GDCh Research Article Angewandte International Edition Chemie
www.angewandte.org

How to cite: Angew. Chem. Int. Ed. **2024**, e202411930
doi.org/10.1002/anie.202411930

Electrochemistry Hot Paper

# Electrochemical Homo- and Crossannulation of Alkynes and Nitriles for the Regio- and Chemoselective Synthesis of 3,6-Diarylpyridines

*Mangish Ghosh, Tirtha Mandal, Mattia Lepori, Joshua P. Barham, Julia Rehbein, and Oliver Reiser**

**Abstract:** We disclose a mediated electrochemical [2+2+2] annulation of alkynes with nitriles, forming substituted pyridines in a single step from low-cost, readily available starting materials. The combination of electrochemistry and a triarylamine redox mediator obviates the requirements of transition metals and additional oxidants. Besides the formation of diarylpyridine moieties via the homocoupling of two identical alkynes, the heterocoupling of two different alkynes depending on their electronic nature is possible, highlighting the unprecedented control of chemoselectivity in this catalytic [2+2+2] process. Mechanistic investigations like cyclic voltammetry and crossover experiments combined with DFT calculations indicate the initial oxidation of an alkyne as the key step leading to the formation of a vinyl radical cation intermediate. The utilization of continuous flow technology proved instrumental for an efficient process scale-up. The utility of the products is exemplified by the synthesis of π-extended molecules, being relevant for material or drug synthesis.

## Introduction

The omnipresence of the pyridine moiety in natural products, pharmaceuticals, organic materials, and catalysts accentuates its privileged character; examples relevant to this work are shown in Figure 1A.[1–6] Given this importance, many metal-catalyzed pathways,[7] such as C–H activation,[8] rearrangement,[9] ring-expansion,[10] multicomponent reactions,[11] and molecular editing approaches[12] have been developed for its synthesis. Transition metal-catalyzed intramolecular [2+2+2] annulations[13] by coupling two alkynes with nitriles, which take advantage of using tethered diynes (Figure 1B) to reduce the entropic penalty have been proven as an effective route to pyridines.[14] Since the pioneering work of Wakatsuki and Yamazaki on CpCo(I)-catalyzed reactions,[15] this cycloaddition has been extensively explored with the aid of various transition metal catalysts, including cobalt,[16] nickel,[17] iron,[18] ruthenium,[19] rhodium,[20] and iridium.[21] Relevant to this work, the *intramolecular* cyclization of two different alkynes could be achieved as well by tethering either the two alkynes or one alkyne with the nitrile moiety[17b,18,20,21a,22] (Figure 1B), thus allowing to control chemoselectivity.

*Intermolecular* transition metal-catalyzed cycloadditions between nitriles and alkynes also represent a straightforward but scarcely explored atom-economical approach for synthesizing multisubstituted pyridines (Figure 1B).[16c,23] However, following this strategy, only the coupling of two identical and symmetrical alkynes was possible, while unsymmetrical, e.g. terminal alkynes, generally give rise to regioisomers. To the best of our knowledge, the intermolecular coupling between two different alkynes and a nitrile was only accomplished in a stepwise fashion using stoichiometric amounts of $Cp_2ZrEt_2$ and $NiCl_2(PPh_3)_2$ by Takahashi and co-workers[24a] or using titanium alkoxide by Sato and co-workers,[24b] alternatively vinyliodonium salts as one coupling partner have been employed.[24c]

Thus, a catalytic strategy to realize a three-component cross-annulation of two different alkynes with nitriles would consist of a valuable expansion of the current state of the art, allowing the synthesis of diverse pyridine scaffolds.

Recent discoveries and upsurge of research in the photo- and electrochemistry domain offer an alternative to classical metal-mediated reaction conditions to construct pyridine rings. Wang, Meng, and co-workers reported a photocatalytic [2+2+2] cyclization of aromatic alkynes with nitriles for the synthesis of 2,3,6-trisubstituted pyridines using a pyrylium salt as the photoredox catalyst (Figure 1C)[25] that was able to overcome the high oxidation potentials of alkynes being the major challenge in this transformation. Electrochemistry has the advantage of employing electrons as traceless redox reagents for activating common and inert organic molecules, particularly alkynes,[26] for generating highly reactive intermediates. Recently, electrochemical transformations have undergone a renaissance,[27] and in the context of this study, [2+2+2] electrochemical homo cyclotrimerizations of alkynes to arenes have been well explored. (Figure 1D).[28] We demonstrate here an intermolecular cyclization strategy of alkynes and nitriles providing 2,3,6-tri-substituted pyridines via constant-current electrolysis using the combination of a

---

[*] M. Ghosh, Dr. T. Mandal, M. Lepori, Dr. J. P. Barham, Prof. Dr. J. Rehbein, Prof. Dr. O. Reiser
Institut für Organische Chemie
Universität Regensburg
Universitätsstrasse 31, 93053 Regensburg (Germany)
E-mail: oliver.reiser@chemie.uni-regensburg.de

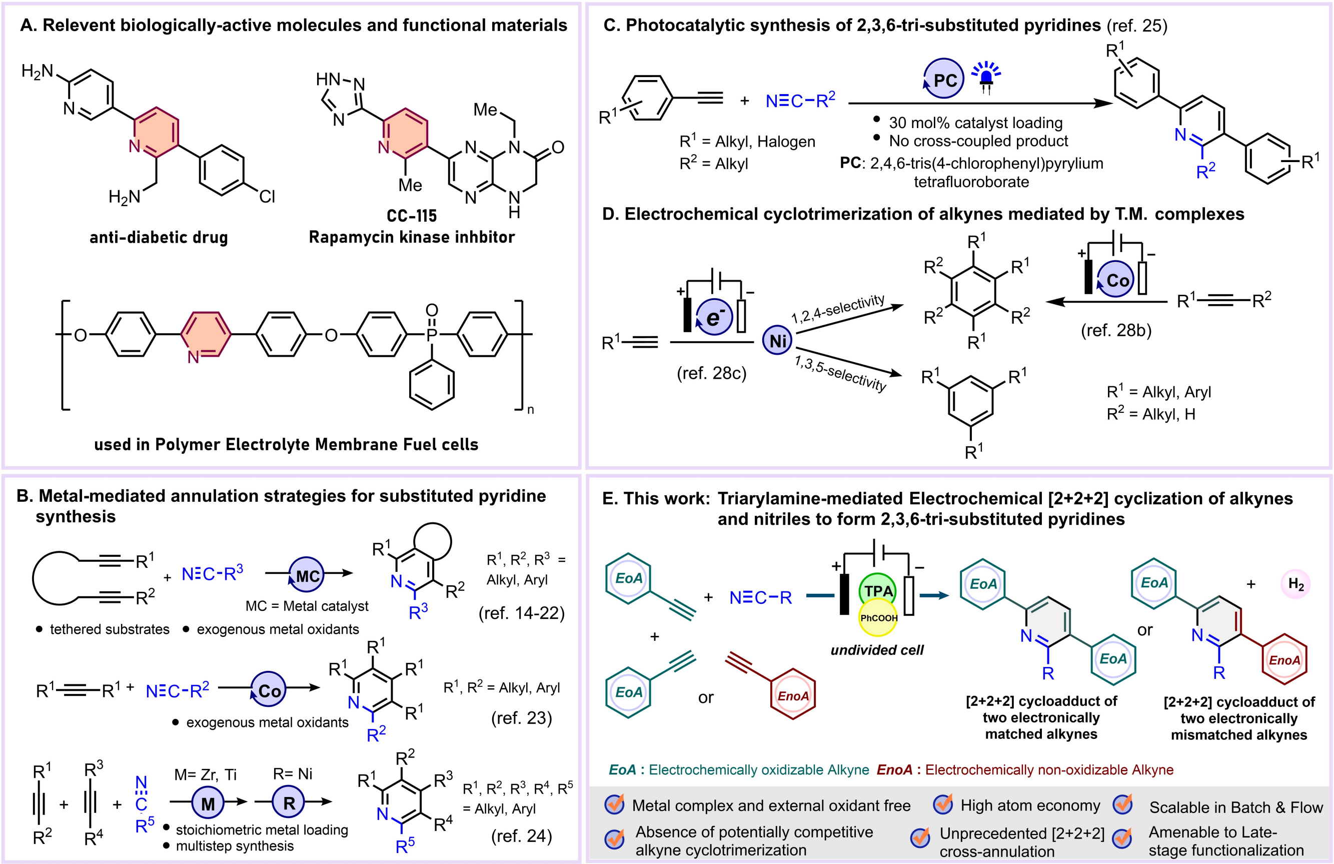


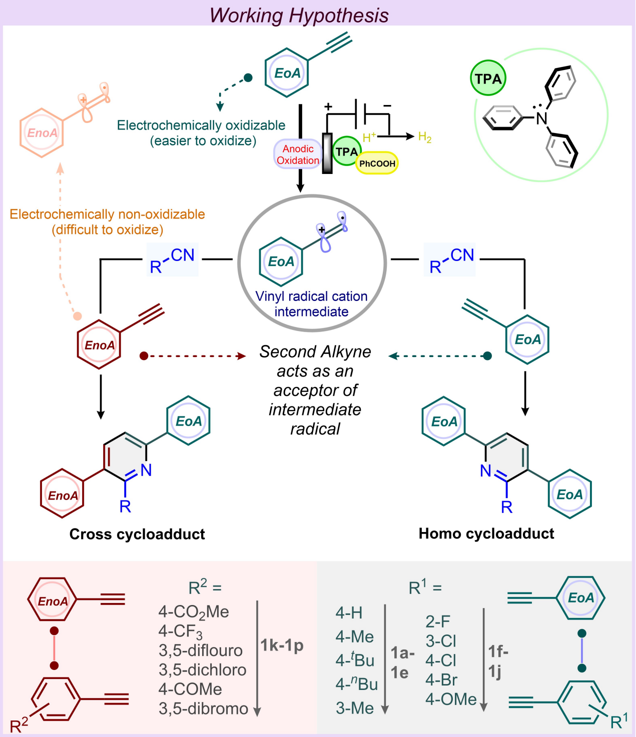
***Figure 1.*** Synthesis of Polysubstituted Pyridines: Literature Survey and Present Work

catalytic amount of triphenylamine (TPA) and benzoic acid as a redox shuttle which obliviates the use of metals and other external additives (Figure 1E). The cross-cyclization of two different alkynes is especially possible, being to the best of our knowledge, unprecedented. Moreover, a competitive alkyne [2+2+2] cyclotrimerization is not observed.

## *Results and Discussion*

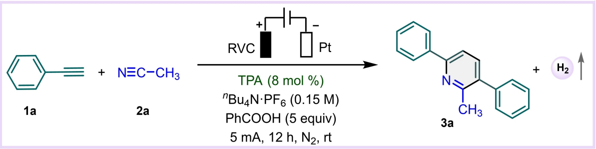
We hypothesized that the key to success for this methodology relies on the formation of an electrophilic radical cation species via the single-electron oxidation of alkynes (Scheme 1). While the direct anodic oxidation of phenylacetylene (**1a**, $E^{ox}_{p/2} = +2.35$ V) in acetonitrile (**2a**) indeed gave rise to the desired cycloadduct **3a**, the yield was only moderate (Table 1, entry 2). Taking learnings from the success of triarylamines as redox mediators in electrochemical reactions,[29] we employed TPA (8 mol %) in a catalytic loading to facilitate the process (*cf* mechanistic discussion, see below), which doubled the yield of **3a** (Table 1, entry 1). TPA, together with tetrabutylammonium hexafluorophosphate ($^n$Bu$_4$NPF$_6$, 0.15 M) as an electrolyte, was optimal, contrasting other combinations tested (Table 1, entries 3–5). Equally important was the employment of benzoic acid (5 equiv) as a sacrificial reductant that generated hydrogen on the cathode, while other proton sources proved less effective (Table 1, entries 6–8). It should be noted that benzoic acid is cost-effective (approximately 10 % of the price of widely used trifluoroacetic acid as an over-stoichiometric additive in electrochemistry)[30] and a benign choice, being abundantly used as a food additive. Furthermore, the choice of the electrode material was crucial: Best results were obtained with a reticulated vitreous carbon (RVC) anode—a microporous, glassy carbon electrode material—and a platinum cathode.A graphite plate was also acceptable as anode, albeit giving a slightly lower yield, while a graphite plate as both electrodes gave no reaction (Table 1, entries 9–10). Decreasing the reaction time or increasing the current decreased the product yield (Table 1, entry 11–12). Divided cell experiments emphasized the benefits of an undivided cell and its operational simplicity (Table 1, entry 13). No product was obtained by constant potential electrolysis controlling the anodic potential at +1.3 V, whereas **3a** was obtained in 23 % yield by applying a constant potential of +2.5 V (Table 1, entry 14). We, therefore, concluded that the anodic oxidation of the alkyne is essential to initiate the cycloaddition reaction. An inert atmosphere was important (Table 1, entry 15), and moreover, no product formation without electricity passed excluded the possibility of a background reaction (entry 16).

With the optimized conditions in hand, we examined the scope of the reaction (Scheme 2). Phenylacetylenes with moderately electron-donating (Alkyl) and electron-with-



***Scheme 1.*** TPA-PhCOOH Assisted Electrosynthetic [2+2+2] Cyclization of Alkynes with Nitriles: Working Hypothesis

***Table 1:*** Reaction Development.[a]



| Entry | Deviation from standard conditions | Yield **3a** (%)[b] |
|---|---|---|
| 1 | None | 76 (74)[c] |
| 2 | without triphenylamine (TPA) | 38 |
| 3 | tris(4-bromophenyl)amine instead of triphenylamine | 17 |
| 4 | $^n$Bu$_4$NBF$_4$ instead of $^n$Bu$_4$NPF$_6$ | 42 |
| 5 | $^n$Bu$_4$NPF$_6$ (0.2 M) | 56 |
| 6 | without PhCOOH | 0 |
| 7 | CF$_3$COOH instead of PhCOOH | $<5$ |
| 8 | PivOH instead of PhCOOH | 48 |
| 9 | Gf(+)/Pt(−) instead of RVC(+)/Pt(−) | 66 |
| 10 | Gf(+)/Gf(−) instead of RVC(+)/Pt(−) | 0 |
| 11 | 5 mA, 6 h instead of 5 mA, 12 h | 47 |
| 12 | 10 mA, 6 h instead of 5 mA, 12 h | 33 |
| 13 | Divided cell (Anodic chamber: **1a**, TPA, 0.15 M $^n$Bu$_4$NPF$_6$, 4 mL MeCN; Cathodic chamber: PhCOOH, 0.15 M $^n$Bu$_4$NPF$_6$, 4 mL MeCN) | 47 |
| 14 | Constant potential: @1.3 V/@2.5 V | 0/23 |
| 15 | under air | 49 |
| 16 | without electricity | 0 |

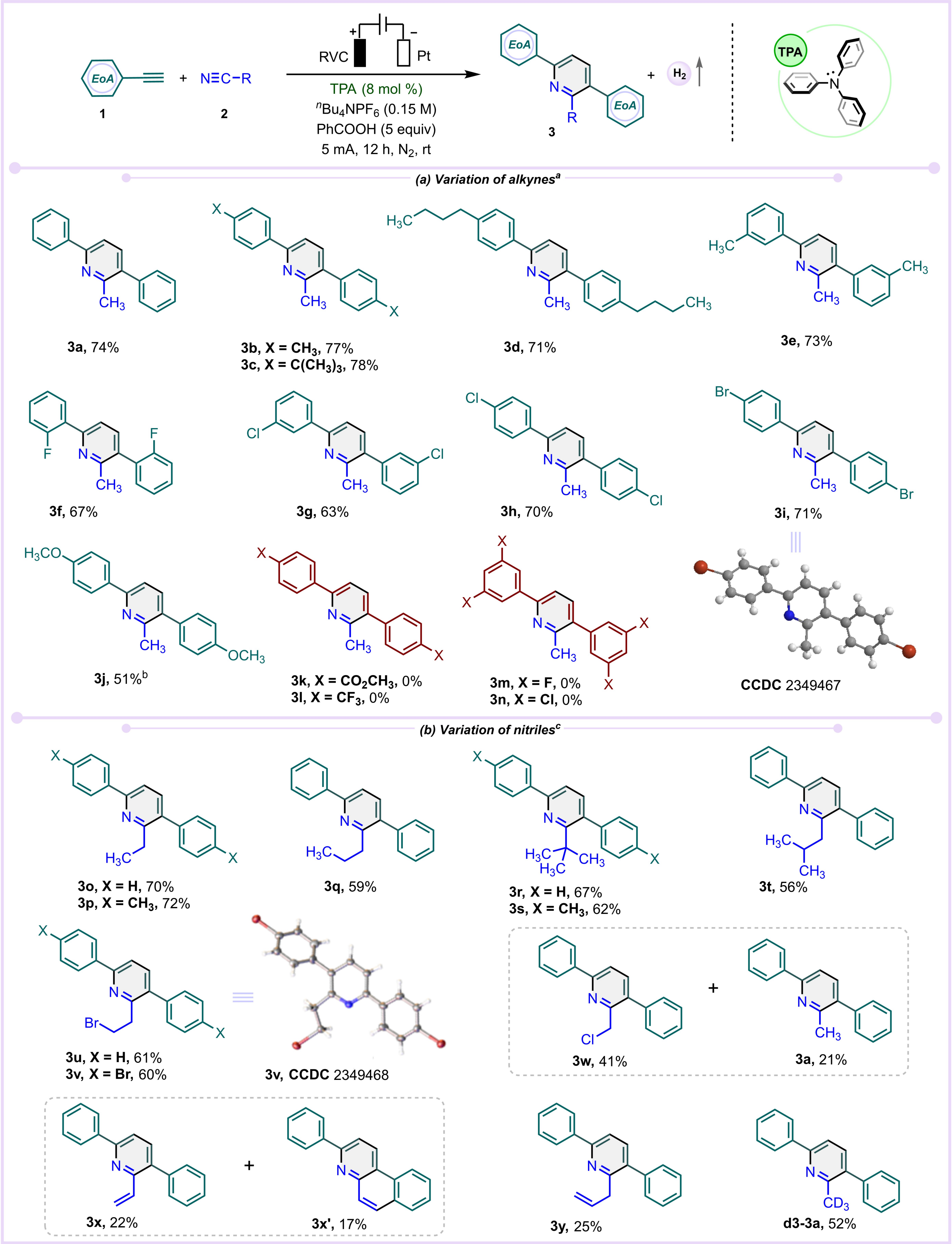
[a] Reaction conditions: **1a** (0.5 mmol, 1 equiv), **2a** (4 mL), TPA (8 mol%), $^n$Bu$_4$NPF$_6$ (0.15 M in 4 mL **2a**), PhCOOH (5 equiv), RVC anode (1.5 cm×0.8 cm×0.5 cm), Pt wire cathode, constant current 5 mA, 12 h, under N$_2$, room temperature, undivided cell. [b] yields were determined by $^1$H NMR spectroscopy. [c] yield of isolated product.

drawing (*ortho*-F, *para*-Cl, Br) groups allowed the coupling with **2a**, giving rise to **3b**–**i** in good to high (51–78%, Scheme 2a) yields. The structure of pyridine **3i**, which proved valuable for further transformations (see below, Scheme 4), was confirmed by single crystal *X*-ray analysis.[31] A phenyl acetylene derivative with a strong electron-donating group at the *para*- position (*p*-OMe) was also coupled successfully, however, in this case pyridine **3j** could be obtained without the TPA additive. Alkynes containing stronger electron-withdrawing substituents (4-carboxylic ester, 4-trifluoromethyl, 3,5-disubstituted halides (F, Cl)) were found to be unreactive (**3k**–**3n**), suggesting that their initial electrochemical oxidation to a radical cation is not possible under these conditions (*cf* mechanistic discussion, see below).

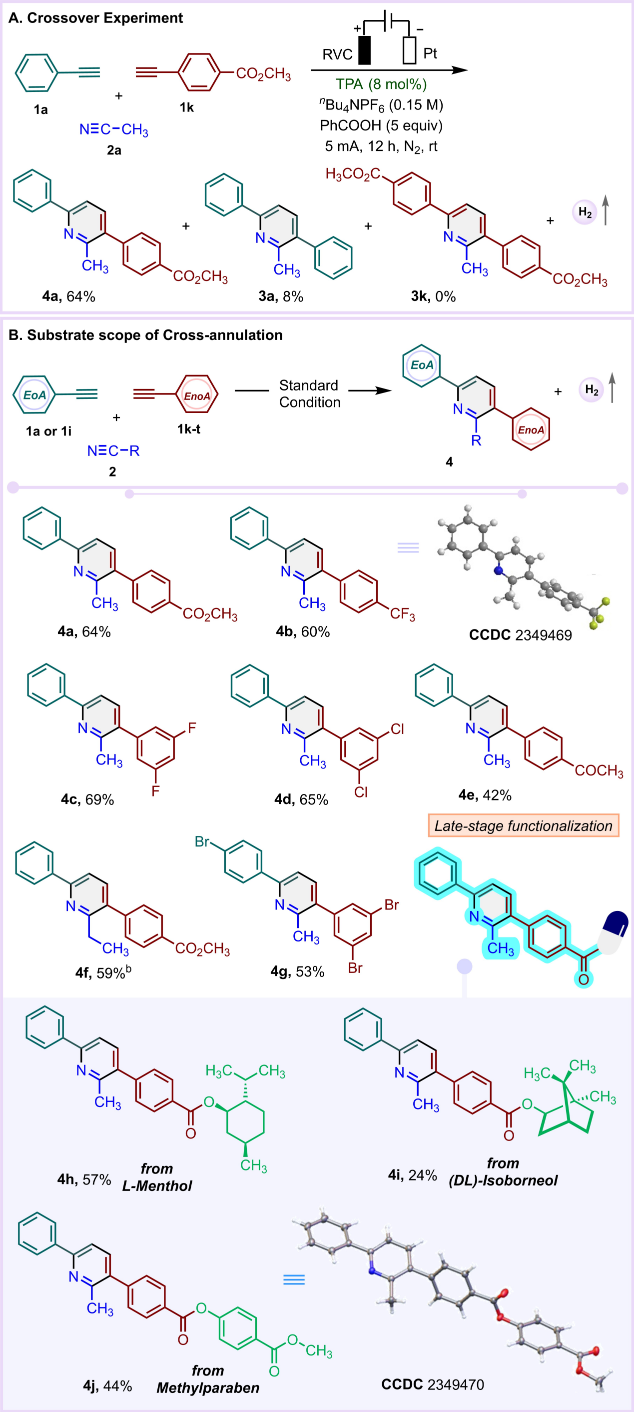
Exploring the scope of nitriles (Scheme 2b) required to identify a suitable solvent other than acetonitrile. After extensive screening (see S.I. for details; Table S10 and S11), we found that nitromethane would allow the coupling of aliphatic nitriles bearing different carbon chains with phenylacetylenes to provide the corresponding 2,3,6-trisubstituted pyridines (**3o**–**3t**, Scheme 2b). Nitriles having a halogen atom at the terminal position were also found to be suitable and afforded the respective pyridine derivatives **3u**, **3v** (confirmed by single crystal *X*-ray analysis)[31] and **3w**; however, competitive reduction to **3a** was observed for the later. Nitriles with a vinylic and allylic double bond were converted to the pyridine derivatives **3x** and **3y**. The lower yields might be explained by a competing radical cyclization of the intermediate arene radical onto the alkene double bond, and indeed, such a process was confirmed with the isolation of **3x′** that was formed along with **3x**. Deuterated acetonitrile (CD$_3$CN) afforded d3-**3a** in good yield with no observable erosion of the deuterium incorporated. However, no product formation was observed if aromatic nitriles were employed.

To turn the inability of electron-poor alkynes (EnoA) to undergo the title transformation into an advantage, we investigated whether coupling nitriles with two electronically different alkynes (EoA and EnoA) is possible. Indeed, by combining **1a** (1 equiv), successful in the homo-annulation, with the unsuccessful alkyne **1k** (1.3 equiv), the cross-annulated product **4a** was obtained in 64% yield (Scheme 3A) along with 8% of the homo-annulated product **3a**, but no homo-coupled product **3k** was observed. Consequently, we successfully combined **1a** with alkynes **1l**–**o** to yield the cross-annulated products **4b**–**4e** (Scheme 3B), unambiguously proven by a single-crystal *X*-ray diffraction analysis of **4b** and **4j**.[32] Noteworthy, pyridine derivative **4g**, synthesized in 53% yield from 4-bromophenylacetylene **1i** (EoA) and 3,5-dibromophenylacetylene **1p** (EnoA), showed that subtle differences in the electronic nature of the alkynes are sufficient to achieve heterocouplings.

Moreover, late-stage functionalization of bioactive molecules and agrochemicals using 4-ester substituted phenylacetylenes derived from (−)-menthol, (±)-isoborneol and



**Scheme 2.** Substrate Scope of Electrochemical [2+2+2] Annulation between EoAs and Nitriles. Reaction conditions: [a]**1** (0.5 mmol, 1 equiv), **2** (4 mL), TPA (8 mol%), $^{n}Bu_4NPF_6$ (0.15 M in 4 mL **2a**), PhCOOH (5 equiv), RVC anode (1.5 cm×0.8 cm×0.5 cm), Pt wire (0.06 cm) cathode, constant current = 5 mA, 12 h, under $N_2$, room temperature, undivided cell. [b] without TPA, [c] **1** (0.5 mmol, 1 equiv), **2** (10 mmol, 20 equiv), TPA (8 mol%), $CH_3NO_2$ (4 mL), $nBu_4NPF_6$ (0.15 M in 4 mL $CH_3NO_2$), PhCOOH (5 equiv), RVC anode (1.5 cm×0.8 cm×0.5 cm), Pt wire (0.06 cm) cathode, constant current = 5 mA, 12 h, under $N_2$, room temperature, undivided cell; yields are of the isolated products.



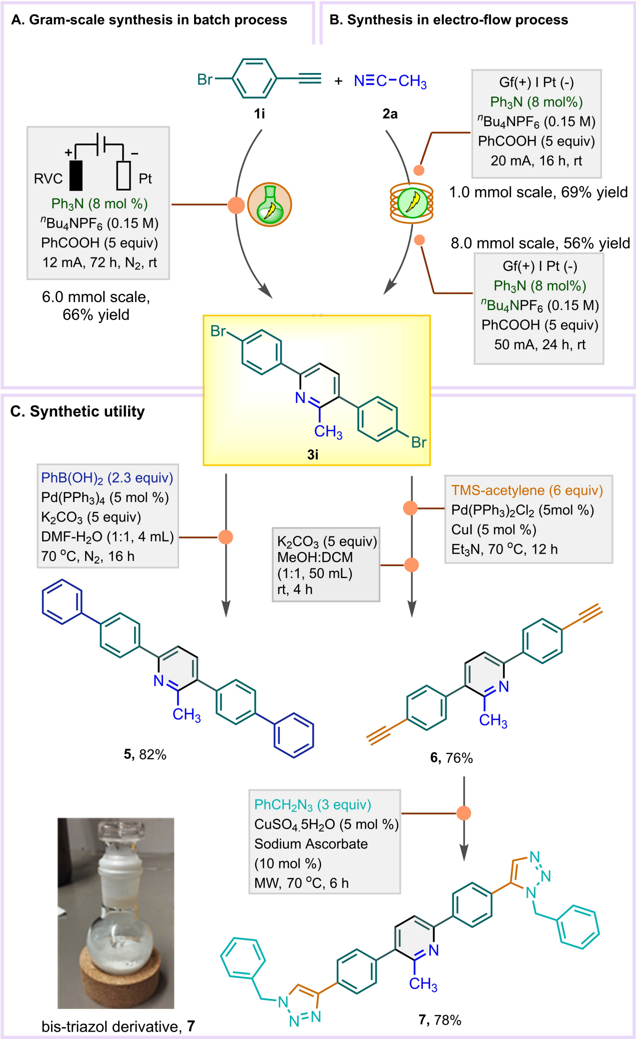
***Scheme 3.*** Three Component Electrochemical [2+2+2] Annulation of EoAs, EnoAs and Nitriles. Reaction conditions: [a]**1** (0.25 mmol, 1 equiv), **2a** (4 mL), **1k–t** (0.325 mmol, 1.3 equiv), TPA (8 mol%), ${}^{n}Bu_4NPF_6$ (0.15 M in 4 mL **2a**), PhCOOH (5 equiv), RVC anode (1.5 cm×0.8 cm×0.5 cm), Pt wire (0.06 cm) cathode, constant current = 5 mA, 12 h, under $N_2$, room temperature, undivided cell. [b] **2b** (10 mmol, 20 equiv), $CH_3NO_2$ (4 mL); yields are of the isolated products.

methylparaben furnished the desired pyridine derivatives **4h–j** in moderate to good yields (Scheme 3B).

Scale-up in batch was demonstrated for coupling **1i** (6 mmol) and **2a** (Scheme 4A), requiring an increase of the current to 12 mA and extending the reaction time to 72 h to give rise to **3i** in 66 % yield. If desired, benzoic acid can partly be recovered (40 %) during the workup (see the S.I. for details).

The transformation could also be performed in a continuous electro-flow reactor: Compared to the batch setup, the reaction time was significantly shorter with similar efficiency (1 mmol scale, 16 h, 69 % yield; $t_R$ = 20 min per pass vs. 72 h, 66 % yield; Scheme 4B, see S.I. for details). Scale up to 8 mmol increased the reaction time to 24 h (56 % yield of **3i**) and proved robust and reproducible.

**3i** set the stage for exploring post-functionalizations (Scheme 4b). Aiming at the extension of the π-system, a Suzuki–Miyaura reaction gave rise to **5** (82 % yield), while the sequence of a Sonogashira coupling, TMS-deprotection, and copper-catalyzed azide-alkyne cycloaddition resulted in bis-triazolyl derivative **7** (59 % yield over 3 steps).



***Scheme 4.*** Gram Scale Synthesis in Batch and Flow and Synthetic Transformations.

Mechanistic studies began with a control reaction, employing the independently prepared TPA radical cation directly instead of the parent TPA (Figure 2A, see S.I. for details): Coupling of **1a** with **2a** gave rise to the desired product **3a** in a similar yield (67 %) but in a decreased reaction time of 8 h instead of 12 h. Continuous product formation was observed from the outset. In contrast, an initial unproductive phase is noted under the standard reaction conditions, presumably required for complete anodic oxidation of the (easier to oxidize) TPA before the alkyne can be oxidized, thus calling for a reaction time of 12 h.

When TEMPO or BHT were added to the reaction mixture as radical scavengers (Figure 2B), the reaction was completely inhibited, which was congruent with an operative radical path. Hydrogen gas evolution was detected on the cathode, which was qualitatively analyzed by GC (Figure 2C, see S.I. for details) or by its utilization for the hydrogenation of 1,2-dihydronapthalene (see S.I. for details).

CV measurements (see S.I. for details) revealed that the oxidation potential of TPA is +0.99 V vs SCE, while that of arylacetylenes is above +2.1 V vs SCE. Thus, TPA should be initially fully oxidized at the anode but due to the difference in potentials, it is unlikely to act as a mediator[29,33] to oxidize the EoAs. We therefore propose that EoAs undergo direct single-electron oxidation at the anode after the complete oxidation of TPA. We then questioned the role of TPA, which, while not necessary for reactivity, is beneficial for an improved yield (Table 1, entries 1 and 2). CV measurements of TPA-PhCOOH mixtures (Figure 2D) show that with an increasing molar ratio of benzoic acid, the oxidation current intensity of TPA steadily decreases, whereas the reduction current intensity of PhCOOH increases gradually. This implies that the 'fresh' TPA concentration at the electrode available for oxidation decreases as the PhCOOH loading increases. EPR measurements show the complete disappearance of the strong signal of TPA radical cation[34] after mixing with potassium benzoate (Figure 2E, see S.I. for details), suggesting the single-electron reduction of the TPA radical cation by benzoate anion.

Based on the above, a plausible mechanistic rationale (Figure 2F) starts with the initial electrochemical oxidation of TPA to furnish the TPA radical cation at a relatively mild potential (1.0 V vs SCE). In turn, the reduction of benzoic acid leads to hydrogen gas evolution and the formation of a benzoate anion ($BA^-$), which creates a charge transfer complex **A** with the TPA radical cation. In the productive phase of the reaction, EoA **1** eventually undergoes a single electron oxidation at the anode to generate a vinyl radical cation intermediate **I**. Subsequent nucleophilic trapping of **I** by nitrile **2** gives rise to intermediate **II**, which undergoes cycloaddition preferentially with EnoA, generating vinyl radical intermediate **III**/**IV**. Single electron transfer from the charge transfer complex **A** with concurrent protonation[35] provides the protonated cross-annulated product **4-H$^+$** with concurrent formation of phenylcarboxylic radical ($BA^\bullet$). Reduction of the latter at the cathode regenerates a phenylcarboxylate anion ($BA^-$), which recombines with the TPA radical cation to **A** ready for the next cycle. Intermediate **IV** also can be directly reduced at the cathode, which we assume is less effective than SET by complex **A**.

To understand the counterintuitive preference of two electron-poor components (**II** and EnOA) interacting with each other selectively to make a cross-annulation possible, the frontier molecular orbitals of the reacting partners **II-1a--2a** and **1a**, **1k**, and **1p** were analyzed (Figure 3).

Based on the orbital energies (ε), the only possible interaction is between the LUMO of the radical cation **II-1a–2a** and the HOMO of the alkyne **1**. Hence, the coupling between **II** and **1** is best described as a formal [4+2] cycloaddition[36] of the C–N and C–C π-bonds with no involvement of the radical center. To match energetically the low lying LUMO of the radical cation **II**, the HOMO of the alkyne must be low enough in energy, favoring acceptor substitution at the alkyne. A good indication that the mechanistic hypothesis of a formal [4+2] is a suitable description is the observation that the FMO-gaps ( Δε) are of predictive power for substrate selectivity. The correlation of Δε-values and the experimentally observed preference of **II-1a–2a** for electron-poor alkynes like **1k** and **1p** over **1a** is readily explained with the smaller FMO-gap, implying a decreasing barrier of this elementary step.

The signs of the interacting orbitals (Figure 3A) suggest that a concerted path is possible, leading to a highly resonance stabilized radical cation **III** that is significantly downhill in regard to the starting structures ($\Delta_R H = -110.1$ kcal/mol for **II-1a–2a+1p**). Also, this concerted path explains the regioselectivity for the observed 1,2,5-substituted **III**, which can delocalize the unpaired electron over the aryl ring of the former alkyne reactant, whereas the opposite regioisomer lacks this possibility (see. S.I. for details).

## Conclusion

In summary, we have developed an operationally simple and scalable methodology from commercially available starting materials for the formation of trisubstituted pyridines through the triphenylamine and benzoic acid promoted electrochemically induced [2+2+2] annulation of aromatic alkynes with nitriles. Especially, we have identified two classes of alkynes (EoAs and EnoAs) depending on their ability to undergo electrochemical oxidation. We have successfully engaged them with nitriles in an intermolecular three-component cross-annulation, being the first of its kind. Additionally, scalability in batch and continuous-flow processes has demonstrated the effectiveness of the developed protocol. The synthetic diversification to access π-extended aromatics emphasizes the utility of this method. A plausible mechanism has been proposed, supported by a series of mechanistic studies, radical quenching experiments, CV, EPR, NMR, and computational studies. The here-developed electrochemical strategy is complementary to the well-established and metal-mediated [2+2+2]-cycloaddition between alkynes and nitriles but stands out in its ability to

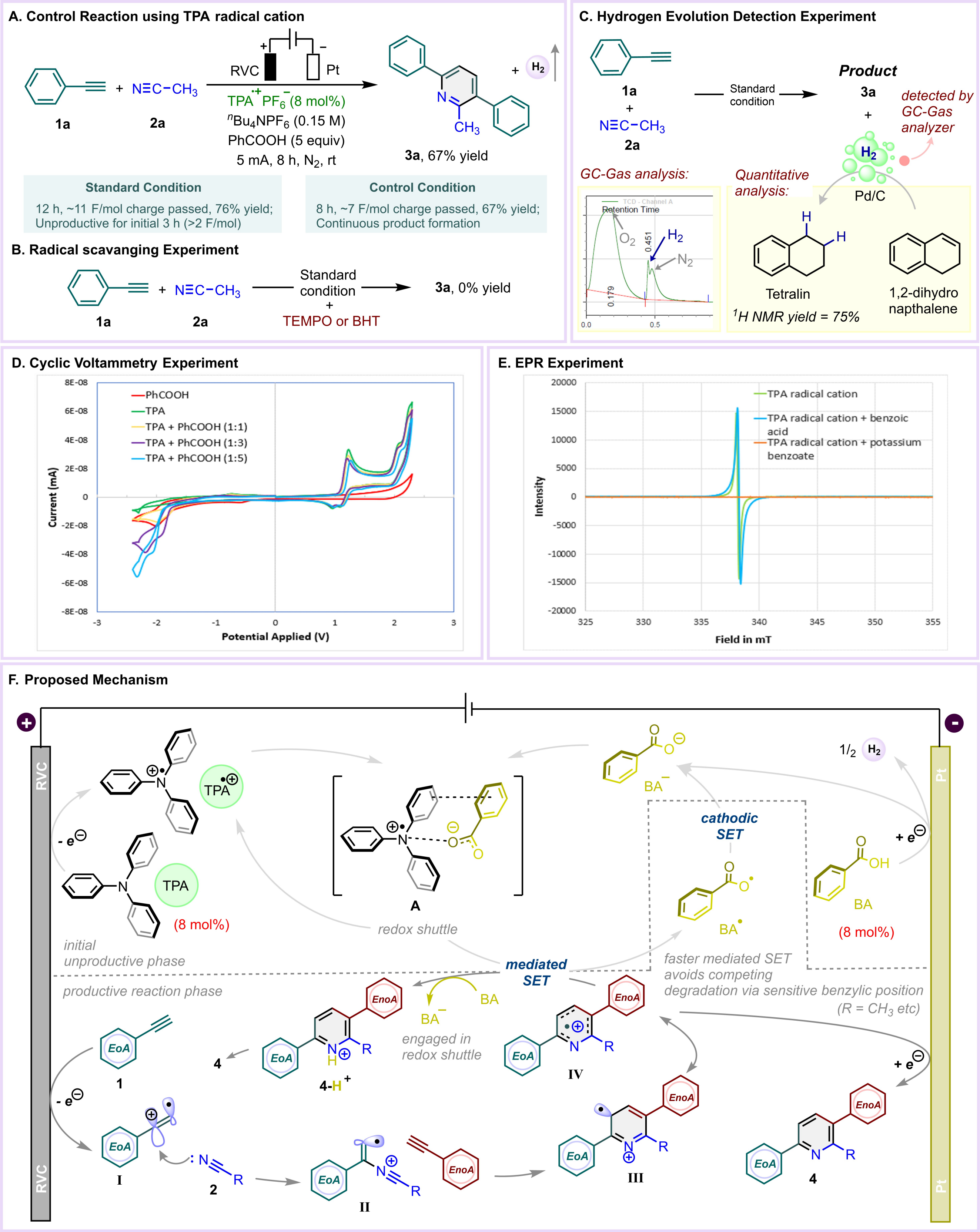


Figure 2. Mechanistic studies and plausible mechanism.

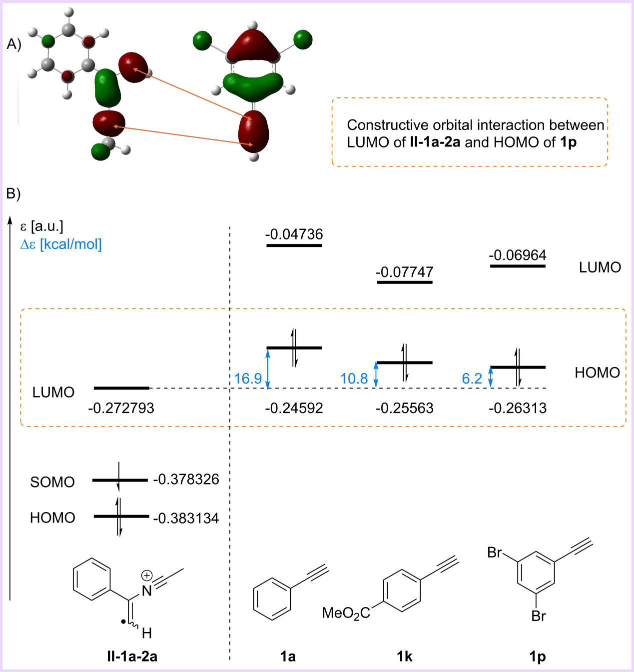


***Figure 3.*** FMO-analysis rationalizing the necessity of electron-poor alkynes and the observed chemoselectivity, i.e., preference of **1p** over **1a** in the reaction with **II-1a–2a**.

allow cross-annulations with two alkynes with high chemo- and regioselectivity.

## Acknowledgements

This work was supported by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation)—TRR 325444632635-A2, the European Commission (Marie Curie Action CuII-VLIH—101066526; postdoctoral research fellowship TM), and the Elite Network of Bavaria Doctoral College: "IDK Chemical Catalysis with Photonic or Electric Energy Input". We thank Sabine Stempfhuber and Birgit Hischa for X-ray analysis, Regina Hoheisel for cyclic voltammetry studies, and Dr. Gábor Balázs for EPR measurements (all University of Regensburg). Open Access funding enabled and organized by Projekt DEAL.

## Conflict of Interest

The authors declare no conflict of interest.

## Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

**Keywords:** Cross-coupling · Chemoselective · Diarylpyridines · Electrochemical cycloaddition · Electro-flow · π-extended molecules

---

[1] a) N. Nicolaus, H.-G. Schmalz, *Synlett* **2010**, 2071–2074; b) C. Yuan, C. T. Chang, A. Axelrod, D. Siegel, *J. Am. Chem. Soc.* **2010**, *132*, 5924–5925; c) B. L. Gray, X. Wang, W. C. Brown, L. Kuai, S. L. Schreiber, *Org. Lett.* **2008**, *10*, 2621–2624.

[2] H. L. Fraser, D. W. Hopper, K. M. K. Kutterer, A. L. Crombie, in *Progress in Heterocyclic Chemistry, G. W. Gribble, J. A. Joule, Vol. 19*, Elsevier, Amsterdam **2008**, pp. 314–352.

[3] a) G. C. Fu, *Acc. Chem. Res.* **2004**, *37*, 542–547; b) B. L. Small, *Acc. Chem. Res.* **2015**, *48*, 2599–2611.

[4] a) T. J. J. Müller, U. H. F. Bunz, *Functional Organic Materials*, Wiley-VCH, Weinheim **2007**; b) B. W. D'Andrade, M. E. Thompson, S. R. Forrest, *Adv. Mater.* **2002**, *14*, 147–151; c) K. M. Bera, P. Hommes, H.-U. Reissig, *Chem. Eur. J.* **2011**, *17*, 11838–11843; d) J. K. Kallitsis, M. Geormezi, S. G. Neophytides, *Polym. Int.* **2009**, *58*, 1226–1233.

[5] a) H. J. Roth, A. Kleemann, *Drug Synthesis in Pharmaceutical Chemistry*, John Wiley and Sons, New York **1988**; b) R. K. Anchoori, M. S. Q. Kortenhorst, M. Hidalgo, T. Sarkar, G. Hallur, R. Bai, P. J. V. Diest, E. Hamel, S. R. Khan, *J. Med. Chem.* **2008**, *51*, 5953–5957.

[6] a) G. de Ruiter, M. Lahav, M. E. van der Boom, *Acc. Chem. Res.* **2014**, *47*, 3407–3416; b) Y. Z. Wang, A. J. Epstein, *Acc. Chem. Res.* **1999**, *32*, 217–224.

[7] M. D. Hill, *Chem. Eur. J.* **2010**, *16*, 12052–12062.

[8] a) D. A. Colby, R. G. Bergman, J. A. Ellman, *J. Am. Chem. Soc.* **2008**, *130*, 3645–3651; b) Z. Shi, D. C. Koester, M. Boultadakis-Arapinis, F. Glorius, *J. Am. Chem. Soc.* **2013**, *135*, 12204–12207.

[9] I. Nakamura, D. Zhang, M. Terada, *J. Am. Chem. Soc.* **2010**, *132*, 7884–7886.

[10] Y.-F. Wang, S. Chiba, *J. Am. Chem. Soc.* **2009**, *131*, 12570–12572.

[11] a) X. Sun, C. Wang, Z. Li, S. Zhang, Z. Xi, *J. Am. Chem. Soc.* **2004**, *126*, 7172–7173; b) R. Tanaka, A. Yuza, Y. Watai, D. Suzuki, Y. Takayama, F. Sato, H. Urabe, *J. Am. Chem. Soc.* **2005**, *127*, 7774–7780.

[12] D. B. Dherange, Q. P. Kelly, P. J. Liles, S. M. Sigman, D. M. Levin, *J. Am. Chem. Soc.* **2021**, *143*, 11337–11344.

[13] For general [2+2+2] cycloaddition reactions, see reviews: a) G. Domínguez, J. Pérez-Castells, *Chem. Soc. Rev.* **2011**, *40*, 3430–3444; b) P. Matton, S. Huvelle, M. Haddad, P. Phansavath, V. Ratovelomanana-Vidal, *Synthesis* **2021**, *54*, 4–32; c) A. Pla-Quintana, A. Roglans, *Molecules* **2022**, *27*, 1332. For early and recent examples see: d) A. Kondoh, H. Yorimitsu, K. Oshima, *J. Am. Chem. Soc.* **2007**, *129*, 6996–6997; e) J. M. Halford-McGuff, A. M. Z. Slawin, A. J. B. Watson, *ACS Catal.* **2023**, *13*, 3463–3470; f) J. M. Halford-McGuff, M. Varga, D. B. Cordes, A. P. McKay, A. J. B. Watson, *ACS Catal.* **2024**, *14*, 1846–1854.

[14] For reviews see: a) H. Bönnemann, *Angew. Chem. Int. Ed.* **1978**, *17*, 505–515; b) K. P. C. Vollhardt, *Angew. Chem. Int. Ed.* **1984**, *23*, 539–556; c) T. Gläsel, M. Hapke, *Cobalt Catalysis in Organic Synthesis* (Eds.: M. Hapke, G. Hilt), Wiley-VCH, Weinheim **2020**; d) J. A. Varela, C. Saa, *Chem. Rev.* **2003**, *103*, 3787–3802; e) B. Heller, M. Hapke, *Chem. Soc. Rev.* **2007**, *36*, 1085–1094; f) K. Cen, M. Usman, W. Shen, M. Liu, R. Yang, J. Cai, *Org. Biomol. Chem.* **2022**, *20*, 7391–7404.

[15] a) Y. Wakatsuki, H. Yamazaki, *J. Chem. Soc. Chem. Commun.* **1973**, 280a–280a; b) Y. Wakatsuki, H. Yamazaki, *Tetrahedron Lett.* **1973**, *14*, 3383–3384.

[16] *Cobalt:* a) M. Hapke, N. Weding, A. Spannenberg, *Organometallics* **2010**, *29*, 4298–4304; b) P. Garcia, Y. Evanno, P.

George, M. Sevrin, G. Ricci, M. Malacria, C. Aubert, V. Gandon, *Chem. Eur. J.* **2012**, *18*, 4337–4344; c) I. Thiel, H. Jiao, A. Spannenberg, M. Hapke, *Chem. Eur. J.* **2013**, *19*, 2548–2554.

[17] *Nickel:* a) P. Kumar, S. Prescher, J. A. Louie, *Angew. Chem. Int. Ed.* **2011**, *50*, 10694–10698; b) R. M. Stolley, H. A. Duong, D. R. Thomas, J. Louie, *J. Am. Chem. Soc.* **2012**, *134*, 15154–15162; c) X. You, X. Xie, G. Wang, M. Xiong, R. Sun, H. Chen, Y. Liu, *Chem. Eur. J.* **2016**, *22*, 16765–16769.

[18] *Iron:* a) C. Wang, X. Li, F. Wu, B. Wan, *Angew. Chem. Int. Ed.* **2011**, *50*, 7162–7166; b) B. R. D'Souza, T. K. Lane, J. Louie, *Org. Lett.* **2011**, *13*, 2936–2939.

[19] *Ruthenium:* a) Y. Yamamoto, R. Ogawa, K. Itoh, *J. Am. Chem. Soc.* **2001**, *123*, 6189–6190; b) Y. Yamamoto, K. Kinpara, T. Saigoku, H. Takagishi, S. Okuda, H. Nishiyama, K. Itoh, *J. Am. Chem. Soc.* **2005**, *127*, 605–613; c) J.-F. Tan, C. T. Bormann, F. G. Perrin, F. M. Chadwick, K. Severin, N. Cramer, *J. Am. Chem. Soc.* **2019**, *141*, 10372–10383.

[20] *Rhodium:* Y. Komine, A. Kamisawa, K. Tanaka, *Org. Lett.* **2009**, *11*, 2361–2364.

[21] *Iridium:* a) G. Onodera, Y. Shimizu, J. N. Kimura, J. Kobayashi, Y. Ebihara, K. Kondo, K. Sakata, R. Takeuchi, *J. Am. Chem. Soc.* **2012**, *134*, 10515–10531; b) R. Takeuchi, S. Fujisawa, Y. Yoshida, J. Sagano, T. Hashimoto, A. Matsunami, *J. Org. Chem.* **2018**, *83*, 1852–1860.

[22] Y. Wang, L.-J. Song, X. Zhang, J. Sun, *Angew. Chem. Int. Ed.* **2016**, *55*, 9704–9708.

[23] a) C.-S. Wang, Q. Sun, F. Garcia, C. Wang, N. Yoshikai, *Angew. Chem. Int. Ed.* **2021**, *60*, 9627–9634; b) Y. Xie, C. Wu, C. Jia, C.-H. Tung, W. Wang, *Org. Chem. Front.* **2020**, *7*, 2196–2201; c) W. Wang, S. Inoue, S. Enthaler, M. Driess, *Angew. Chem. Int. Ed.* **2012**, *51*, 6271–6275; d) Y. Komine, K. Tanaka, *Org. Lett.* **2010**, *12*, 1312–1315; e) N. A. Spahn, M. H. Nguyen, J. Renner, T. K. Lane, J. Louie, *J. Org. Chem.* **2017**, *82*, 234–242.

[24] a) T. Takahashi, F.-Y. Tsai, M. Kotora, *J. Am. Chem. Soc.* **2000**, *122*, 4994–4995; b) D. Suzuki, R. Tanaka, H. Urabe, F. Sato, *J. Am. Chem. Soc.* **2002**, *124*, 3518–3519; c) J. Sheng, Y. Wang, X. Su, R. He, C. Chen, *Angew. Chem. Int. Ed.* **2017**, *56*, 4824–4828.

[25] K. Wang, L.-G. Meng, L. Wang, *Org. Lett.* **2017**, *19*, 1958–1961.

[26] For selected reviews, see: a) G. M. Martins, B. Shirinfar, T. Hardwick, A. Murtaza, N. Ahmed, *Catal. Sci. Technol.* **2019**, *9*, 5868–5881; b) M. Bortolami, R. Petrucci, D. Rocco, V. Scarano, I. Chiarotto, *ChemElectroChem* **2021**, *8*, 3604–3613; c) K. Sun, J. Lei, Y. Liu, B. Liu, N. Chen, *Adv. Synth. Catal.* **2020**, *362*, 3709–3726; d) H. Mei, Z. Yin, J. Liu, H. Sun, J. Han, *Chin. J. Chem.* **2019**, *37*, 292–301.

[27] For selected reviews, see: a) H. Wang, X. Gao, Z. Lv, T. Abdelilah, A. Lei, *Chem. Rev.* **2019**, *119*, 6769–6787; b) Y. Jiang, K. Xu, C. Zeng, *Chem. Rev.* **2018**, *118*, 4485–4540; c) S. R. Waldvogel, S. Lips, M. Selt, B. Riehl, C. J. Kampf, *Chem. Rev.* **2018**, *118*, 6706–6765; d) M. D. Kärkäs, *Chem. Soc. Rev.* **2018**, *47*, 5786–5865; e) C. Kingston, M. D. Palkowitz, Y. Takahira, J. C. Vantourout, B. K. Peters, Y. Kawamata, P. S. Baran, *Acc. Chem. Res.* **2020**, *53*, 72–83; f) J. C. Siu, N. Fu, S. Lin, *Acc. Chem. Res.* **2020**, *53*, 547–560; g) F. Wang, S. S. Stahl, *Acc. Chem. Res.* **2020**, *53*, 561–574. For recent examples, see: h) M. Selt, B. Gleede, R. Franke, A. Stenglein, S. R. Waldvogel, *J. Flow Chem.* **2020**, *11*, 143–162; i) M. Selt, S. Mentizi, D. Schollmeyer, R. Franke, S. R. Waldvogel, *Synlett* **2019**, *30*, 2062–2067; j) T. Shen, T. H. Lambert, *J. Am. Chem. Soc.* **2021**, *143*, 8597–8602; k) S. Panja, S. Ahsan, T. Pal, S. Kolb, W. Ali, S. Sharma, C. Das, J. Grover, A. Dutta, D. B. Werz, A. Paul, D. Maiti, *Chem. Sci.* **2022**, *13*, 9432–9439; l) Y. Hioki, M. Costantini, J. Griffin, K. C. Harper, M. P. Merini, B. Nissl, Y. Kawamata, P. S. Baran, *Science* **2023**, *380*, 81–87; m) S. H. Park, G. Bae, A. Choi, S. Shin, K. Shin, C. H. Choi, H. Kim, *J. Am. Chem. Soc.* **2023**, *145*, 15360–15369; n) G.-Q. Sun, P. Yu, W. Zhang, W. Zhang, Y. Wang, L.-L. Liao, Z. Zhang, L. Li, Z. Lu, D.-G. Yu, S. Lin, *Nature* **2023**, *615*, 67–72; o) D. E. Holst, D. J. Wang, M. J. Kim, I. A. Guzei, Z. K. Wickens, *Nature* **2021**, *596*, 74–79; p) Z. Lin, A. Oliveira, A. Scheremetjew, L. Ackermann, *J. Am. Chem. Soc.* **2023**, *146*, 228–239.

[28] For general transition metal-free cyclotrimerization of alkynes, see review: a) M. Hapke, *Tetrahedron Lett.* **2016**, *57*, 5719–5729. For recent examples, see: b) K. Liang, L. Lu, X. Liu, D. Yang, S. Wang, Y. Gao, H. Alhumade, H. Yi, A. Lei, *ACS Catal.* **2021**, *11*, 14892–14897; c) S. Arepally, P. Nandhakumar, G. A. González-Montiel, A. Dzhaparova, G. Kim, A. Ma, K. M. Nam, H. Yang, P. Ha-Yeon Cheong, J. K. Park, *ACS Catal.* **2022**, *12*, 6874–6886.

[29] a) X. Wu, A. P. Davis, A. J. Fry, *Org. Lett.* **2007**, *9*, 5633–5636; b) L.-J. Li, Y.-Y. Jiang, C. M. Lam, C.-C. Zeng, L.-M. Hu, R. D. Little, *J. Org. Chem.* **2015**, *80*, 11021–11030; c) C.-Y. Cai, H.-C. Xu, *Nat. Commun.* **2018**, *9*, 3551; d) S. Wu, J. Zurauskas, M. Domanski, P. S. Hitzfeld, V. Butera, D. J. Scott, J. Rehbein, A. Kumar, E. Thyrhaug, J. Hauer, J. P. Barham, *Org. Chem. Front.* **2021**, *8*, 1132–1142; e) M. D. Hareram, A. A. M. A. El Gehani, J. Harnedy, A. C. Seastram, A. C. Jones, M. Burns, T. Wirth, D. L. Browne, L. C. Morril, *Org. Lett.* **2022**, *24*, 3890–3895.

[30] a) H. Huang, T. H. Lambert, *J. Am. Chem. Soc.* **2022**, *144*, 18803–18809; b) T. Shen, T. H. Lambert, *Science* **2021**, *371*, 620–626.

[31] CCDC deposition number 2349467 and 2349468 contain the supplementary crystallographic data of compound **3i** and **3v** for this paper.

[32] CCDC deposition number 2349469 and 2349470 contain the supplementary crystallographic data of compound **4b** and **4j** for this paper.

[33] For selected reviews, see: a) R. Francke, R. D. Little, *Chem. Soc. Rev.* **2014**, *43*, 2492–2521; b) E. Steckhan, *Angew. Chem. Int. Ed.* **1986**, *25*, 683–701.

[34] a) D. N. Stamires, J. Turkevich, *J. Am. Chem. Soc.* **1963**, *85*, 2557–2561; b) H. van Willigen, *J. Am. Chem. Soc.* **1967**, *89*, 2229–2230.

[35] The pyridine products **3** and **4** are not detected (TLC monitoring) in the reaction mixture before aqueous basic work up (see the Supporting Information for details). Based on $pK_a$ values reported for benzoic acid (12.6) and pyrdine$\cdot H^+$ (12.5) in acetonitrile, it appears plausible that the excess of benzoic acid (5 equiv) employed is protecting the pyridine products as salts. *Cf.* a) M. Lõkov, S. Tshepelevitsh, A. Heering, P. G. Plieger, R. Vianello, I. Leito, *Eur. J. Org. Chem.* **2017**, *2017*, 4475–4489; b) A. Kütt, S. Tshepelevitsh, J. Saame, M. Lõkov, I. Kaljurand, S. Selberg, I. Leito, *Eur. J. Org. Chem.* **2021**, *2021*, 1407–1419.

[36] For reviews see: a) X.-E. Cai, Z.-Y. Wang, W.-C. Tian, H. Liu, W. Wei, K. Lei, *Org. Biomol. Chem.* **2023**, *21*, 6068–6082. For examples see: b) S. Tang, D. Wang, Y. Liu, L. Zeng, A. Lei, *Nat. Commun.* **2018**, *9*, 798; c) P. Huang, P. Wang, S. Wang, S. Tang, A. Lei, *Green Chem.* **2018**, *20*, 4870–4874; d) K. Rybicka-Jasińska, Z. Szeptuch, H. Kubiszewski, A. Kowaluk, *Org. Lett.* **2023**, *25*, 1142–1146; e) K. Liang, S. Wang, H. Cong, L. Lu, A. Lei, *CCS Chem.* **2021**, *4*, 1557–1564.

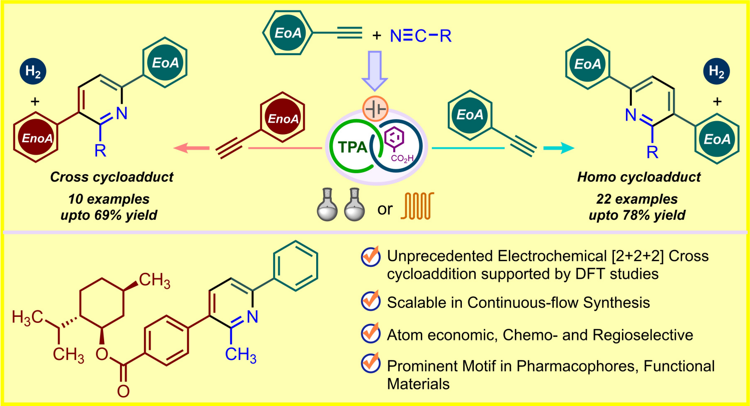
Manuscript received: June 25, 2024
Accepted manuscript online: August 26, 2024
Version of record online: ■■, ■■

## Research Article

### Electrochemistry

M. Ghosh, T. Mandal, M. Lepori,
J. P. Barham, J. Rehbein,
O. Reiser* ________________ **e202411930**

Electrochemical Homo- and Crossannulation of Alkynes and Nitriles for the Regio- and Chemoselective Synthesis of 3,6-Diarylpyridines



**Intermolecular Homo-couplings, but especially Cross-couplings are challenging**! We reported an electrochemical [2+2+2] annulation of alkynes with nitriles using triarylamine as a redox mediator to form substituted pyridines. Our process demonstrates unprecedented control of chemoselectivity, allowing both homo- and heterocouplings of alkynes and nitriles. A mechanistic rationale is proposed, supported by CV, EPR, NMR, and computational studies.