

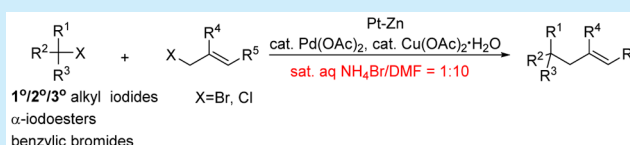
Palladium-Catalyzed Electrochemical Allylic Alkylation between Alkyl and Allylic Halides in Aqueous Solution

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Supporting Information

ABSTRACT: A new route for the direct cross-coupling of alkyl and allylic halides using electrochemical technique has been developed in aqueous media under air. Catalyzed by Pd(OAc)₂, the Zn-mediated allylic alkylations proceed smoothly between a full range of alkyl halides (primary, secondary, and tertiary) and substituted allylic halides. Protection–deprotection of acidic hydrogen in the substrates is avoided.



Transition-metal-catalyzed allylic alkylation between a carbon nucleophile and an allylic substrate has emerged as one of the most robust tool for C–C bond formation in the past decades.¹ Among the various carbon nucleophiles,² organometallic reagents such as alkylzinc or Grignard reagents are widely employed. However, prior stoichiometric formation of organometallic reagents, air/moisture sensitivity, and poor functional-group compatibility limit their synthetic applications. Thus, in terms of step economy and practicality, the direct cross-couplings between alkyl halides and allylic electrophiles would be advantageous, since the preformation of organometallic reagents can be avoided.³ To date, there are only a few reports involving such direct coupling in this field.³ It is noticed that these coupling reactions were carried out in aprotic media and sometimes strict exclusion of moisture and air were still required. Whereas, the direct allylic alkylations in aqueous media under air are still unknown.

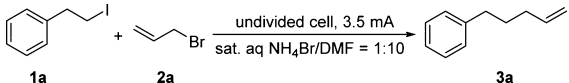
On the other hand, Barbier-type reaction is a one-pot, powerful strategy for the facile construction of valuable C–C bonds, among which Barbier-type nucleophilic additions on carbonyl groups have been extensively developed in aqueous media.⁴ Elegant examples studied by Lipshutz demonstrated Pd-catalyzed Barbier–Negishi-type coupling reactions between aryl/alkenyl and alkyl halides in water to form C_{sp}²–C_{sp}³ linkages.⁵ Very recently, Baudoin disclosed a nonaqueous Negishi coupling between alkyl bromide with aryl or alkenyl triflate to deliver linear products.⁶ These appealing reports prompted us to envision that the construction of C_{sp}³–C_{sp}³ bonds between an alkyl halide and an allylic halide might also be accomplished by the strategy of a Pd-catalyzed aqueous Barbier–Negishi-type reaction. Nevertheless, with two sp³ carbon electrophilic species and two metals (Zn and Pd) in one pot, it is challenging to selectively umpolung one of them to a nucleophile to achieve the cross-coupling.⁷ Thus, exploration of suitable reaction conditions, probably employing unconventional synthetic techniques, might solve this problem.

The electrochemical method is an alternative approach to efficient transformation in organic chemistry.⁸ During the course

of our studies on aqueous Barbier–Grignard-type allylation/alkylation of the carbonyl and imine compounds, we discovered that the electrochemically generated active Zn particles could promote the desired reactions.⁹ Taking this chemistry further to aqueous Barbier–Negishi-type coupling reactions, herein we report the Zn-mediated electrochemical allylic alkylations between alkyl and allylic halides catalyzed by Pd(OAc)₂ under air in aqueous solution.

To initiate our investigation, 1-(2-iodoethyl)benzene **1a**, allylic bromide **2a**, LiCl, and PEG 400 (polyethylene glycol 400) were added into a one-compartment cell with 3.3 mL of electrolyte solution (sat. aq NH₄Br/DMF = 1:10) fitted with a zinc foil (1.5 cm²) cathode and a Pt wire anode. And then the electrolysis was carried out under a constant current (3.5 mA) at 0 °C. A trace amount of the desired product **3a** was detected after the reaction mixture was stirred for 12 h (Table 1, entry 1). When Pd(OAc)₂ was added as a catalyst (Table 1, entry 2), the yield of **3a** increased sharply to 68%. If a catalytic amount of copper salt, such as Cu(OAc)₂·H₂O or CuCN was added in the absence of Pd(OAc)₂, the reaction turned out to be much less efficient (Table 1, entries 3–4). It was interesting to observe that the yield was improved to 88% in the presence of both Pd(OAc)₂ and Cu(OAc)₂·H₂O (Table 1, entry 5). Although other Pd catalysts, Pd(CH₃CN)₂Cl₂, PdCl₂, and Pd(PPh₃)₄, showed inferior activities toward this reaction (Table 1, entries 6–8), Pd(OAc)₂ demonstrated to be the best catalyst. Studies on the effect of current density showed that decreasing or increasing the current both led to a decrease in the product yield (Table 1, entries 9–10). Other electrolyte solutions: sat. aq NH₄Cl/DMF (1:10), sat. aq NH₄OAc/DMF (1:10), sat. aq NH₄Br/THF (1:10), and sat. aq NH₄Br/CH₃CN (1:10) gave somewhat lower yields (Table 1, entries 11–14). In addition, attempts to vary the surfactants, such as PEG-600 (polyethylene glycol 600), 18-crown-6 (1,4,7,10,13,16-hexaoxacyclooctadecane), and SDS (sodium

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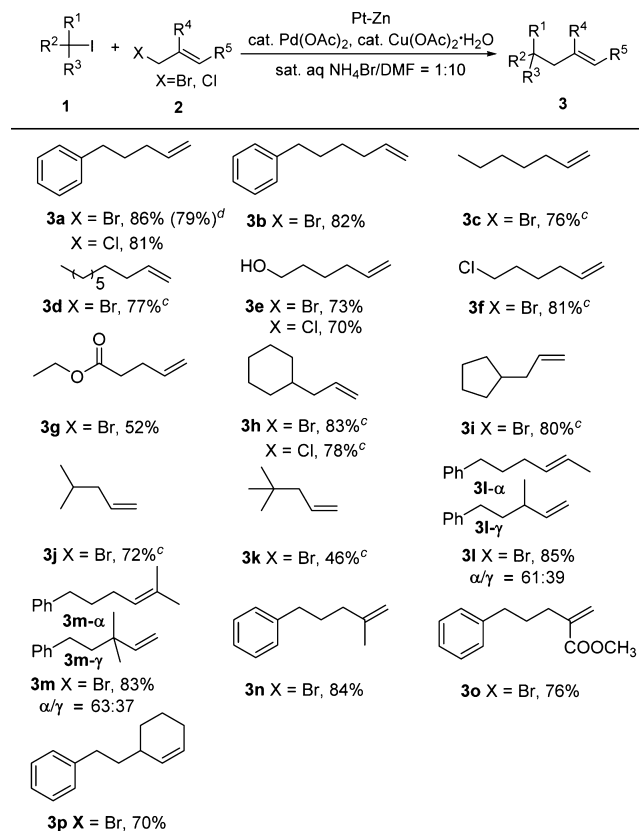
Table 1. Optimization of Reaction Conditions^a


| entry | electrodes | catalyst | cocatalyst | yield ^b (%) |
|-----------------|------------|---|--|------------------------|
| 1 | Pt–Zn | – | – | trace |
| 2 | Pt–Zn | Pd(OAc) ₂ | – | 68 |
| 3 | Pt–Zn | – | Cu(OAc) ₂ ·H ₂ O | 22 |
| 4 | Pt–Zn | – | CuCN | 20 |
| 5 | Pt–Zn | Pd(OAc) ₂ | Cu(OAc) ₂ ·H ₂ O | 88 |
| 6 | Pt–Zn | Pd(CH ₃ CN) ₂ Cl ₂ | Cu(OAc) ₂ ·H ₂ O | 75 |
| 7 | Pt–Zn | PdCl ₂ | Cu(OAc) ₂ ·H ₂ O | 78 |
| 8 | Pt–Zn | Pd(PPh ₃) ₄ | Cu(OAc) ₂ ·H ₂ O | 49 |
| 9 ^c | Pt–Zn | Pd(OAc) ₂ | Cu(OAc) ₂ ·H ₂ O | 77 |
| 10 ^d | Pt–Zn | Pd(OAc) ₂ | Cu(OAc) ₂ ·H ₂ O | 81 |
| 11 ^e | Pt–Zn | Pd(OAc) ₂ | Cu(OAc) ₂ ·H ₂ O | 71 |
| 12 ^f | Pt–Zn | Pd(OAc) ₂ | Cu(OAc) ₂ ·H ₂ O | 68 |
| 13 ^g | Pt–Zn | Pd(OAc) ₂ | Cu(OAc) ₂ ·H ₂ O | 70 |
| 14 ^h | Pt–Zn | Pd(OAc) ₂ | Cu(OAc) ₂ ·H ₂ O | 66 |
| 15 ⁱ | Pt–Zn | Pd(OAc) ₂ | Cu(OAc) ₂ ·H ₂ O | 74 |
| 16 ^j | Pt–Zn | Pd(OAc) ₂ | Cu(OAc) ₂ ·H ₂ O | 63 |
| 17 ^k | Pt–Zn | Pd(OAc) ₂ | Cu(OAc) ₂ ·H ₂ O | 77 |
| 18 | Pt–Sn | Pd(OAc) ₂ | Cu(OAc) ₂ ·H ₂ O | 45 |
| 19 | Pt–Al | Pd(OAc) ₂ | Cu(OAc) ₂ ·H ₂ O | 9 |
| 20 | Pt–In | Pd(OAc) ₂ | Cu(OAc) ₂ ·H ₂ O | 32 |
| 21 ^l | Pt–Zn | Pd(OAc) ₂ | Cu(OAc) ₂ ·H ₂ O | 27 |

^aUnless otherwise noted, **1a** (0.3 mmol), **2a** (0.9 mmol), catalyst (10 mol %), cocatalyst (20 mol %), LiCl (0.6 mmol), PEG400 (0.15 mmol), 3.3 mL of electrolyte solution (sat. aq. NH₄Br/DMF = 1:10), a zinc foil (1.5 cm²) as cathode, a Pt wire (diameter = 0.5 mm, height = 2.0 cm) as anode, constant current (3.5 mA), undivided cell at 0 °C for 12 h. ^bThe yield of the product was determined by ¹H NMR spectroscopy. ^c2.0 mA. ^d5.0 mA. ^eElectrolyte solution: sat. aq. NH₄Cl/DMF = 1:10. ^fElectrolyte solution: sat. aq. NH₄OAc/DMF = 1:10. ^gElectrolyte solution: sat. aq. NH₄Br/THF = 1:10. ^hElectrolyte solution: sat. aq. NH₄Br/CH₃CN = 1:10. ⁱPEG-600 (0.15 mmol) instead of PEG400. ^j18-c-6 (0.15 mmol) instead of PEG400. ^kSDS (0.15 mmol) instead of PEG400. ^lElectrolyte solution: 0.1 M Bu₄NBF₄ in DMF.

dodecyl sulfate) also resulted in lower yields (Table 1, entries 15–17). When other cathodes (Sn, Al, or In) were used, the yields decreased significantly (Table 1, entries 18–20). It was found that when the reaction was carried out in pure organic solvent with Bu₄NBF₄ as the electrolyte, the yield was attenuated to 27% (Table 1, entry 21).

Using the optimized reaction conditions (Table 1, entry 5), the reactions of various alkyl halides and substituted allylic halides were surveyed. As presented in Scheme 1, the reactions occurred smoothly to afford good yields of the corresponding products in most cases. The reactions proceeded well with long-chain alkyl halides (**3b–d**). Functional groups, such as hydroxyl, chloro, and ester, were also compatible with the current protocol (**3e–g**). It is worth noting that ethyl 2-iodoacetate could also couple with allylic bromide to produce the desired product in a yield of 52% (**3g**). The challenging secondary alkyl halides, which often suffer from E2 elimination,^{2d,n,10} could participate in this reaction to afford the products (**3h–j**) in 72–83% yields. Furthermore, tertiary halide of *tert*-butyl iodide (**1k**) proved to be a competent coupling partner, and the corresponding product (**3k**) was obtained in a reasonable yield. Next, substituted allylic halides (**3l–o**) were studied and the coupling products were obtained under the optimal reaction conditions with good

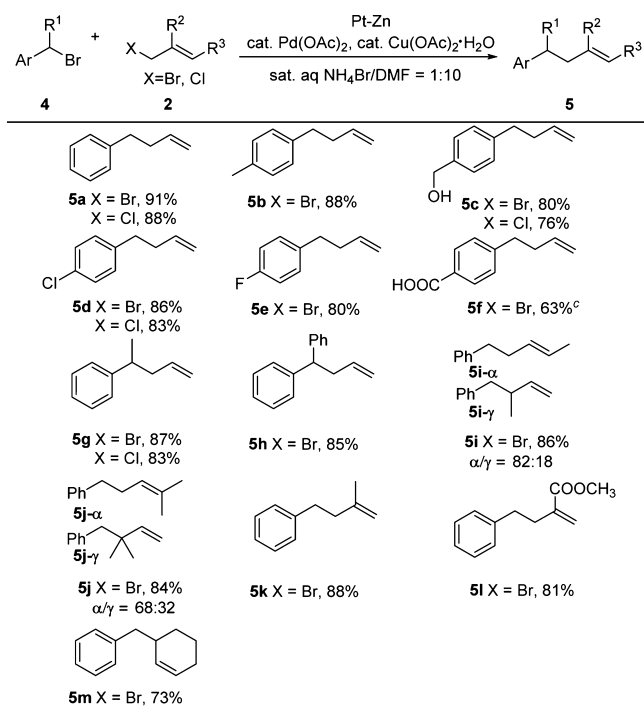
Scheme 1. Substrates Scope of Allylation of Alkyl Iodides^{a,b}

^aUnless otherwise noted, **1** (0.3 mmol), **2** (0.9 mmol), Pd(OAc)₂ (10 mol %), Cu(OAc)₂·H₂O (20 mol %), LiCl (0.6 mmol), PEG400 (0.15 mmol), 3.3 mL of electrolyte solution (sat. aq. NH₄Br/DMF = 1:10), a zinc foil (1.5 cm²) as cathode, a Pt wire (diameter = 0.5 mm, height = 2.0 cm) as anode, constant current (3.5 mA) in an undivided cell at 0 °C for 12 h. ^bIsolated yield. ^cGC yield with *n*-tetradecane as an internal standard after acidification and aqueous workup. ^dIsolated yield based on **1a** at the 1 mmol scale.

combined yields and moderate selectivities (**3l**, 61:39, **3m**, 63:37). Importantly, the secondary allylic bromide, 3-bromocyclohex-1-ene can be coupled effectively with **1a** to give the product **3p** in 70% yield.

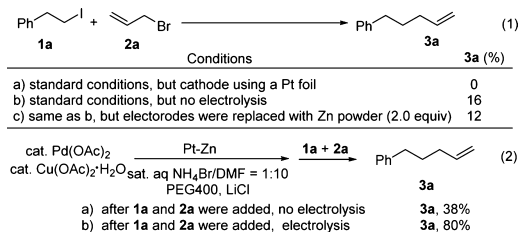
Apart from the unactivated alkyl halides, the activated alkyl halides were also suitable coupling partners in our system (Scheme 2). The coupling reactions between primary/secondary benzylic bromides and allylic halides produced the corresponding products in good to excellent yields. Notably, benzylic bromides bearing valuable functional groups (hydroxyl, chloro, fluoro, and carboxyl) were well tolerated in this electrochemical process (**5c–f**). Similarly, the reactions of benzylic bromide with methyl/ester substituted allylic bromides occurred to afford the desired products in good yields (**5i–l**). Again, the secondary allylic halide, 3-bromocyclohex-1-ene, was tested, and the coupling product **5m** was obtained in 73% yield.

Further studies were carried out to gain more insights into the reaction mechanism. Initially, several control experiments were performed (Scheme 3). When the cathode was replaced with a Pt foil, no desired product **3a** was obtained (Scheme 3, eq 1a). If no power was applied to the reaction, only a 16% yield of **3a** was isolated (Scheme 3, eq 1b). Moreover, when both of the electrodes were removed and activated Zn powder was added into the reaction solution, **3a** was obtained in 12% yield after

Scheme 2. Substrates Scope of Allylation of Benzylic Bromides^{a,b}

^aUnless otherwise noted, **4** (0.3 mmol), **2** (0.9 mmol), Pd(OAc)₂ (10 mol %), Cu(OAc)₂·H₂O (20 mol %), LiCl (0.6 mmol), PEG400 (0.15 mmol), 3.3 mL of electrolyte solution (sat. aq. NH₄Br/DMF = 1:10), a zinc foil (1.5 cm²) as cathode, a Pt wire (diameter = 0.5 mm, height = 2.0 cm) as anode, constant current (3.5 mA) in an undivided cell at 0 °C for 12 h. ^bIsolated yield. ^cAllylic bromide **2a** (1.5 mmol).

Scheme 3. Control Experimental Studies



stirring for 12 h in the absence of power (Scheme 3, eq 1c). These findings demonstrated that the electricity and Zn cathode likely played crucial roles in the cross-coupling process. Based on the above results and our previous work,⁹ we proposed that, during the course of this Barbier–Negishi-type coupling reactions, deposition of Zn(II) on the cathode occurred continuously and the in situ generated active Zn particles might participate in the coupling reactions.¹¹

A control reaction was performed by adding **1a** and **2a** to the reaction mixture after the electrolysis had proceeded for 45 min (Scheme 3, eq 2) to allow the reduction of Pd(OAc)₂ to Pd(0). If the electrolysis was stopped after **1a** and **2a** were added, a 38% yield of **3a** was collected (Scheme 3, eq 2a). This result indicated that the slightly improved yield from 16% to 38% was attributed to the catalysis of the initially formed Pd(0) species from the electrochemical reduction of Pd(OAc)₂. However, if the current was passed through the cell for the entire duration of the experiment, the yield of the desired product **3a** increased to 80% (Scheme 3, eq 2b). As such, although the exact role of the current

in this Barbier–Negishi-type reaction system is unclear, it was presumed that a high level of active Pd catalyst has been maintained.¹²

Next, cyclic voltammetry (CV) was employed to investigate the Pd catalyst. The reduction peak of Pd(II) was observed at $E_p = -0.69$ V vs SCE (in Figure 1, I). Treatment of allylic bromide

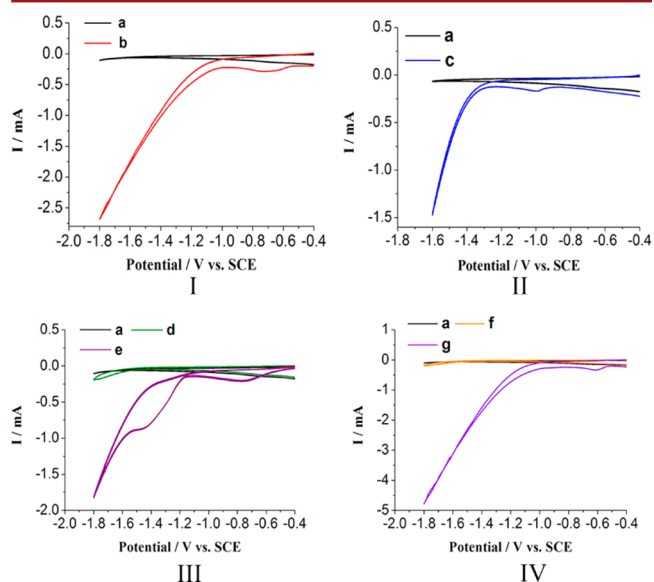


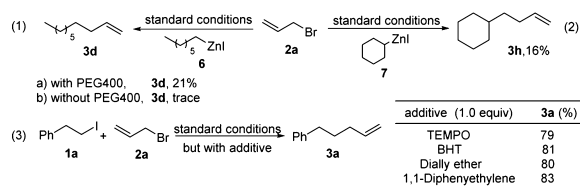
Figure 1. Cyclic voltammograms of the relevant compounds in sat. aq. NH₄Br/DMF = 1:10, using a glassy carbon electrode (GCE) as working electrode ($d = 3$ mm), a Pt wire as counter electrode, and a saturated calomel electrode (SCE) as a reference electrode, at a scan rate of 0.1 V/s⁻¹: (a) none; (b) 0.01 M Pd(OAc)₂; (c) 0.01 M Cu(OAc)₂·H₂O; (d) 0.02 M allylic bromide; (e) 0.01 M Pd(OAc)₂ and 0.02 M allylic bromide. (f) 0.02 M 1-(2-iodoethyl)benzene. (g) 0.01 M Pd(OAc)₂ and 0.02 M 1-(2-iodoethyl)benzene.

with the Pd(OAc)₂ solution resulted in a new reduction peak at $E_p = -1.41$ V vs SCE (in Figure 1, III), due to the reduction of the allylic palladium complex.¹³ In the mixture solution of 1-(2-iodoethyl)benzene and Pd(OAc)₂, only the reduction peak of Pd(OAc)₂ was observed (in Figure 1, IV). These results suggested that π -allylic palladium, instead of alkyl palladium, was formed in the electrolysis cell.

It has been observed that the yield was improved by 20% (Table 1, entries 2 and 5) with the aid of the cocatalyst Cu(II). CV studies had shown that the reduction peak of Cu(II) was observed at $E_p = -0.88$ vs SCE (in Figure 1, II). At the current stage, it was tentatively proposed that a Zn/Cu couple might have been formed from the electrochemical reduction of metal ions, and it could have promoted the process of the formation of alkyl intermediates for the coupling reaction.¹⁴

In order to further study the intermediates for this reaction, alkylzinc reagents heptylzinc iodide **6** and cyclohexylzinc iodide **7** were reacted, and the couplings of these alkylzinc reagents with allylic bromide were carried out under standard conditions. The desired products **3d** and **3h** were obtained in 21% and 16% yields, respectively (Scheme 4, eqs 1a and 2). These observations indicated that the organozinc reagents could survive within a certain period of time in our reaction system and the allylation process is likely to proceed through an in situ alkylzinc/Negishi pathway. When no PEG 400 was added into the above reaction mixture, only a trace of product was obtained (Scheme 4, eq 1b). We proposed that the surfactants (PEG 400) might have slowed

Scheme 4. Further Studies on the Mechanism



down the competitive proto-demetalation prior to transmetalation. Additionally, we found that both radical scavengers (TEMPO or BHT) and radical clocks (diallyl ether or 1,1-diphenylethylene) had limited impact on the yields of this reaction (Scheme 4, eq 3). These preliminary studies suggested in situ formation of an alkylzinc reagent as an intermediate for the coupling reaction, although the possibility of involvement of alkyl radical intermediate as a minor path could not be ruled out.

In summary, a straightforward and ligand-free method for the Pd-catalyzed electrochemical coupling between alkyl and allylic halides has been developed. This protocol is efficient for the coupling reaction of substituted allylic halides with a variety of alkyl halides, including unactivated primary, secondary, and tertiary halides as well as activated halides. Prior formation of an organozinc reagent, strict exclusion of moisture and air, and protection–deprotection of acidic hydrogen in the substrates are avoided. Further investigation to determine the mechanism of this reaction and to expand its scope is underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: [10.1021/acs.orglett.7b00473](https://doi.org/10.1021/acs.orglett.7b00473).

Experimental procedures and spectroscopic data (PDF)

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Notes

The authors declare no competing financial interest.

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