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Three-Component Chlorophosphinoylation of Alkenes via Anodically Coupled Electrolysis

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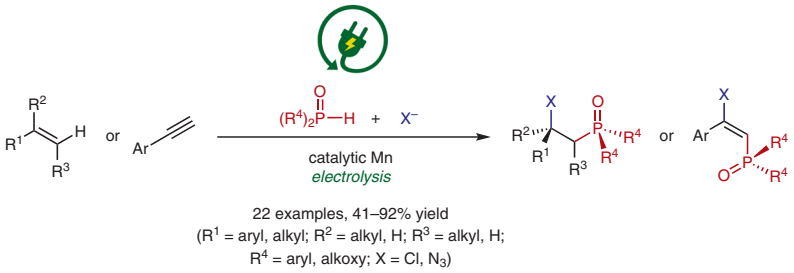

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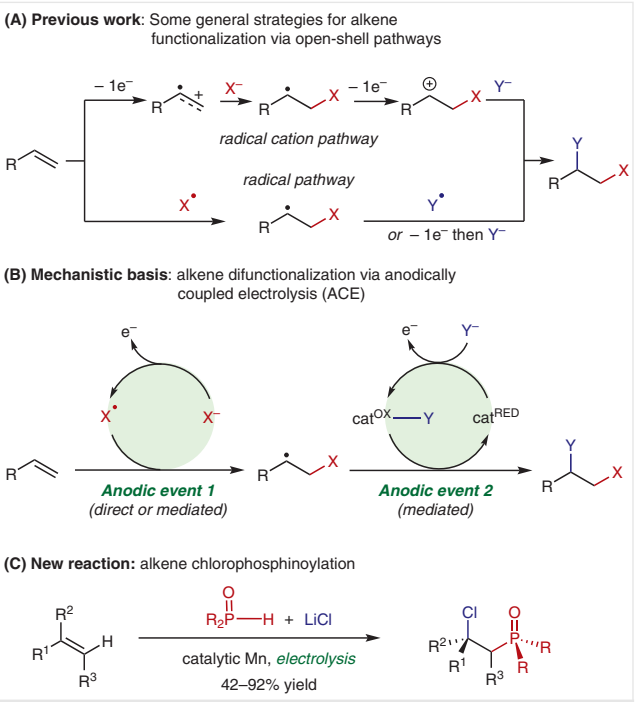
Abstract We report the development of an electrocatalytic protocol for the chlorophosphinoylation of simple alkenes. Driven by electricity and mediated by a Mn catalyst, the heterodifunctionalization reaction takes place with high efficiency and regioselectivity. Cyclic voltammetry data are consistent with a mechanistic scenario based on anodically coupled electrolysis in which the generation of two distinct radical intermediates occur simultaneously on the anode and are both mediated by the Mn catalyst.

Key words electrochemistry, electrocatalysis, anodically coupled electrolysis, alkene difunctionalization, radical addition, chlorination, phosphine oxide

Electrocatalysis[1] has recently emerged as a powerful tool for the synthesis of vicinally difunctionalized molecular structures from simple and readily available alkenes.[2] In general, two distinct mechanistic design principles may be employed to achieve electrochemical alkene difunctionalization. The first scenario entails the direct activation of the alkene via oxidation to the corresponding radical cation (Scheme 1A).[3] This approach, however, can often be limited by the oxidation potential of the alkene and is applicable primarily to electron-releasing substrates. A second scenario entails the oxidation of the reagents to be added across the C=C π-bond rather than oxidation of the alkene itself.[4] This strategy frequently generates radical intermediates capable of sequential addition to the alkene substrate. Nonetheless, due to the formation of multiple transient radicals en route to the desired product, promiscuous reactivity of these high-energy intermediates frequently induces chemo- and regioselectivity issues during the addition events.

To overcome these challenges, we recently developed a complementary approach by combining electrochemistry with redox catalysis.[5] In particular, we demonstrated that



Scheme 1 Electrochemical alkene chlorophosphinoylation via anodically coupled electrolysis (ACE)

three-component heterodifunctionalization of alkenes could be achieved using anodically coupled electrolysis (ACE) (Scheme 1B).[2a] In this mechanistic scheme, two parallel anodic events were combined to activate two distinct nucleophilic reagents. The resultant pair of radical intermediates will then add across the alkene substrate chemo- and regioselectively in the presence of an appropriate transition-metal catalyst. For example, we developed electrochemical chlorotrifluoromethylation[5c] and chloroalkylation[5d] reactions using ACE. These reaction systems entail

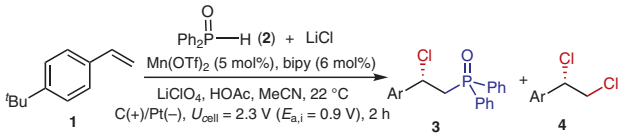
the simultaneous generation of a transient C-centered free radical via direct or mediated anodic oxidation and a persistent open-shell metal chloride via a catalyst-assisted process. Subsequently, the sequential radical addition to the C=C bond occurs chemo- and regioselectively as predicted by the persistent radical effect.[6] On the basis of these previous developments, we herein report the extension of ACE to the electrocatalytic chlorophosphinoylation reaction[7] (Scheme 1C). Organophosphorus compounds are widely used in agrochemistry and phosphine oxides are commonly used in metal and organocatalysis;[8] alkyl chlorides are versatile synthetic intermediates. The proposed transformation would give rise to multifunctional phosphine-containing compounds from readily available starting materials.

We set out to investigate the chlorophosphinoylation reaction by electrolyzing a mixture of *t*-butylstyrene (**1**), diphenylphosphine oxide (**2**), and LiCl. We found that the desired product **3** could be observed in 82% yield when $Mn(OTf)_2$ was used as the catalyst along with bipyridine (bipy) as the ligand, acetic acid (HOAc) as the terminal oxidant (reduced to H_2 at the cathode), lithium perchlorate ($LiClO_4$) as the electrolyte, and MeCN as the solvent under a constant cell voltage (U_{cell}) of 2.3 V (initial anodic potential, $E_{a,i}$ = 0.9 V) (Table 1, entry 1). Meanwhile, dichlorination product **4** was also formed in a trace amount (<5%). In the absence of the Mn catalyst, only 5% of the heterodifunctionalized product was generated together with 23% of byproduct **4** (entry 2). Without bipy, the reaction was sluggish and provided **3** in 63% yield during the same time span, along with an increased amount of byproduct **4** (entry 3). The role of bipy was not simply that of a base, as reaction with pyridine (12 mol%) instead of bipy resulted in a nearly identical reaction outcome to that without bipy (entries 4 vs 3). The electrolysis was also carried out at a constant current of 5 mA for 2 hours (2 F charge passed), which furnished **3** in a comparable 85% yield (85% Faradaic efficiency) with 5% of **4** (entry 5).

We also tested various reaction conditions that would lead to a more practical reaction setup. For example, replacing LiCl with NaCl resulted in a 56% yield of **3**; an elevated temperature of 50 °C was necessary to enhance the solubility of NaCl (entry 6). The electrolyte $LiClO_4$ did not play an explicit role in the chlorophosphinoylation, as substituting it with tetrabutylammonium tetrafluoroborate ($TBABF_4$) or lithium triflate (LiOTf) resulted in comparable reactivity (entries 7 and 8). In fact, owing to the ionic nature of LiCl employed in the reaction, an exogenous electrolyte proved unnecessary (entry 9). Finally, using commercial ElectraSyn 2.0[9] as the reaction vessel and power supply gave the desired product in a satisfactory yield alongside 10% of byproduct **4** (entry 10).

The optimal electrolysis conditions were successfully applied to the synthesis of a variety of chlorophosphinoylation products starting from simple alkenes (Scheme 2A).[10]

Table 1 Reaction Optimization



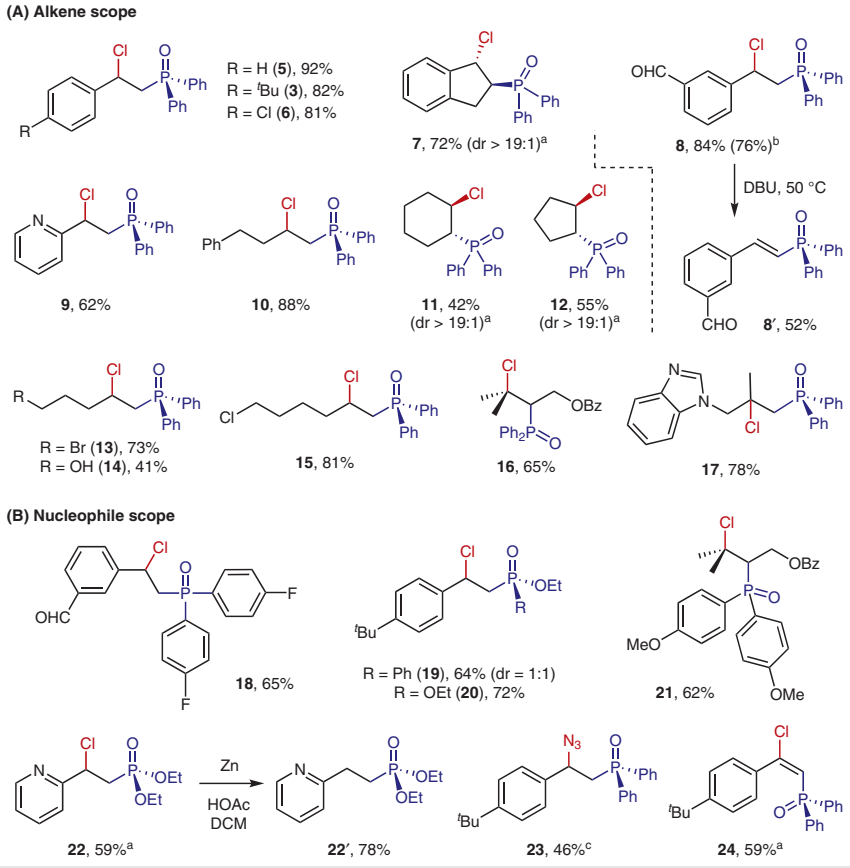
Entry	Variation from optimal conditions	Yield of **3** (%)[a]	Yield of **4** (%)[a]
1	**none**	**82**	**<5**
2	without Mn	5	23
3	without bipy	63	8
4	with pyridine (12 mol%) instead of bipy	62	6
5	constant current (5 mA) electrolysis	85	5
6	NaCl instead of LiCl[b]	56	<5
7	$TBABF_4$ instead of $LiClO_4$	75	6
8	LiOTf instead of $LiClO_4$	72	<5
9	no $LiClO_4$, *i* = 3 mA (constant current)[c]	55	8
10	Using ElectraSyn 2.0[d]	84	10

[a] Reactions are conducted on 0.2 mmol scale and yields are determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as the internal standard.
[b] Reaction at 50 °C.
[c] Full cell voltage (U_{cell}) varies between 2.1 and 2.5 V.
[d] Using 1.5 equiv of **2**, 0.3 mmol scale.

In addition to substituted styrenes (**3**, **5**, **6**, **8**), vinylpyridine also reacted smoothly to form **9**. Electronically unactivated alkenes with mono-, di-, and trisubstitution all underwent the desired electrochemical reaction. In the cases with cyclic alkenes, the product diastereoselectivity was excellent, presumably owing to the large steric profile of the phosphine oxide group (**7**, **11**, **12**). Functional groups such as aldehyde (**8**), alkyl halide (**13**, **15**), alcohol (**14**) and benzimidazole (**17**) were also compatible with the reaction system, providing the corresponding adducts in high yield.

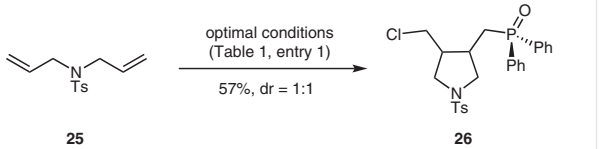
We also surveyed several different nucleophiles (Scheme 2B). Substituted aromatic secondary phosphine oxides (**18**, **21**), phosphinate (**19**), and phosphonates (**20**, **22**) all readily underwent the desired chlorofunctionalization. Moreover, using $TMSN_3$ instead of LiCl, azidophosphinoylation product **23** was isolated in a synthetically useful yield.[11] Our reaction was also applied to *t*-butylphenylacetylene and a single alkene geometric isomer (*E*)-**24** was isolated in 59% yield. However, extending this methodology to bromophosphinoylation proved challenging at this stage, as only the dibromination product was observed when using various bromide salts instead of LiCl. Finally, the heterodifunctionalized products could be further derivatized via elimination (**8′**) and reduction (**22′**) reactions.

The stepwise, radical nature of the reaction was supported by a radical cyclization experiment using diene **25**, which resulted in pyrrolidine **26** as a pair of diastereomers.



Scheme 2 Substrate scope. Reactions are conducted on 0.2 mmol scale under optimal conditions (see Table 1, entry 1);[10] isolated yields are reported. [a] Stereochemistry was determined from coupling constants (**7**, **11**, **12**) or 2D NOESY for **24**; see the Supporting Information for more details. [b] 3 mmol scale. [c] Using $TMSN_3$ instead of LiCl and DMF in place of MeCN as the solvent

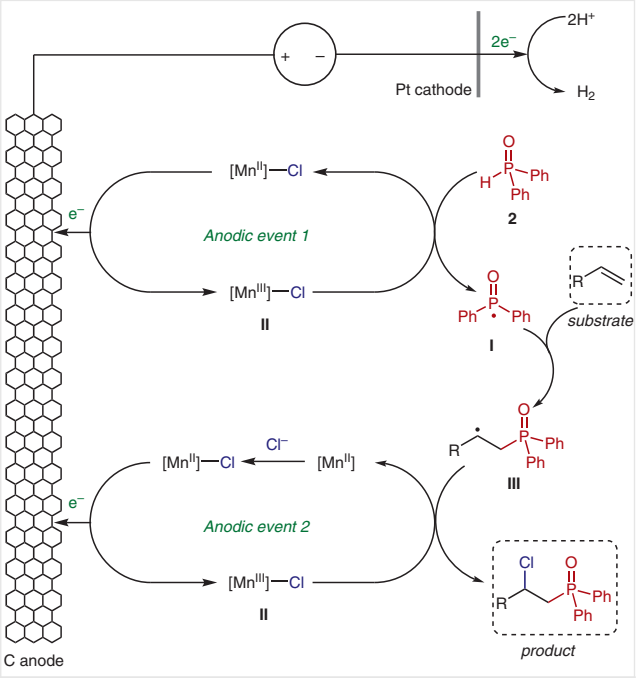
The observed cyclization activity is consistent with the hypothesized reaction pathway involving P- and C-centered radical intermediates (Scheme 3).



Scheme 3 Radical cyclization experiment

Finally, we conducted a set of cyclic voltammetry experiments. The results are consistent with the proposed catalytic mechanism in Scheme 4 in which both P-centered radical **I**[12] and [Mn^{III}]–Cl (**II**),[13] the latent Cl radical, were generated on the anode via Mn-mediated processes. The catalyst combination [$Mn(OTf)_2$+bipy] displayed several weak oxidative features between 0.6 and 1.2 V (Figure 1, top panel, black line). However, the addition of HOAc/NaOAc—species that are present in the electrocatalytic reaction—led to a significant increase of the redox activity of the Mn complex (red line). Phosphine oxide **2** proved difficult to oxidize directly on the anode (blue line). The addition of Mn+bipy to **2** led to new oxidative features but minimal current enhancement (orange and green lines).

LiCl alone can be oxidized on the anode directly, presumably forming the Cl radical, resulting in a peak at ca. 1.1 V (Figure 1, bottom panel, red line). Synonymous to our previous observation in the context of electrocatalytic chlorofunctionalization reactions,[5a,c,d] addition of the Mn catalyst to a solution of LiCl in MeCN led to current enhancement of the oxidative wave (blue line vs red line), indicating that Mn promotes the oxidation of Cl^-, presumably via the formation of [Mn^{III}]–Cl.[14] Interestingly, mixing **2** and LiCl together with the catalyst combination led to a marked catalytic current, which increased as the amount of **2** was increased (purple and green lines). These observations are consistent with [Mn^{III}]–Cl being capable of oxidizing **2**, presumably to the corresponding radical **I**.



Scheme 4 Proposed mechanism

Upon formation of open-shell intermediates **I** and **II**, the addition of **I** to the alkene will occur preferentially over the addition of **II**, leading to C-centered radical **III**. This selectivity arises from the highly reactive nature of transient radical **I** in comparison to the more stable, persistent intermediate **II**. Subsequently, per the persistent radical effect, the cross-coupling of **III** with another equivalent of **I** to form the bisphosphinoylation product is challenging due to the transient nature of both **III** and **I**. On the contrary, the reaction of **III** with **II**, a persistent open-shell complex, is favorable, which results in transfer of the Cl atom from **II** to **III** to deliver the desired chlorophosphinoylation product. This process regenerates [Mn^{II}], which is then turned over on the anode.[15]

In conclusion, we report the application of ACE in the development of an electrocatalytic chlorophosphinoylation reaction for the heterodifunctionalization of alkenes. Regulated by a Mn catalyst, this three-component coupling reaction takes place with high chemo- and regioselectivity. Future work will focus on the structural elucidation of the Mn catalyst that is responsible for the anodic generation of key radical intermediates and the further use of this electrocatalytic strategy in new reaction discovery.[16]

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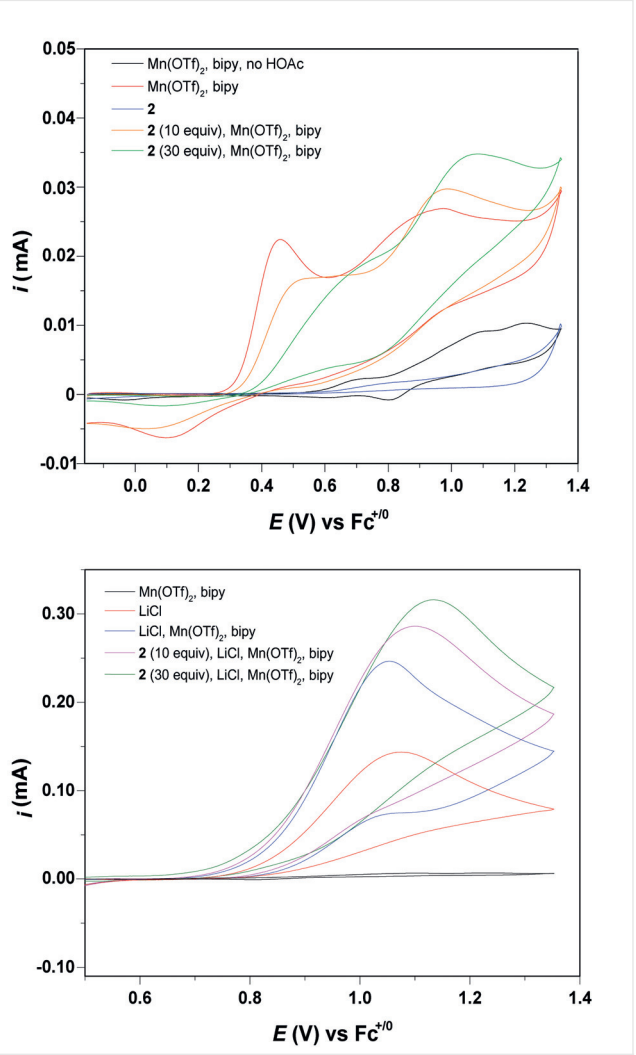

Figure 1 Cyclic voltammetry (CV) data. Top panel: characterization of the Mn catalytic complex in the absence or presence of acetate. Bottom panel: catalytic effect of Mn in the generation of Cl and P radical equivalents. Medium: 0.1 M $LiClO_4$ in HOAc/MeCN, unless otherwise noted in the figure; scan rate = 100 mV/s. See the Supporting Information for detailed conditions and full CV plots

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0039-1689935.

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(10) **Chlorophosphinoylation; General Procedure**
An oven-dried, 10 mL two-neck glass tube was equipped with a magnetic stir bar, a rubber septum, a Teflon cap fitted with electrical feedthroughs, a carbon felt anode (1.0 × 0.5 cm^2) (connected to the electrical feedthrough via a 9 cm in length, 2 mm in diameter graphite rod), and a platinum foil cathode (0.5 × 1.0 cm^2). To this reaction vessel, bipy (1.9 mg, 0.012 mmol, 6 mol%), $Mn(OTf)_2$ (3.6 mg, 0.01 mmol, 5 mol%), phosphorous source (0.2 mmol, 1.0 equiv), and lithium chloride (17.0 mg, 0.4 mmol, 2.0 equiv) were added. The cell was sealed, 3 mL of electrolyte solution (0.10 M $LiClO_4$ in acetonitrile) was added, and the mixture was flushed with nitrogen gas for 5 min, followed by the addition, via syringe, of a mixture of olefin substrate (0.2 mmol, 1.0 equiv), 0.5 mL of electrolyte solution, and acetic acid (0.40 mL). A nitrogen-filled balloon was connected through the septum to sustain a nitrogen atmosphere. Electrolysis was initiated at a constant cell voltage of 2.3 V at 22 °C. The reaction was stopped after 3.0 F charge was passed. The entire reaction mixture was then transferred to a short silica gel column (7–10 cm in length, ca. 10 g) and flushed through with 100 mL of a 1:1 mixture of hexanes and acetone to eliminate the inorganic salts, and the product solution was concentrated in vacuo. The residue was subjected to flash column chromatography on silica gel (eluted with hexanes/ethyl acetate) to yield the pure product. See the Supporting Information for full details and graphical guide.
Representative Product Characterization; 3-Chloro-2-(diphenylphosphoryl)-3-methylbutyl Benzoate (16)
Yield: 54.9 mg (65%); white solid; IR (film): 2982, 1972, 1719, 1438, 1273, 1182, 1114, 1100, 1072, 1026, 704, 524 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 8.00 (dd, *J* = 8.3, 1.4 Hz, 4 H), 7.80–7.70 (m, 2 H), 7.63–7.51 (m, 4 H), 7.45 (t, *J* = 7.8 Hz, 2 H), 7.30 (td, *J* = 7.3, 1.4 Hz, 1 H), 7.25–7.19 (m, 2 H), 4.90 (ddd, *J* = 21.8, 12.2, 3.4 Hz, 1 H), 4.64–4.35 (m, 1 H), 3.35 (dt, *J* = 10.3, 3.7 Hz, 1 H), 2.02 (s, 3 H), 1.68 (s, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 165.69, 134.79 (d, *J* = 97 Hz), 133.24, 132.42 (d, *J* = 98 Hz), 132.00 (d, *J* = 2.8 Hz), 131.79 (d, *J* = 2.8 Hz), 130.87 (d, *J* = 8.9 Hz), 130.69 (d, *J* = 8.7 Hz), 129.99, 129.55, 129.08 (d, *J* = 10 Hz), 128.59 (d, *J* = 11 Hz), 128.51, 74.30, 74.27, 62.79, 62.77, 50.50 (d, *J* = 62 Hz), 35.20, 31.12; ^{31}P NMR (202 MHz, $CDCl_3$): δ = 27.38; HRMS (DART): *m*/*z* [M + H]$^+$ calcd for $C_{24}H_{25}ClO_3P^+$: 427.1224; found: 427.1222 .

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