EurJOC
European Journal of Organic Chemistry

Communication
doi.org/10.1002/ejoc.202000422

Electrochemical Phosphonylation

Nickel-Catalyzed Electrosynthesis of Aryl and Vinyl Phosphinates

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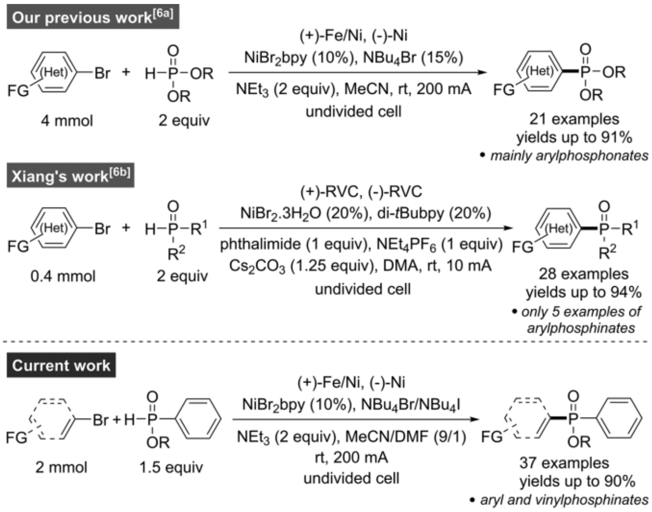
Abstract: A mild and useful nickel-catalyzed electrochemical phosphonylation of aryl and vinyl bromides is described. We show that alkyl *H*-phenylphosphinates can be coupled electrochemically with functionalized aryl and vinyl bromides using very simple conditions (Fe/Ni anode, bench-stable nickel pre-catalyst, undivided cell, galvanostatic electrolysis) to furnish the corresponding aryl and vinyl phosphinates in satisfactory to good yields. Couplings can also be applied to heteroaromatic bromides with some limitations like increased propensity to hydro-dehalogenation.

The development of more and more sustainable chemical processes has gained much attention in the past years due to the ever-increasing awareness of environmental issues. Under the combined impetus of historic electroorganic and mainstream chemists, organic electrosynthesis, a non-conventional tool for alternative synthetic transformations, has been recently subjected to a tremendous development.[1] In such an electrochemical approach, electrons are employed as a green and non-toxic reductant or oxidant surrogates. In addition, in a strong willingness to put experimental simplicity at a center stage, intensive efforts have been devoted to the development of useful electrosynthetic procedures. In this context, electrochemical methods employing undivided cells, galvanostatic mode, and avoiding an external source of heating can be considered as particularly relevant. This is the case of electrooxidative or transition metal-catalyzed electroreductive cross-couplings, ranging from the well-documented $C(sp^2)–C(sp^2)$ bond formation,[2] to $C(sp^2)$–heteroatom such as nitrogen,[3] oxygen,[4] sulfur[5] or phosphorus.[6] In 2018, our group reported the reductive $C(sp^2)–P$ cross-coupling of aryl bromides and dialkyl phosphites for the preparation of aryl and heteroaryl phosphonates.[6a] The cheap and affordable bench-stable nickel bromide bipyridine was used as pre-catalyst and electrolyses were performed under galvanostatic mode in acetonitrile as less toxic solvent. Very recently, Xiang and co-workers[6b] described the synthesis of aryl and heteroaryl phosphonates, and some phosphinates and phosphine oxides (Scheme 1). However, it can be noted that only a few examples of aryl phosphinates and, to the best of our knowledge, no example of vinyl phosphinates preparations have been described through electrochemical routes. Since phosphinates derivatives are known as interesting phosphates bioisosteres,[7] the development of new synthetic approaches is desirable. Therefore, as a part of our activity devoted to electrochemical nickel-catalyzed $C(sp^2)–P$ couplings, we report herein as an extension of our previous work,[6a] the synthesis of aryl and vinyl phosphinates using a Fe/Ni sacrificial anode and a nickel catalyst in an undivided cell under constant current electrolysis.



Scheme 1. Nickel-catalyzed C–P couplings.

We first examined the electrochemical coupling of 4-bromobenzotrifluoride and methyl *H*-phenylphosphinate using triethylamine as a base, Fe/Ni (64/36) rod as the anode, Ni foam as the cathode, NBu_4Br as the supporting electrolyte, 10 % $NiBr_2bpy$ as the pre-catalyst, at 200 mA constant current in acetonitrile at room temperature (Table 1). It was anticipated that a large excess of the phosphorus compound would be

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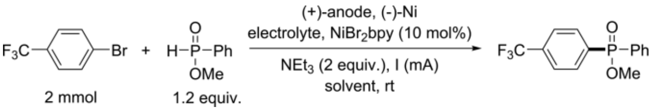
mandatory, as previously reported[6a] (entry 1). However, whereas the expected coupling product could be successfully obtained after short time electrolysis, a flash chromatography on silica gel did not allow to separate the desired product from the remaining methyl *H*-phenylphosphinate. This issue was addressed by reducing the amount of phosphinate to 1.2 equivalents (entry 2), thus leading to the desired product in 45 % yield. When iron/nickel alloy anode was replaced either by pure iron (entry 3) or pure nickel (entry 4), the cross-coupling was much less efficient. In these cases, it was observed the significant formation of the hydro-dehalogenation product of bromobenzotrifluoride (with nickel anode) or low conversion despite 3 h electrolysis (with an iron anode). However, the addition of DMF (20 %) to acetonitrile improved both the solubility of the nickel pre-catalyst and allowed to reduce the reaction time from 2 to 1.5 h without impact on the yield (entry 5). As anticipated, no reaction occurred in the absence of electric current (entry 6). By examining other supporting electrolytes (entries 7–10), it was found that the yield can be slightly improved using lithium chloride or a 2:1 mixture of tetrabutylammonium bromide and -iodide as supporting electrolyte. However, the mixture of tetrabutylammonium halides was maintained for the rest of the study, not only because it is less hygroscopic than lithium chloride, but also because it promotes less reductive homocoupling of bromobenzotrifluoride. In the last series of experiments, the proportion of DMF was reduced to 10 % (entry 11) and the amount of phosphorus reagent was increased from 1.2 to 1.5 equivalent to furnish 57 % of the expected coupling product (entry 12). Additionally, it can be mentioned the yield decreases slightly when imposing the electric current at 100 (entry 13) or at 300 mA (entry 14), 54, and 48 % respectively. It is noteworthy that phosphorus reagent needs to be employed in its ester form. Indeed, a control electrolysis involving the reaction of 4-bromobenzotrifluoride with the commercial phenylphosphinic acid failed, with no coupling product being detected after 1.5 h electrolysis.

With the most efficient C(sp^2)–P reaction conditions in hands (entry 12), the coupling of various aryl bromides with methyl *H*-phenylphosphinate was then evaluated (Table 2). It was found that the electrochemical process tolerates a large range of functional groups borne by the aromatic ring, including electron-withdrawing (trifluoromethyl **2a**–**a′**, cyano **2b**–**b′**, oxo **2c**–**c′**, ester **2d**) and electron-donating groups [1,2-(methylenedioxy) **2g**, methoxy **2h**–**h′′**, dimethylamino **2i**, alkyl **2j**–**j′** and **2k**]. Reactions proceed over a period of 1 to 1.5 h in the majority of cases (see the supporting information for details). The presence of a second halogen atom is also compatible with the process (chlorine **2e**–**e′**, fluorine **2f**–**f′′**). As already noticed previously,[6a] it is important to point out that with the chlorinated substituents, neither the double coupling product, nor the hydro-dechlorination product are observed, showing a particularly selective reaction at the C-Br bond. This interesting result allows a potential second coupling using a conventional chemical method (e.g. Suzuki-Miyaura). In the case of some sterically-hindered *ortho*-substituted phenyl bromides (**2a′′** and **2c′′**), coupling products are formed in reduced amounts at the expense of hydro-dehalogenation side-products. The coupling was then extended successfully to fused polyaromatic bromides

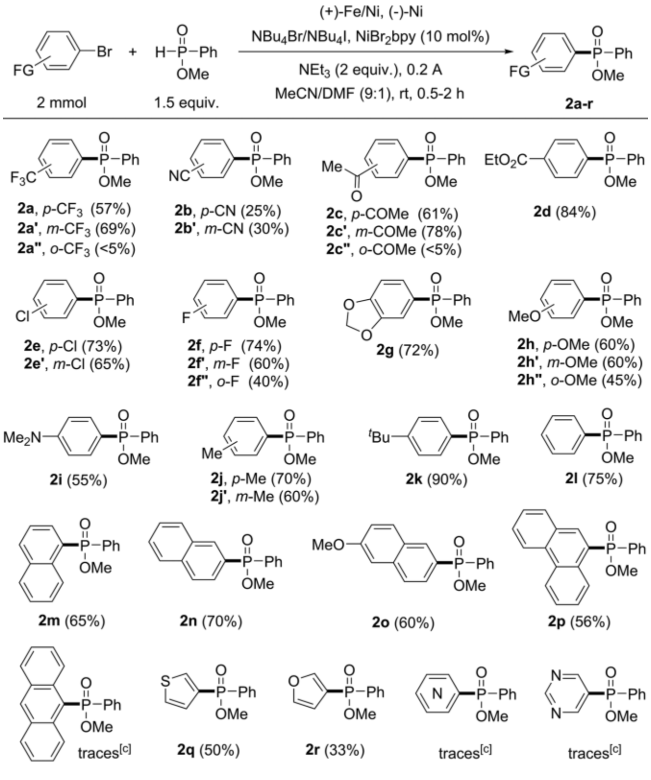
Table 1. Optimization of the experimental conditions.



Entry	Anode	Solvent	Electrolyte	*I* [mA]	Yield [%][a]
1	Fe/Ni	MeCN	NBu$_4$Br	200	–[b]
2	Fe/Ni	MeCN	NBu$_4$Br	200	45
3	Fe	MeCN	NBu$_4$Br	200	< 10
4	Ni	MeCN	NBu$_4$Br	200	< 10
5	Fe/Ni	MeCN/DMF (8:2)	NBu$_4$Br	200	45
6	Fe/Ni	MeCN/DMF (8:2)	NBu$_4$Br	0	n.r.
7	Fe/Ni	MeCN/DMF (8:2)	NEt$_4$BF$_4$	200	45
8	Fe/Ni	MeCN/DMF (8:2)	NaI	200	44
9	Fe/Ni	MeCN/DMF (8:2)	LiCl	200	48
10	Fe/Ni	MeCN/DMF (8:2)	NBu$_4$Br/NBu$_4$I	200	48
11	Fe/Ni	MeCN/DMF (9:1)	NBu$_4$Br/NBu$_4$I	200	50
12	**Fe/Ni**	**MeCN/DMF (9:1)**	**NBu$_4$Br/NBu$_4$I**	**200**	**57**[c]
13	Fe/Ni	MeCN/DMF (9:1)	NBu$_4$Br/NBu$_4$I	100	54[c]
14	Fe/Ni	MeCN/DMF (9:1)	NBu$_4$Br/NBu$_4$I	300	48[c]

[a] Isolated yield. [b] 2 equiv. of methyl *H*-phenylphosphinate were used. The coupling product could not be separated of the excess of methyl *H*-phenylphosphinate. [c] 1.5 equiv. of methyl *H*-phosphinate instead of 1.2 equiv.

Table 2. Scope of aryl bromides.[a,b]



[a] Typical procedure: undivided cell, iron/nickel (64/36) anode, nickel cathode, tetrabutylammonium bromide/tetrabutylammonium iodide (0.15 mmol/0.068 mmol), acetonitrile/DMF (18/2 mL, v/v), NiBr$_2$bpy (10 mol-%), (hetero)aromatic bromide (2 mmol), methyl *H*-phenylphosphinate (3 mmol), triethylamine (4 mmol), constant current: 200 mA, room temperature. [b] Isolated yield. [c] Hydro-dehalogenation product as main side-product.

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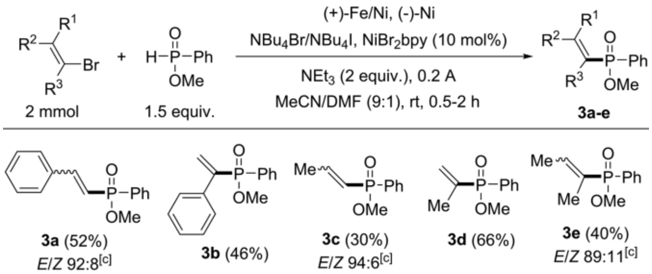
such as bromonaphthalene derivatives (**2m**–**o**) or 9-bromophenanthrene (**2p**). However, the reaction of 9-bromoanthracene failed, probably due to a steric effect. Some heteroaromatic bromides were next assessed. Only electron-rich heteroaromatic bromides such as 3-bromothiophene and 3-bromofuran were able to couple successfully with methyl *H*-phenylphosphinate in 50 and 33 % yields respectively (products **2q** and **2r**) together with hydro-dehalogenation products. On the contrary, electron-poor heteroaromatic bromides like 2-, 3- and 4-bromopyridine, or 5-bromopyrimidine resulted in traces of coupling products, hydro-dehalogenation products being mainly observed.

The optimized conditions were then extended to commercially available vinyl bromides (Table 3). Thus, β- and α-bromostyrenes, 1- and 2-bromoprop-1-ene and 2-bromobut-2-ene were successfully coupled with methyl *H*-phenylphosphinate in moderate to good yields (products **3a**, **3b**, **3c**, **3d** and **3e**). In the case of 1-bromoprop-1-ene (product **3c**), the yield is particularly limited due to the formation of a larger amount of hydro-dehalogenation product as well as to the volatility of the coupled product. Moreover, it can be mentioned that the coupling of β-bromostyrene, 1-bromoprop-1-ene, or 2-bromobut-2-ene with methyl *H*-phenylphosphinate was achieved without noticeable isomerization of the C-C double bond (products **3a**, **3c**, and **3e**).

Table 3. Scope of vinyl bromides.[a,b]

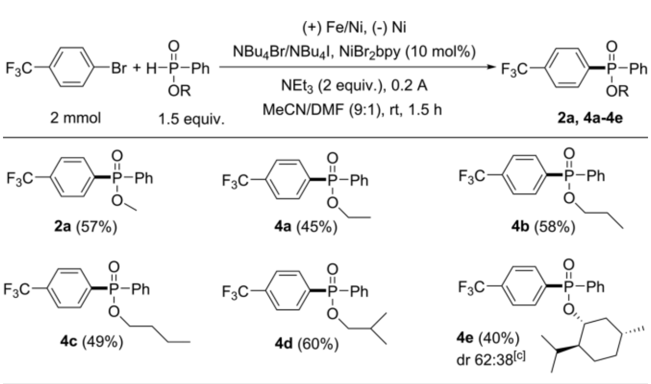


[a] Typical procedure: undivided cell, iron/nickel (64/36) anode, nickel cathode, tetrabutylammonium bromide/tetrabutylammonium iodide (0.15 mmol/0.068 mmol), acetonitrile/DMF (18/2 mL, v/v), $NiBr_2bpy$ (10 mol-%), vinyl bromide (2 mmol), methyl *H*-phenylphosphinate (3 mmol), triethylamine (4 mmol), constant current: 200 mA, room temperature. [b] Isolated yield. [c] *E*/*Z* ratio was determined by ^{31}P NMR.

The successful coupling between aryl/vinyl bromides and methyl *H*-phenylphosphinate prompted us to examine the reactivity of other alkyl *H*-phenylphosphinates in the reaction. Therefore, starting phosphorus compounds were efficiently prepared by esterification of phenylphosphinic acid with alkyl chloroformates according to a standard procedure.[8] Methyl, ethyl, propyl, *n*-butyl, isobutyl, and (1*R*,2*S*,5*R*)-menthyl *H*-phosphinates thus obtained were subsequently used in C-P cross-couplings (Table 4).

All alkyl *H*-phenylphosphinates led to the corresponding coupling products in moderate to good yields (**2a** and **4a**–**d**). It is of note that (1*R*,2*S*,5*R*)-menthyl *H*-phenylphosphinate was also successfully coupled with 4-bromobenzotrifluoride to furnish **4e** as diastereoisomers mixture in 62:38 ratio.

Table 4. Scope of alkyl *H*-phenylphosphinates.[a,b]



[a] Typical procedure: undivided cell, iron/nickel (64/36) anode, nickel cathode, tetrabutylammonium bromide/tetrabutylammonium iodide (0.15 mmol/0.068 mmol), acetonitrile/DMF (18/2 mL, v/v), $NiBr_2bpy$ (10 mol-%), 4-bromobenzotrifuoride (2 mmol), alkyl *H*-phenylphosphinate (3 mmol), triethylamine (4 mmol), constant current: 200 mA, room temperature. [b] Isolated yield. [c] Diastereomeric ratio (*dr*) was determined by ^{1}H NMR.

In summary, a mild and useful nickel-catalyzed electrochemical phosphonylation of aryl and vinyl bromides has been developed. Alkyl *H*-phenylphosphinates were coupled electrochemically with functionalized aryl and vinyl bromides using very simple conditions (Fe/Ni anode, bench-stable nickel pre-catalyst, undivided cell, simple power supply) to furnish the corresponding aryl and vinyl phosphinates in satisfactory to good yields. Couplings were successfully applied to heteroaryl bromides. However, the limitation was observed with electron-poor heteroaryl bromides, which lead majorly to the corresponding hydro-dehalogenation products.

Experimental Section

To a 25 mL undivided electrochemical cell, fitted by an iron/nickel (64/36) anode surrounded by a nickel foam as the cathode (surface: 15 cm^2, Nitech, porosity 500 μm) were added acetonitrile (18 mL), *N*,*N*′-dimethylformamide (2 mL), tetrabutylammonium bromide/tetrabutylammonium iodide (0.15 mmol/0.068 mmol) and 1,2-dibromoethane (100 μL, 1.16 mmol). The mixture is electrolyzed at a constant current intensity of 200 mA for 15 minutes at room temperature. Then, the current is stopped and were sequentially added: $NiBr_2bpy$ (75 mg, 0.2 mmol, 10 mol-%), (hetero)aryl or vinyl bromide (2 mmol, 1.0 equiv.), phosphorus reagent (3 mmol, 1.5 equiv.) and triethylamine (560 μL, 4 mmol, 2.0 equiv.). The solution is electrolyzed at 200 mA for 1–2 h (GC monitoring). A saturated EDTA aqueous solution (30 mL) was added, and the resulting solution is extracted with AcOEt (3 × 30 mL). The combined organic layers were washed with H_2O (2 × 100 mL) then with a saturated NaCl aqueous solution (100 mL), dried with Na_2SO_4, filtered and the solvents evaporated under vacuum. The crude product was purified by flash chromatography on silica (granulometry 70–200 μm), eluted with a gradient mixture of solvents (CH_2Cl_2/AcOEt or CH_2Cl_2/acetone) to afford the pure product.

Acknowledgments

The financial support of this work by the CNRS, the University Paris-Est Créteil and the University Paris-Est (PhD grant to F. D.) is gratefully acknowledged.

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Keywords: Electrosynthesis · Cross-coupling · Nickel · Phosphinates · Synthetic methods

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Received: March 30, 2020

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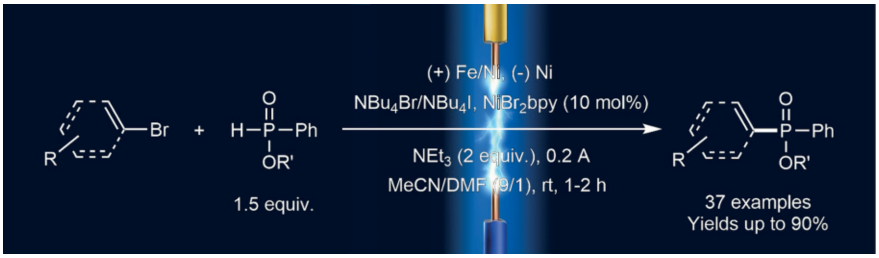

A mild nickel-catalyzed electrochemical approach for phosphonylation of aryl and vinyl bromides is reported. The used of iron/nickel alloy sacrificial anode process in undivided cell and under constant current electrolysis allowed to achieve C(sp^2)–P cross-couplings from alkyl *H*-phenylphosphinates and aryl or vinyl bromides. This electrochemical method enabled to prepare more than 30 new (hetero)aryl and vinyl phenylphosphinates with good yields.

doi.org/10.1002/ejoc.202000422

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