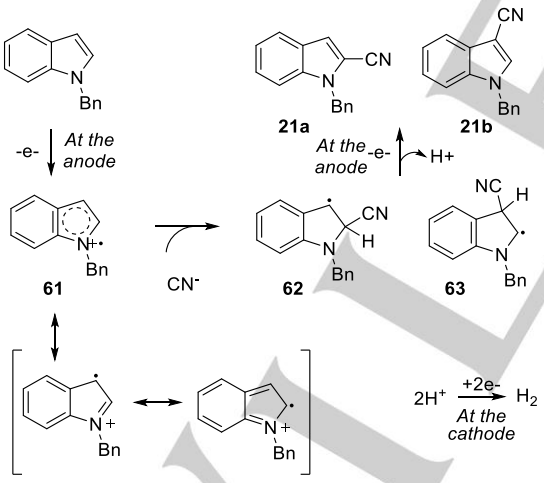
Cyclic voltammograms of 1-benzyl- and 1-phenyl-1*H*-indoles were recorded. Unsurprisingly, both compounds displayed a chemically non-reversible oxidation wave, showing the high reactivity of the anodically generated radical-cation (see Supporting Information). A chemically non-reversible anodic wave

was also observed for tetrabutylammonium cyanide, presumably accounting for the formation of a cyanide radical. A mixture of *N*-benzyl indole and nBu$_4$NCN was also subjected to cyclic voltammetry analysis and confirmed that the indole displayed a lower oxidation potential than the cyanide salt.



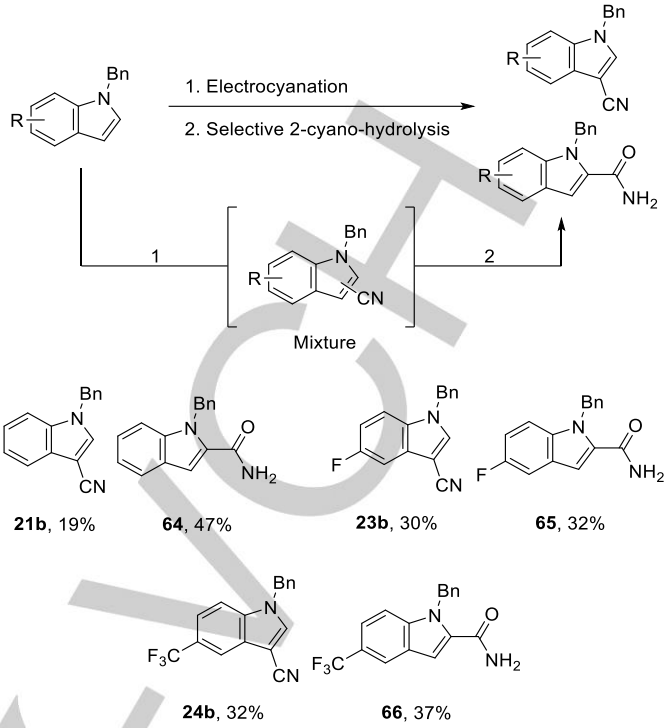
Scheme 3. Scope of tandem Boc-deprotection/C-H cyanation of *N*-Boc-indoles by flow-electrochemistry.

To account for these experimental observations, the following mechanism for the direct C(sp^2)-H cyanation of *N*-heteroarenes is proposed (Scheme 4). First, the indole is oxidized into its corresponding radical-cation **61**. The highly electrophilic species **61** is then attacked by a cyanide anion leading to formation of the corresponding radical intermediates **62** and **63**. These intermediates are subsequently oxidized by the anode, which gives isomers **21a** and **21b** after a loss of proton.[53]



Scheme 4. Proposed mechanism of direct anodic C(sp^2)-H cyanation.

Interestingly, in the case of the mixture of 2- and 3-cyanoindoles, the 2-cyanoindole derivatives could be selectively hydrolyzed to the corresponding primary carboxamide **64**, **65** and **66** by stirring the mixture at 60 °C for six hours (Scheme 5). Under these mild conditions, the 3-cyanoindole derivatives remained untouched. This telescoped reaction allows to access indole-2-carboxamides from their corresponding 2-unsubstituted indole analogues directly in one step and could simplify the separation of the isomers.



Scheme 5. Selective hydrolysis of the nitrile group at position 2 of indoles. Conditions: 1) Pt/Pt, 10 mA, 2.5 *F*/mol, nBu$_4$NCN at rt in 2-Me-THF/MeOH/H$_2$O (5/2/0.1); 2) nBu$_4$NCN, 60 °C, 6 h in 2-Me-THF/MeOH/H$_2$O (5/2/0.1).

In summary, a straightforward method for the regioselective electrochemical C(sp^2)-H cyanation of *N*-heteroarenes is disclosed. The reactions are conducted in a simple undivided cell at room temperature and obviate the need for transition-metal catalysts, hazardous reagents, or expensive mediators. Following a successful proof-of-concept in batch, the method was next transposed to a user-friendly flow-electrochemical set-up, successfully overcoming scalability limitations and broadening the substrate scope. With exquisite functional group tolerance, the direct functionalization of complex *N*-heterocycles, including the previously undescribed cyanation of unprotected indoles, is demonstrated. Moreover, a melatonin derivative and Meridianin C were also successfully cyanated, highlighting the potential of this method for late-stage functionalization. Lastly, we provide one example of tandem electrosynthesis but, given the versatility of nitriles, many more opportunities for “domino” reactions are conceivable, some of which will be disclosed in due course.

Acknowledgements

The authors are grateful for the financial support provided by Business France through the V.I.E. grant program. The authors thank Dr. Jesus Alcazar, Dr. Marcus Bauser, Dr. Jose Das Dores Sousa, Dr. Harrie Gijsen, Dr. Soufyan Jerhaoui, and Dr. Alexander Jones for their assistance and support.

Keywords: C-H cyanation • Heteroarene • Flow-electrochemistry • Electrosynthesis • Direct Anodic oxidation

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[49] Versatile conditions: also possible with dichloromethane and acetonitrile instead of 2-methyltetrahydrofuran. Since nBu$_4$NCN is hydroscopic, an excess of water was added to the mixture to obtain an accurate methodology.
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[53] Trapping experiments were conducted in the presence of 1 equivalent of TEMPO. Although we haven't observed the formation of the TEMPO adduct, the electrochemical cyanation reaction is completely inhibited in the presence of TEMPO (see SI).

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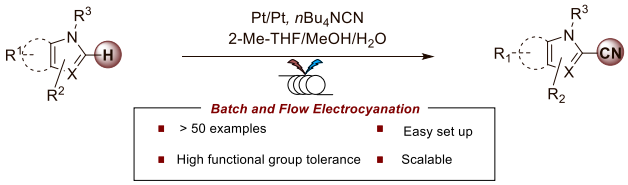

A robust direct C(sp^2)-H electrocyanation using nBu$_4$NCN in an undivided Pt cell was developed in batch as well as in flow, demonstrating scalability of the new methodology. A total of 44 examples were synthesized in batch, and 14 in flow using our conditions, including pyrroles, imidazoles, (aza)indoles and indazoles. The method displays high functional group tolerance and, for the first time, allows to directly cyanate unprotected *N*-H indoles.