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Very Important Publication

Electrosynthesis of Aryliminophosphoranes in Continuous Flow

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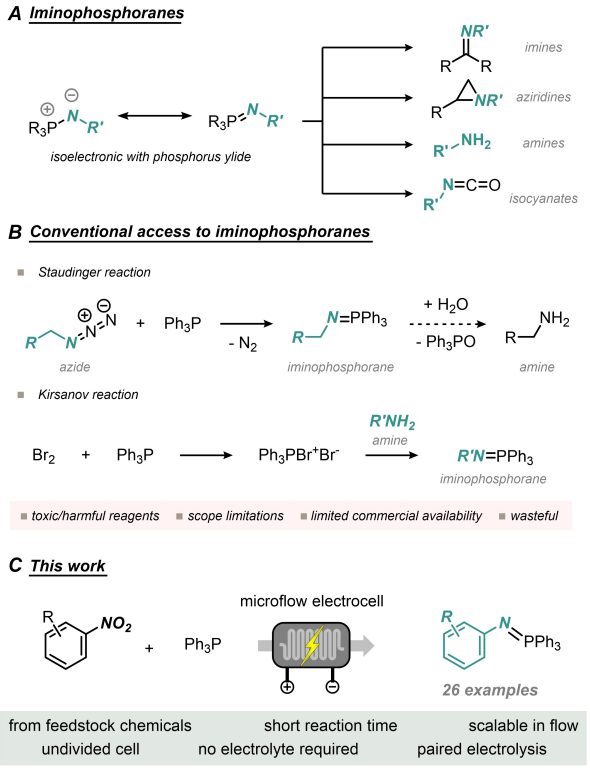
Abstract: A practical electrochemical method for synthesizing aryliminophosphoranes from widely available nitro(hetero)arenes in a continuous-flow system is presented. The utilization of flow technology offers several advantages to our approach, including the elimination of the need for a supporting electrolyte and enhanced scalability. Our method demonstrates good tolerance towards various functional groups, with electron-deficient nitroarenes being particularly suitable for this strategy. In addition, we have demonstrated the versatility of aryliminophosphoranes as intermediates in synthesizing anilines, amines, and amides. To further enhance the utility of our approach, we have developed a telescoped method that utilizes a tube-in-tube setup for the in-situ production of isocyanates.

Keywords: iminophosphoranes; flow electrochemistry; nitroarenes; paired electrolysis; undivided cell

Iminophosphoranes, also known as phosphinimines, hold significant potential in the field of synthetic chemistry as essential precursors for a wide range of organic compounds. They are isoelectronic with phosphorus ylides and, as such, their chemistry is very similar. In fact, apart from their promising applications as superbases[1] and ligands in cross-coupling or hydrogenation reactions,[2] iminophosphoranes also serve as convenient starting materials for the synthesis of heterocycles,[3] aldimines and ketimines through aza-Wittig reactions,[4] aziridines,[5] amines[4,6] and isocyanates through carbonylation with CO_2 (Scheme 1A).[7]

Despite the significant synthetic potential of iminophosphoranes, as of today, a safe and scalable method for their synthesis has not been established. Conventional approaches, such as the Staudinger and Kirsanov reactions, rely on the utilization of toxic and hazardous reagents like azides and molecular bromine (Scheme 1B). These conditions are unsustainable, especially when considering the necessity for a smooth transition from academic research to industrial-scale production.

In light of the limitations in existing synthetic methods for iminophosphoranes, the utilization of electrochemistry could represent a promising alternative. Electrochemistry has emerged as a sustainable and enabling technology in organic synthesis.[8] By flipping the electrical switch for connecting molecules, electrochemical methods provide an ideal solution, especially when aiming for a seamless transition from academic research to industrial production.[9] Furthermore, these electrosynthetic approaches bring multiple



Scheme 1. A) Iminophosphoranes as versatile intermediates in synthesis; B) Conventional ways to access iminophosphoranes: the Staudinger and Kirsanov reactions; C) This work.

benefits, including a substantial reduction in chemical waste, enhanced reaction control, and improved safety.

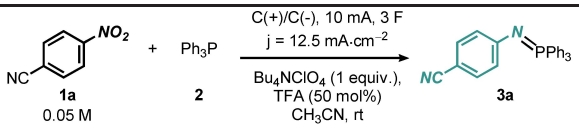
Notably, the ability to switch off electrochemical reactions at any given time eliminates the possibility of runaway reactions.

Electrochemical reactions, by their nature, are heterogeneous processes that involve a redox event occurring between an electrode surface and a molecule in solution. Consequently, efficient mass transfer from the bulk to the electrode surface becomes a critical parameter for scaling up these reactions. Continuous-flow technology presents a viable approach to address this challenge, as it minimizes the impact of poor mass transfer due to its larger surface-to-volume ratio.[10] Microreactors offer a distinct advantage in terms of reduced interelectrode distances, which in turn leads to a decreased Ohmic voltage drop. This characteristic of microreactors translates into a reduced requirement for supporting electrolyte in the reaction mixture, thereby making them an efficient and cost-effective option.

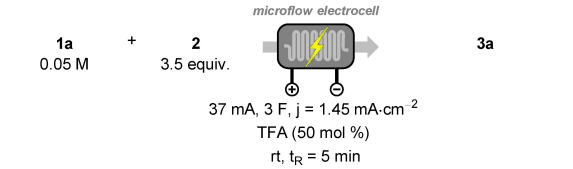
In this study, we present our findings on the electrochemical synthesis of aryliminophosphoranes using a continuous-flow electrochemical reactor (Scheme 1C). Our approach involves the paired electrolysis of easily accessible and cost-effective triphenylphosphine and nitroarenes. Remarkably, this method can be conducted without the need for any additional supporting electrolyte, offering a simplified and efficient process. Furthermore, our electrochemical synthesis is highly scalable, enabling gram-scale production with ease. The versatility of this chemistry extends to a diverse range of medicinally relevant heterocycles and complex scaffolds, making it applicable to a wide portfolio of compounds. Additionally, our method exhibits excellent tolerance towards various functional groups, further enhancing its practicality and potential utility in organic synthesis.

We initiated our investigation by optimizing the paired electrolysis of 4-nitrobenzonitrile (**1a**) and triphenylphosphine (**2**) in a batch electrochemical cell on a 0.1 mmol scale to obtain iminophosphorane **3a** (Table 1, see Supporting Information). Thus, when a 0.05 M CH_3CN solution of **1a** and **2** (4 equiv.) was electrolyzed in galvanostatic mode (C(+)/C(−), I = 10 mA, 2 F) using two graphite electrodes in the presence of Bu_4NBF_4 (2 equiv.) as the supporting electrolyte, **3a** was obtained in 21% ^{1}H-NMR yield (Table 1, Entry 1). Notably, the observed cell potential was relatively high at 2.97 V. In contrast, when trifluoroacetic acid (TFA) was used as an additive (50 mol%), 53% yield was obtained, accompanied by a reduced cell potential of 1.65 V (Table 1, Entry 2).

Table 1. Optimization of reaction conditions in batch and flow.



Entry	2	Additive	Electrolyte	Electrodes	F	Yield (%)
1	4 equiv.	No additive	Bu_4NBF_4 2 equiv.	C(+)/C(-)	2	21
2	4 equiv.	TFA 50 mol%	Bu_4NBF_4 2 equiv.	C(+)/C(-)	2	53
3	4 equiv.	TFA 50 mol%	Bu_4NClO_4 2 equiv.	C(+)/C(-)	2	63
4	4 equiv.	TFA 50 mol%	Bu_4NClO_4 1 equiv.	C(+)/C(-)	2	67
5	4 equiv.	TFA 50 mol%	Bu_4NClO_4 1 equiv.	C(+)/Fe(-)	2	54
6	4 equiv.	TFA 50 mol%	Bu_4NClO_4 1 equiv.	C(+)/C(-)	3	90
7	**3.5 equiv.**	**TFA 50 mol%**	**Bu_4NClO_4 1 equiv.**	**C(+)/C(-)**	**3**	**90**



Entry	Current (mA)	Flow rate (mL·min^{-1})	Residence time (min)	Electrolyte	Yield (%)
8	74	0.300	2.5	Bu_4NClO_4 1 equiv.	63
9	37	0.150	5	Bu_4NClO_4 1 equiv.	91
10	**37**	**0.150**	**5**	**none**	**95**

During our investigation of supporting electrolytes, we discovered that the inclusion of Bu_4NClO_4 resulted in improved yields, with a significant increase to 63% (Table 1, Entry 3). The reaction remained efficient when the loading of the electrolyte was decreased to 1 equivalent (67%, Table 1, Entry 4). We conducted a comprehensive screening of various electrodes and observed that the initial combination of graphite/graphite allowed us to obtain the highest yield for the compound **3 a**. Interestingly, a comparable result (54%, Table 1, Entry 5) was obtained using a stainless steel cathode. Furthermore, we explored the effect of applied charge (F) while maintaining a constant current (10 mA). By increasing the charge to 3 F, we could obtain **3 a** in 90% yield, even when decreasing the equivalents of **2** (Table 1, Entries 6 and 7, respectively). In our optimized conditions, we employed a current density of 12.5 $mA \cdot ^{cm-2}$ to achieve reproducible and favorable results.

Finally, in order to reduce reaction times and minimize the amount of supporting electrolyte used for the transformation, we translated our batch conditions to a continuous micro-flow process (Table 1, Entries 8–10) by using an electrochemical flow cell developed by our research group (see Supporting Information, inter electrode gap 250 μm).[11] Remarkably, through this flow process, we were able to reach excellent yields (95%, Table 1, Entry 10) in just 5 minutes of residence time, all in the absence of any supporting electrolyte. Further details regarding the optimization of reaction conditions in both batch and flow modes can be found in the Supporting Information file. It is important to mention that the insolubility of other commercially available triaryl phosphines (e.g., tris(4-methoxyphenyl)phosphine and tris(p-tolyl)phosphine) made them unsuitable for flow applications. On top of that, the use of **2** has dramatic advantages in terms of cost-effectiveness.

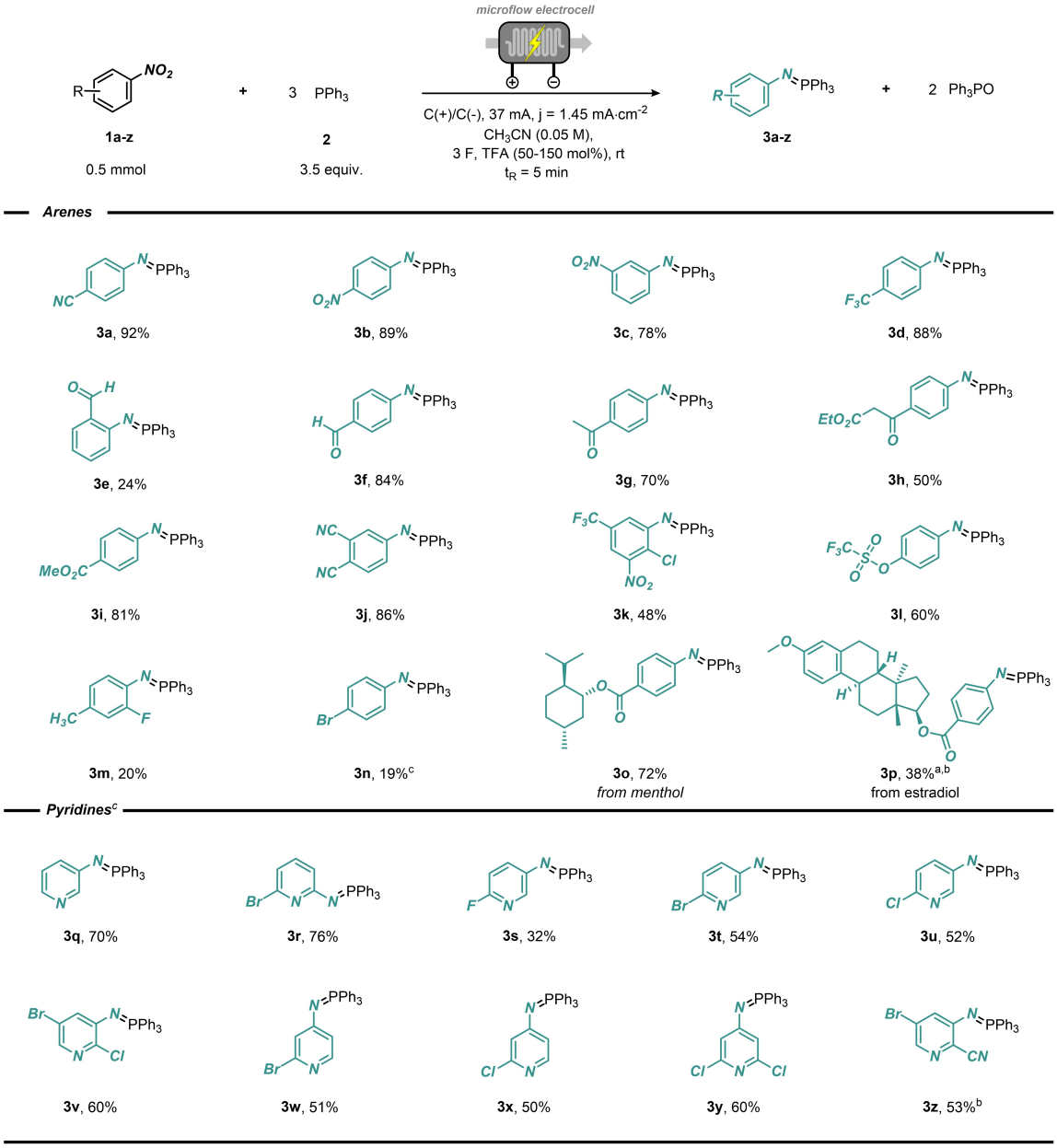
With the optimized conditions in hands, we proceeded to evaluate the scope of the transformation by examining various nitroarenes (Scheme 2, **1 a**–**1 p**). Electron-poor nitroarenes proved to be excellent substrates for this electrochemical transformation. Notably, substrates bearing strong electron-withdrawing groups (EWGs) such as cyano, nitro, and trifluoromethyl exhibited the highest yields of the corresponding iminophosphoranes (78–92%, **3 a**–**3 d**). It is worth noting that the presence of multiple nitro groups on the arene did not lead to multi-functionalization (see compounds **3 b**–**3 c**, 78–89%). Remarkably, the reaction exhibited excellent tolerance towards unprotected carbonyl and ester groups, resulting in the formation of products **3 f**–**3 i** in excellent yields upon isolation (50–84%). However, it is worth noting that the *ortho*-formyl-functionalized compound displayed diminished reactivity in this context (**3 e**, 24%). Furthermore, densely functionalized arenes consistently yielded the expected products (**3 j**–**3 k**, 48–86%), demonstrating the reliability of the transformation. Similarly, nitroarenes containing halides or pseudohalides (such as triflates) could be efficiently transformed into the corresponding iminophosphoranes (**3 k**–**n**), with yields ranging from 19% to 60%. These iminophosphoranes serve as valuable building blocks, allowing for further diversification through methods such as cross-coupling chemistry. We also showcased the suitability of this approach for the late-stage functionalization of complex organic molecules or natural scaffolds, as successfully demonstrated by the synthesis of compounds **3 o**–**3 p** (72–88%).

Lastly, our protocol could be seamlessly extended to the synthesis of iminophosphoranes derived from pyridines by increasing the loading of trifluoroacetic acid to 1.5 equivalents. This straightforward modification resulted in the successful synthesis of compounds (**3 q**–**3 z**, 32–76%).

As a limitation of the present transformation, we found that the use of more electron-rich nitroarenes led to poor selectivity and/or conversion. As an example, when 4-nitrotoluene was employed, 26% of the corresponding aniline was detected as well as 48% of remaining starting material.

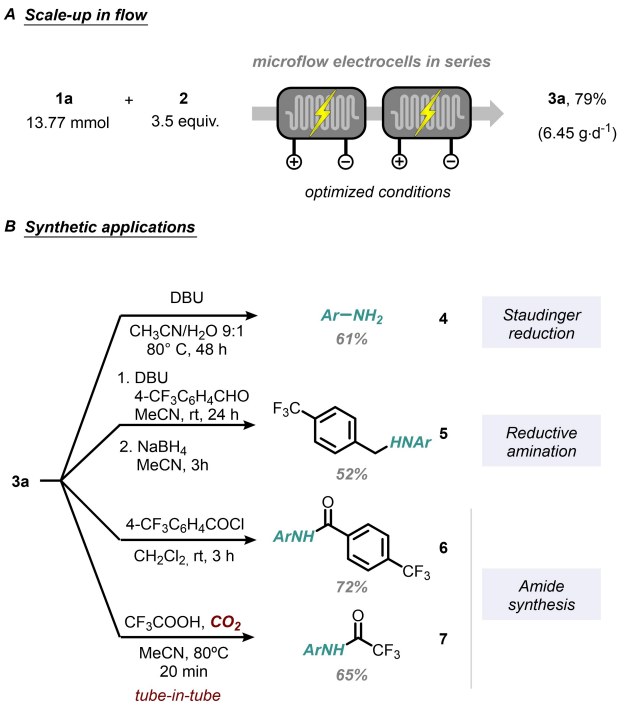
Next, we aimed to scale our electrochemical aryliminophosphorane protocol by connecting two identical microfluidic electrocells in series (also called a sizing up strategy of the reactor length)[12] and conducted an experiment using approximately 14 mmol of nitroarene **1 a**. In order to maintain an overall electrolysis time of 5 minutes, we employed a flow rate of 0.30 $mL \cdot min^{-1}$, leading to a higher overall throughput.[12] The reaction proved to be very robust and reproducible, and we were able to collect about 4.1 g of product **3 a** (79% yield) in 15.2 hours of operation, which equates to a productivity of 6.45 $g \cdot d^{-1}$ (Scheme 3A). Further scale up should be feasible by using a combination of a sizing up and numbering up approach.[12]

Finally, we initiated the demonstration of the synthetic value of these compounds by integrating our electrochemical flow process with subsequent transformations. These transformations were carried out either in batch mode (using a fed-batch operation) or in flow mode (employing a telescoped protocol), without the need for intermediate purification of the iminophosphorane (Scheme 3B). As a first example, we introduced the outflow from the electrochemical reactor into a stirred solution of DBU in CH_3CN/H_2O 9:1 solution kept at 80 °C. After 48 h, the corresponding aniline **4** was obtained in 61% overall yield. This streamlined approach for synthesizing anilines from readily accessible nitroarenes holds significant relevance for industrial applications. In fact, the conventional method for this transformation often involves the use of noble metal catalysts, such as gold and



Scheme 2. Scope of the transformation. Reaction conditions: a CH_3CN solution of **1a–z** (0.05 M), **2** (3.5 equiv.) and TFA (50-150 mol%) was pumped through the flow electrochemical reactor equipped with two graphite electrodes operated in galvanostatic mode. Residence time: 5 min. All yields refer to products isolated via column chromatography. [a] Conversion: 43%, yield based on remaining starting material: 88%. [b] The reaction was performed in batch on 0.2 mmol (Table 1, entry 7) due to the scarce solubility of the nitroarene. [c] 1.5 equivalents of trifluoroacetic acid were used.

platinum, to facilitate the hydrogenation of nitro compounds.[13] In the second example, we introduced the continuous stream containing compound **3a** into a CH_3CN solution of 4-(trifluoromethyl)benzaldehyde. This resulted in the formation of the corresponding aza-Wittig intermediate within 24 h. Instead of isolating the intermediate compound, we directly treated it with $NaBH_4$, leading to the formation of amine **5** in 52% overall yield. In the third example, we conducted the acylation of compound **3a** to deliver amide **6** in 72% yield. In this case, we isolated compound **3a** before reacting it with 4-(trifluoromethyl)benzoyl chloride. And finally, we developed a telescoped approach for the carbonylation of compound **3a**. Specifically, we connected the stream exiting from the electrochemical reactor to a tube-in-tube system charged with CO_2 (4 bar),[14] generating isocyanate as an intermediate. The isocyanate was subsequently transformed into amide **7** through coupling with trifluoroacetic acid.[7]



Scheme 3. A) Scale-up of the reaction in continuous-flow; B) Selected synthetic applications of aryliminophosphoranes: Staudinger reduction (hydrolysis), reductive amination and amide bond formation. All yields given refer to isolated product.

In conclusion, our study has successfully established a robust and scalable protocol for the flow electrosynthesis of aryliminophosphoranes.[15] Importantly, our methodology stands out when compared to previously reported approaches for synthesizing these compounds.[16] Our method also eliminates the need for the use of harmful or hazardous reagents, such as azides and molecular bromine, and operates smoothly at room temperature. Moreover, the flow approach enables easy scale-up of the reaction, even in the absence of any supporting electrolyte. Ongoing efforts in our lab include a detailed mechanistic investigation of this transformation, which will be presented in due course.

Experimental Section

General procedure for the flow electrosynthesis of 3a: A mixture of **1a** (1 mmol), **2** (3.5 mmol), and trifluoroacetic acid (37 µL, 50 mol%) in acetonitrile (0.05 M) was prepared in a 20 mL volumetric flask. The solution was pumped through the microflow electrocell at 0.150 mL·min^{-1} equipped with graphite electrodes and electrolyzed at 37 mA by using a power supply.

The steady state was reached (after 4 residence times) and 10 mL of the reaction mixture was collected, corresponding to 0.5 mmol of processed starting material.

The solvent was removed *in vacuo*, the crude redissolved in EtOAc and washed with a saturated aqueous $NaHCO_3$; the aqueous phase was back-extracted with EtOAc. The combined organic phases were finally washed with brine, dried with sodium sulfate, filtrated, and the solvent was evaporated. The product was isolated after purification by column chromatography using a silica gel column.

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