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Electrochemical Difunctionalization of Alkenes via Four-component Reactions Cascade Mumm Rearrangement: Rapid Access to Functionalized Imides

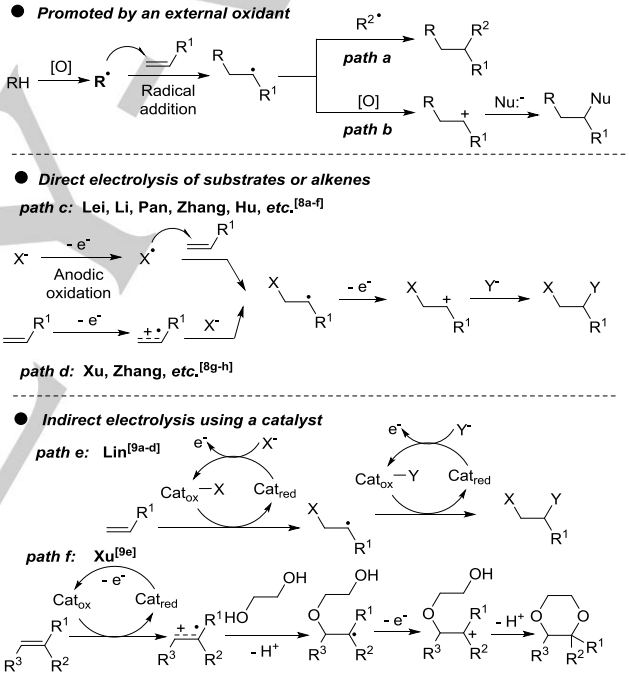
Xiaofeng Zhang, Ting Cui, Xin Zhao, Ping Liu,* and Peipei Sun*

In memory of Professor Yong-Min Zhang

Abstract: An electrochemical four-component reaction cascade Mumm rearrangement was developed, representing a rare example of in situ generation of *O*-acyl isoamides for 1,3-(O→N) acyl transfer. Inexpensive, commercially available arylethylenes, aryl or heterocyclic acids, acetonitrile, and alcohols were used as substrates. A wide range of aryl acids and alcohols were found to be tolerated and provided imides in satisfactory yields. Subsequent hydrolysis of imides could be utilized to synthesize valuable amides and β-amino alcohol derivatives.

Multicomponent reactions (MCRs) combine three or more reactants in a single chemical step and incorporate substantial portions of all the components into the same products.[1] During the past decades, this strategy has been successfully used for natural products synthesis and drug discovery.[2] One-pot multicomponent reactions are synthetically attractive because they enable access to diverse and complex molecules with several distinctive features, such as step efficiency, atom economy, operational simplicity and environmental friendliness, etc.[3] In general, multicomponent processes are initiated by addition of highly reactive reagents (e.g. isocyanides in Ugi or Passerini reactions) or capture of active intermediates generated in situ.[4] As one type of active intermediates, radical can also be involved in multicomponent reactions.[5]

Alkenes are one of common and versatile radical acceptors, and recent years have witnessed the considerable progress in the field of radical alkenes difunctionalization.[6] These three-component processes are mainly initiated by oxidation of a reagent, followed by intermolecular radical addition to C=C double bond to generate a new radical, which then undergoes potential alternative pathways: (a) radical cross-coupling (Scheme 1, **path a**), or (b) oxidation to generate a carbocation, and the sequential addition of an external nucleophile (**path b**).[6c] Electrochemistry has currently emerged as an important approach in olefin difunctionalization due to the high chemoselectivity and relatively mild conditions, which allows reactions to be conducted in the absence of oxidizing agents.[7] Electrochemical difunctionalization of alkenes is proposed to occur via direct or indirect electrolysis. The direct electrolysis of a substrate produces a radical, and the subsequent addition to an alkene generates a new radical, which undergoes further anodic oxidation to form a cation, and finally combines with other nucleophiles (**path c**),[8a-f] or alkene itself is directly converted to radical cation by anodic oxidation (**path d**)[8g-h]. The indirect electrolysis using redox catalysts lowers the potential of substrates (**path e**) or alkenes (**path f**) and enables the stepwise addtion of radicals or nucleophiles to alkene moiety.[9]



Scheme 1. Difunctionalization of alkenes involving radical or radical cation

Imides extensively exist in natural products,[10] pharmaceuticals[11] and exhibit diverse biological properties, such as anticancer,[12] antifungal[13] and antibacterial activities[14]. In view of their wide applications, great efforts have been devoted to develop efficient methods for the synthesis of imides. Conventionally, approaches were established by the *N*-acylation of amides with acyl halides, aldehydes, esters, thioesters, methylarenes, or potassium acyltrifluoroborates.[15] Other methods, including the direct oxidation of *N*-alkyl acetamides or cyclic amines, can also be used for the construction of imides.[16] The abovementioned methods, however, possess one even several drawbacks, involving requirement of strong bases, dangerous oxidants, expensive transition-metal catalysts or complicated substrates.

The classical Ugi four-component reactions involve

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interaction of a carbonyl compound, an amine, an isonitrile and a carboxylic acid to produce an α-acylaminoamide (Figure 1-A).[4a] The reaction of imine intermediates with isonitriles and carboxylic acids can generate *O*-acyl isoamide intermediates. The final step is a 1,4-(O→N) acyl transfer of *O*-acyl isoamides to give α-acylamino amides. Similarly, 1,3-(O→N) acyl transfer (Mumm rearrangement) of *O*-acyl isoamides was utilized to synthesize imides in several very early reports, but required preparation of unstable precursor imidoyl chlorides.[17] Synthesis of imides using in situ generated *O*-acyl isoamides from readily available substrates under mild conditions is environmentally desirable. As a part of our continuous studies on design of radical MCRs,[18] herein, we demonstrate the feasibility of electrochemical 4CR of alkenes, aryl acids, acetonitrile and alcohols cascade Mumm rearrangement to construct functionalized imides (Figure 1-B).

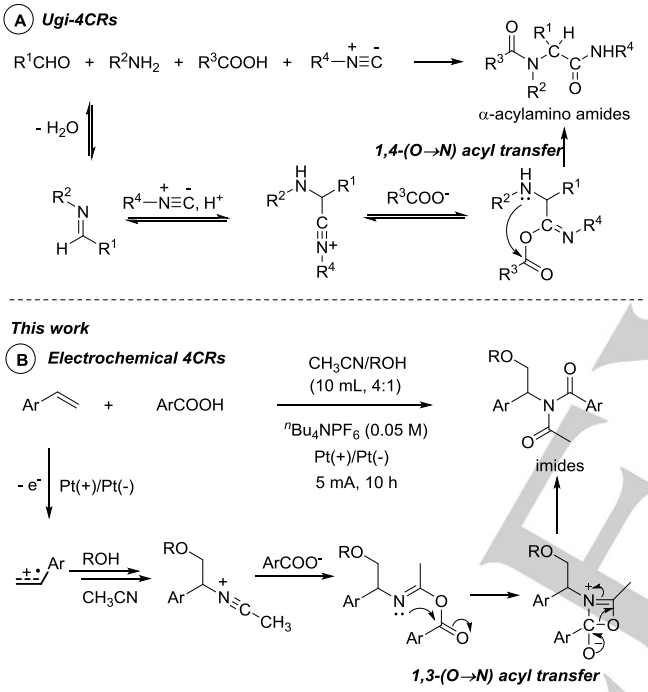
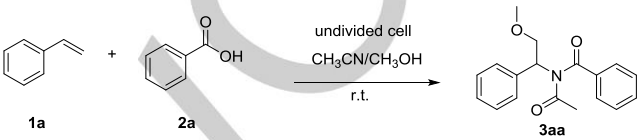


Figure 1. 4CRs via acyl transfer to generate α-acylamino amides or imides

Initially, we selected styrene (**1a**) and benzoic acid (**2a**) as the model substrates and performed the reaction in acetonitrile and methanol (Table 1). The electrolysis was conducted under 8 mA constant current in an undivided cell equipped with a platinum plate anode and cathode containing electrolyte $^{n}Bu_4NPF_6$ under air. Gratifyingly, the electrochemical 4CR indeed occurred and an imide product *N*-acetyl-*N*-(2-methoxy-1-phenylethyl)benzamide (**3aa**) was obtained in 80% yield (entry 1). Encouraged by this result, more investigations about the reaction conditions were conducted. A similar yield (79%) was obtained when the reaction was performed under Ar atmosphere (entry 2). Changing the platinum plate anode or cathode to graphite plate led to lower yields (entries 3–4). The replacement of platinum plate cathode with other metal material such as Ni electrode also showed inferior results (entries 5). Supporting electrolyte had obvious influence on the reaction efficiency. The transformation was much less efficient using other supporting electrolyte such as $^{n}Bu_4NBF_4$ or $LiClO_4$ (entries 6–7). Changing the ratio of CH_3CN and CH_3OH revealed the optimal conditions employed a 4:1 ratio of CH_3CN to CH_3OH (entries 1, 8–9). Further improvements were realized through decreasing the current density to 5 mA and 6 mA with the same amount of electricity, providing **3aa** in 83% and 81% yields, respectively (entries 10–11). However, increasing the current density was unfavorable for the formation of **3aa** (entry 12). Finally, the reaction was completely abolished in the absence of electric current (entry 13).

Table 1. Optimization of reaction conditions.[a]

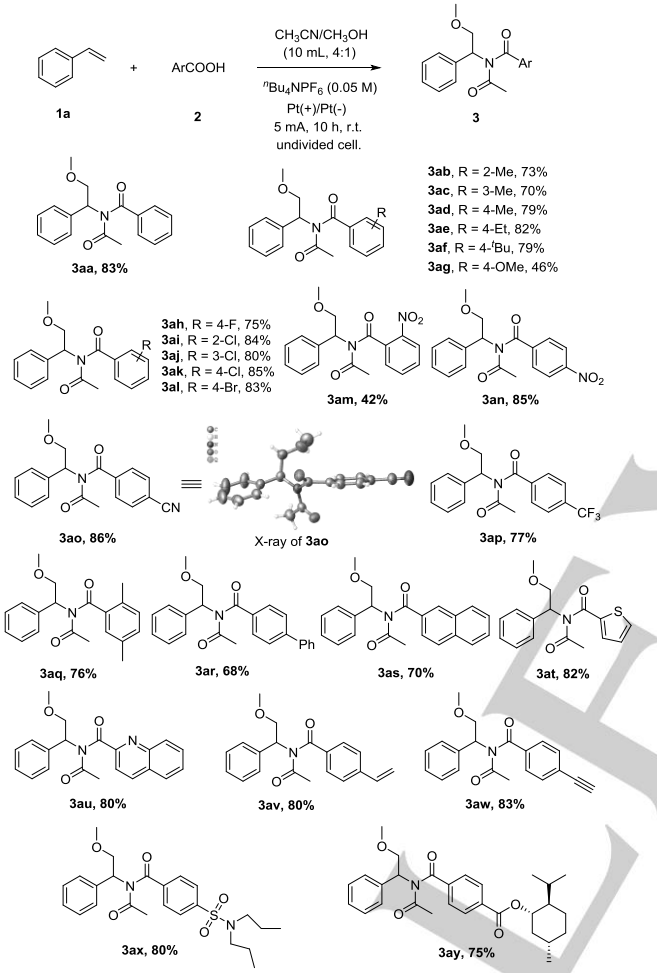


Entry	Anode/ Cathode	CH_3CN (x mL)/ CH_3OH (y ml)	Current/ Time	Yield (%)[b]
1	Pt(+)/Pt(-)	8/2	8 mA/6.25 h	80
2[c]	Pt(+)/Pt(-)	8/2	8 mA/6.25 h	79
3	C(+)/Pt(-)	8/2	8 mA/6.25 h	40
4	Pt(+)/C(-)	8/2	8 mA/6.25 h	45
5	Pt(+)/Ni(-)	8/2	8 mA/6.25 h	75
6[d]	Pt(+)/Pt(-)	8/2	8 mA/6.25 h	31
7[e]	Pt(+)/Pt(-)	8/2	8 mA/6.25 h	34
8	Pt(+)/Pt(-)	5/5	8 mA/6.25 h	72
9	Pt(+)/Pt(-)	9/1	8 mA/6.25 h	78
10	**Pt(+)/Pt(-)**	**8/2**	**5 mA/10 h**	**83**
11	Pt(+)/Pt(-)	8/2	6 mA/8.33 h	81
12	Pt(+)/Pt(-)	8/2	10 mA/5 h	56
13	Pt(+)/Pt(-)	8/2	0/10 h	0

[a] Reaction conditions: platinum plate anode (10 mm × 10 mm), platinum plate cathode (10 mm × 10 mm), **1a** (0.6 mmol), **2a** (0.9 mmol), $^{n}Bu_4NPF_6$ (0.05 M), CH_3CN/CH_3OH (10 mL), under air, r.t., 6 h, undivided cell. [b] Isolated yields based on **1a**. [c] Under Ar. [d] $^{n}Bu_4NBF_4$ instead of $^{n}Bu_4NPF_6$. [e] $LiClO_4$ instead of $^{n}Bu_4NPF_6$.

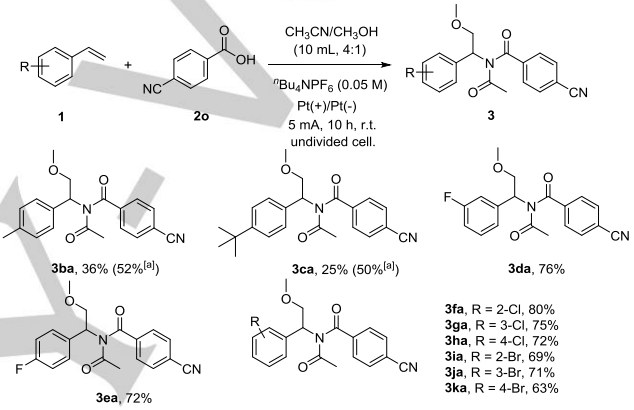
With the optimized reaction condition in hand, we firstly explored the generality of the electrochemical 4CR by the variation of aryl acids (Scheme 2). Aryl acids bearing electron-donating groups (Me, Et, ^{t}Bu) and halogen substituents (F, Cl, Br) could provide the imide products (**3ab**–**3af**, **3ah**–**3al**) in good yields (70–85%), regardless of these substituents at the *ortho*-, *meta*- or *para*-position of the benzene ring. Strongly electron-donating methoxy group was less efficient and gave the desired product **3ag** in moderate yield (46%). To our delight, electron-deficient aromatic acids with nitro, cyano and trifluoromethyl groups were also suitable for this transformation, and gave the corresponding products in moderate to excellent yields (**3am**–**3ap**). The structure of the imide **3ao** was characterized by X-ray crystallography (CCDC number 1942912). The aryl acid bearing two substituents such as 2,5-dimethylbenzoic acid was good reaction partner and furnished the desired product **3aq** in 76% yield. Notably, 4-biphenylcarboxylic acid, 2-naphthoic acid and unsaturated heterocyclic acids (**2t**, **2u**) were suitable for this electrochemical reaction as well, and comparable yields were obtained under the optimal reaction conditions (**3ar**–**3au**). It was

noteworthy that alkeny and alkynyl of the aryl acids (**2v**, **2w**) were well tolerated, either (**3av**, 80%; 3**aw**, 83%). We also anticipated that the present protocol might be applicable to the late-stage functionalization of pharmaceutical molecules and natural products. For instance, probenecid, which was primarily used in treating gout and hyperuricemia,[19] provided the expected product **3ax** in 80% yield. The menthol derivative **2y** delivered the desired product **3ay** in good yield (75%). It should be noted that the use of aliphatic carboxylic acids as the starting materials under the same conditions did not give the desired imides.



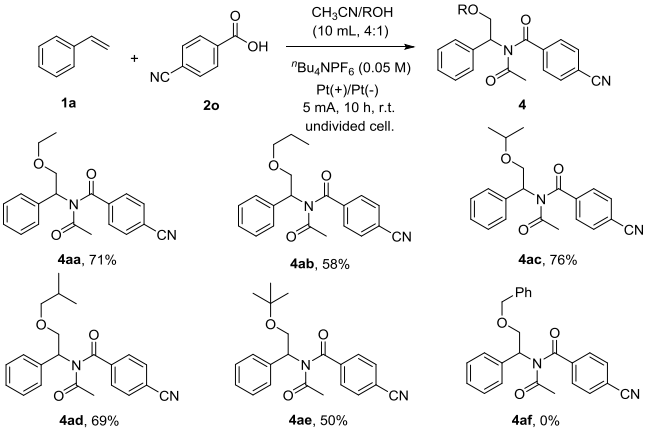
Scheme 2. Reaction scope of aryl acids **2**.

Subsequently, the scope of arylethylenes was examined by using 4-cyanobenzoic acid (**2o**) as the reaction partner (Scheme 3). It should be pointed out that electronic effects of substituents of arylethylenes had significant influence on their reaction efficiency. Arylethylenes substituted with moderately electron-donating groups, such as 4-methylstyrene and 4-*tert*-butylstyrene, delivered the products **3ba** and **3ca** in 36% and 25%, respectively. Low yields could be attributed to the formation of complicated byproducts. Gratifyingly, a series of arylethylenes possessing halogen groups (F, Cl, Br) at different position of the benzene ring participated smoothly in the reaction and furnished the desired products **3da**–**3ka** in satisfactory yields (63–80%). It should be noted that arylethylenes containing halogen groups at *ortho*-position also work well, regardless of the steric hindrance (**3fa** and **3ia**). Unfortunately, other electron-deficient or electron-rich arylethylenes, and alkylalkenes were not suitable for this electrochemical difunctionalization reaction. Due to the limitation of the olefins, we attempted to do more in-depth research. Electron-deficient olefins, such as 4-cyanostyrene, showed no distinct oxidation potential in the range of 0–2.5 V. Electron-rich olefins such as 1,1-diphenylethylene more easily formed the dimethoxylation product under the standard condition (see the Supporting Information).[8h] Bromo substituted triarylamines were frequently used as electron mediators.[20] Indeed, we found that the yields of **3ba** and **3ca** were improved to 52% and 50% respectively when tris(4-bromophenyl)amine (10 mol%) was added.



Scheme 3. Reaction scope of arylethylenes **1**. [a] Tris(4-bromophenyl)amine (10 mol%) was added.

Additionally, we further explored the generality and scope of the alcohols. As shown in Scheme 4, primary alcohols such as ethanol, *n*-propanol, isobutanol as well as secondary alcohol such as isopropanol and tertiary alcohol such as tertiary butanol could tolerate the reaction and furnished the desired products **4aa**–**4ae** in good yields (50–76%). Unfortunately, no desired reaction occurred when benzyl alcohol was used as the substrate.



Scheme 4. Reaction scope of alcohols.

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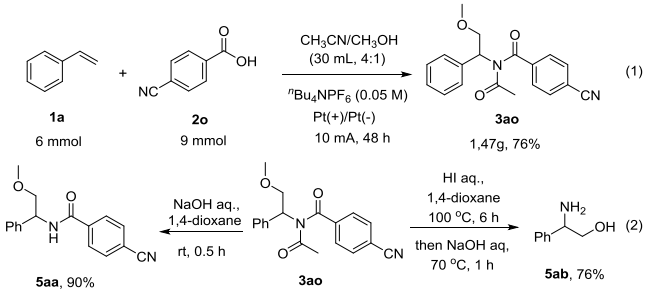
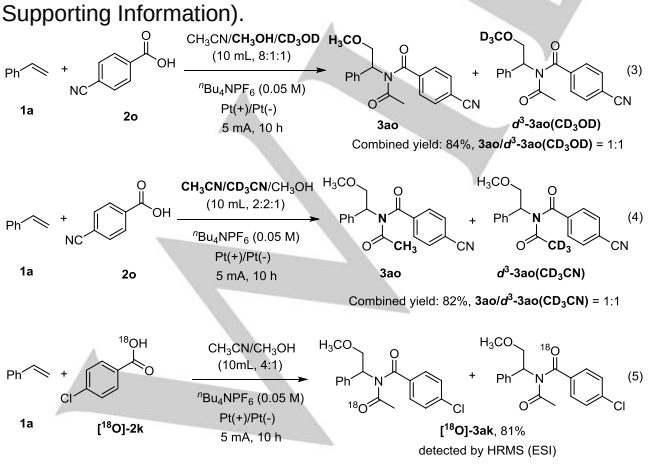
To evaluate the practicality and scalability of the electrochemical 4CR, we performed the reaction on a 6 mmol scale (Scheme 5, eq 1). By increasing the current density to 10 mA and prolonging the reaction time to 48 h, the product **3ao** was obtained in 76% yield (4.56 mmol), which demonstrated the synthetic utility of this methodology. The imide **3ao** could easily be transformed to corresponding amide **5aa** (90%) by treatment with NaOH aq. at room temperature (eq 2, left). Interestingly, the product **3ao** could be hydrolyzed completely in the presence of concentrated hydriodic acid, and DL-phenylglycinol (**5ab**) was obtained in 76% yield (eq 2, right).



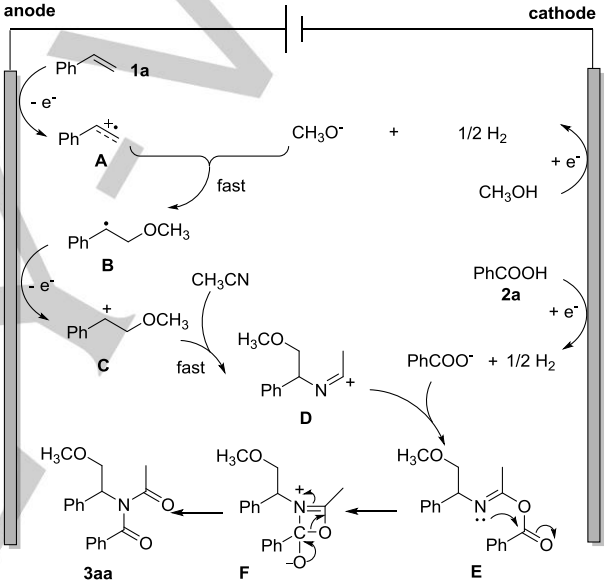
Scheme 5. Gram-scale synthesis and product transformations.

In order to probe the reaction mechanism, several deuterium-labeling experiments were designed and conducted (Scheme 6). Two parallel reactions, one with CH_3OH and CD_3OD (2 mL, 1:1) and the other with CH_3CN and CD_3CN (8 mL, 1:1), were respectively conducted under standard conditions (eq 3 and 4). The relative ratio of the product **3ao** and ***d*^{3}-3ao(CD$_3$OD)** or ***d*^{3}-3ao(CD$_3$CN)** was 1:1, indicating that the introduction of methoxy group and acetonitrile in this electrochemical 4CR may not be the rate-determining step (see the Supporting Information). The ^{18}O-labeled experiment suggested that an oxygen atom of the imide **[^{18}O]-3ak** came from the O^{18}-labeled 4-chlorobenzoic acid **[^{18}O]-2k** (eq 5). This result indicated that a rearrangement was likely involved in this electrochemical reaction. Cyclic voltammetry studies indicated that styrene had the lowest oxidation potential (1.60 V vs SCE) than methanol and benzoic acid (both with no distinct oxidation peak) in the range of 0–2.5 V, revealing that the initial step of the electrochemical 4CR may be the oxidation of styrene (see the Supporting Information).



Scheme 6. Isotope labeling reactions.

Based on the control experiments, the cyclic voltammetry studies and relative literature reports, we proposed a possible mechanism for the electrochemical 4CR as follows: Initially, the anodic oxidation of styrene (**1a**) through single-electron-transfer produced a radical cation **A** (Scheme 7).[8g-h, 21] The nucleophilic addition of cation **A** with CH_3O^- generated from cathodic reduction of methanol resulted in the formation of carbon-centered radical **B**, followed by the anodic oxidation to deliver another carbocation **C**. The intermolecular trapping of cation **C** with acetonitrile led to carbocation **D**, which could smoothly combine with $PhCOO^-$ generated from the cathodic reduction of PhCOOH. Finally, due to its structural instability,[17] the intermediate **E** would soon undergo Mumm rearrangement to furnish the desired product **3aa**.



Scheme 7. Proposed mechanism for the electrochemical 4CR.

In summary, we have developed an electrochemical four-component reaction for the synthesis of imides from arylethylenes, aryl or heterocyclic acids, acetonitrile and alcohols. The electrochemical 4CR can perform on a gram scale and the products can be easily converted to amide and β-amino alcohol. This organic electrosynthesis enables generation of unstable *O*-acyl isoamides precursor for Mumm rearrangement from very common substrates, which is difficult for previous methods. The protocol features low cost, oxidant- and catalyst-free conditions, and good scalability. Our developed transformation provides a modular approach for the synthesis of imides, and relative electrochemical MCRs are ongoing in our laboratory.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: four-component reaction • difunctionalization of alkenes • electrochemistry • imide • Mumm rearrangement

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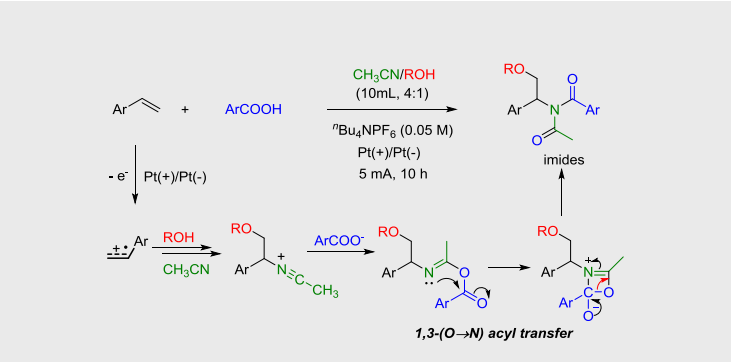

Xiaofeng Zhang, Ting Cui, Xin Zhao, Ping Liu, and Peipei Sun**

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Electrochemical Difunctionalization of Alkenes via Four-component Reactions Cascade Mumm Rearrangement: Rapid Access to Functionalized Imides

A four-component reaction based on arylethylenes, aryl acids, acetonitrile, and alcohols has been designed that enables the difunctionalization of alkenes and the formation of imides under electrochemical conditions. Mechanistic studies support a 1,3-(O→N) acyl transfer of *O*-acyl isoamides via Mumm rearrangement.