Organic & Biomolecular Chemistry

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Journal:	*Organic & Biomolecular Chemistry*
Manuscript ID	OB-COM-10-2024-001605
Article Type:	Communication
Date Submitted by the Author:	04-Oct-2024
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COMMUNICATION

Paired electrocatalysis enabled oxidative coupling of styrenes with alkyl radicals

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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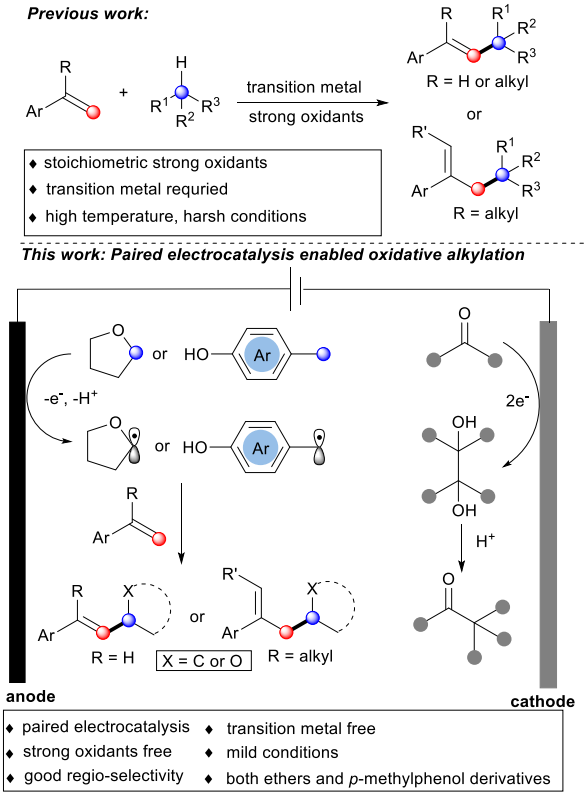
A paired electrocatalysis strategy for intermolecular oxidative cross-dehydrocoupling between styrenes and ethers or *p*-methylphenol derivatives using ketone as mild oxidant is described. This approach allows Csp^3 carbon-centered radicals to be generated by anodic oxidation, cross-coupled reductive coupling of ketone on the cathode, providing valuable oxidative alkylation products.

The direct functionalization of alkenes, an inexpensive and readily available feedstock, represents one of the most appealing transformations in organic chemistry.[1] Among which, the direct oxidative coupling of alkenes with alkyl radicals, following β-H elimination stands out as the most ideal yet challenging strategy for obtaining valuable highly substituted olefins and analogues.[2] In this context, cross-dehydrocoupling of alkenes and alkyl carbon-centered radicals generated via oxidation of Csp^3 -H bond[3] from various precursors has been developed.[4] In particular, α-functionalized ether derivatives, which are prevalent in a wide range of natural products and biologically active molecules,[5] have been synthesized via cross-dehydrocoupling of alkenes and ethers.[4c,4i,4j] Despite these advances, these elegant protocols usually require strong oxidants, transition-metal catalysts, high temperature and harsh conditions. Therefore, the development of a green, mild and metal-free method for direct oxidative coupling of olefins and alkyl radicals via oxidation of Csp^3 -H bond remains challenging and still in highly desirable.

Utilizing electrons as inherently safe and sustainable redox reagents, electrochemistry offers an eco-friendly approach to organic synthesis.[6] Typically, a single half-electrode reaction is necessary, with either cathodic H_2 evolution or the use of a sacrificial anode required to maintain electroneutrality. Paired electrolysis, which simultaneously activates reactants on both electrodes, has remained underexploited.[7] Significant challenges arise with two-electrode reactions, particularly in matching the reaction scale and rate required for convergent



Scheme 1 Oxidative coupling of styrenes with alkyl radicals

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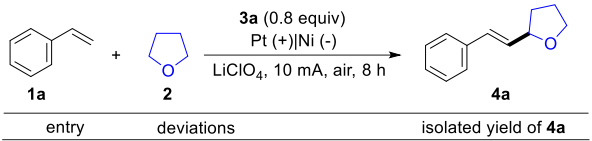
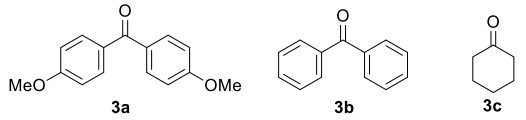
Supplementary Information available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

synthesis. Despite electrocatalyzed[8] and photocatalyzed[9] allylic C–H alkylation reaction with carbon nucleophiles have been reported, the substrates are limited to active, protic malonates and their derivatives. Thus, we anticipated whether a paired electrolysis, wherein the anodic oxidation of active alkyl substrates such as ether or toluene derivatives for C(sp^3)–H bond activation to generate the Csp^3 radical intermediates, and the cathodic reduction of suitable oxidants could lead to the highly efficient oxidative alkylation of alkenes. Herein we present a direct paired electrocatalysis strategy for intermolecular cross-dehydrocoupling between styrenes and alkyl radicals generated from ethers or *p*-methylphenol derivatives using ketone as mild oxidant (Scheme 1). Notable features of this protocol include: (a) Paired electrocatalysis, two kinds of valuable products were obtained simultaneously; (b) transition metal-free; (c) strong oxidants-free, ketone was used as a mild oxidant and was reduced on cathode to deliver valuable pinacol rearrangement products; (d) both ethers and *p*-methylphenol derivatives serve as Csp^3 radical precursors.

Table 1 Optimization Study for paired electrocatalysis enabled oxidative alkylation.



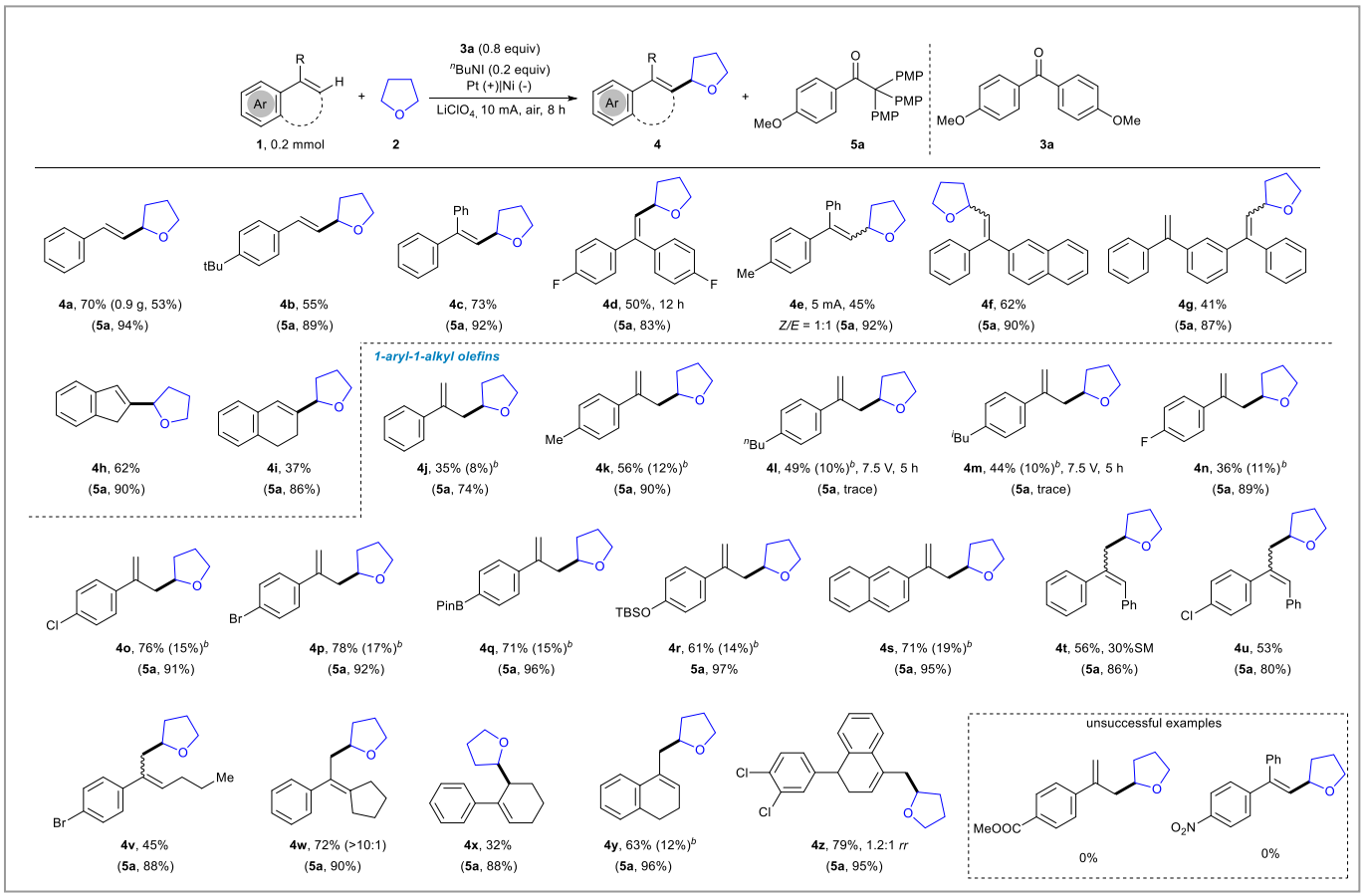
entry	deviations	isolated yield of **4a**
1	none	53%
2	C (+)|Ni (-)	0%
3	**^{n}Bu$_4$NI (0.2 equiv)**	**70%**
4	2.0 equiv. **3a**	55%
5	2.0 equiv. **3b**	31%
6	2.0 equiv. **3c**	20%
7	no **3a**	14%
8	no current	0%



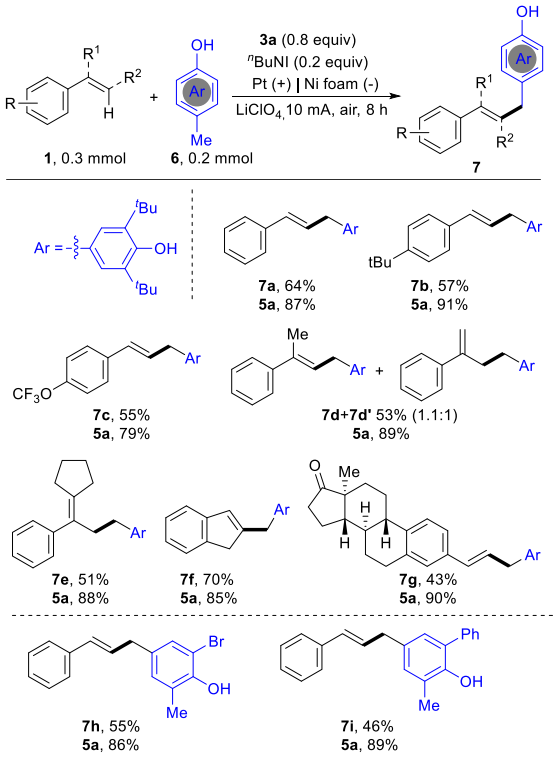
Initially, styrene (**1a**) was employed as model substrate to examine various reaction conditions under a constant current for the oxidative alkene alkylation with THF. We found that alkylation product **4a** was obtained in 53% isolated yield under a constant current (10 mA) in THF with 0.8 equivalents of ketone **3a** under air conditions, $LiClO_4$ as electrolyte, Pt plate as the anode and Ni plate as the cathode (Table 1, entry 1). The control experiment showed that Pt was essential as anode as other materials such as GF could not lead to desire product (entry 2). Interestingly, the presence of I^- anion species significantly improved the yield to 70% (entry 3), consistent with previous reports.[4c] Surprisingly, increasing the amount of ketone **3a** to 2.0 equivalents did not significantly enhance the yield (entry 4), indicating that other species are being reduced at the cathode. Other ketones, such as benzophenone and cyclohexanone, produced the desired product in much lower yields (entries 5 and 6), suggesting that the redox potential of the ketone may be a key factor in this transformation. Control reactions conducted without ketone **3a** (entry 7) resulted in very low yield of product formation, while without current (entry 8) resulted in no product formation, demonstrating the essential roles of both current and ketone in the reaction.

With the optimized reaction conditions (entry 3, Table 1), we next explored the scope of this transformation (Scheme 2). Initially, various representative styrenes afforded the corresponding alkylation products in good yields (**4a** and **4b**). To enhance the synthetic value of this green method, a gram-scale synthesis of **4a** was conducted. 1,1-Diphenylethene derivatives with either electron-rich or electron-poor substituents on the benzene ring reacted effectively, producing the corresponding alkenylation products in good yields (**4c** to **4f**). 1,3-Bis(1-phenylvinyl)benzene underwent efficient conversion to adduct **4g**, with only one of the alkene groups being alkenylated. Cycloalkenes such as *1H*-indene and 1,2-dihydronaphthalene, which serve as important cores of drugs, smoothly converted into the corresponding products **4h** and **4i**, respectively. 1-Aryl-1-alkyl olefins typically suffer from poor regioselectivity in previous methods[4c] due to two different elimination patterns, resulting in nearly 1:1 isomer ratios. To our delight, much better regioselectivity was achieved for most 1-aryl-1-alkyl olefins (about 5:1, **4j** to **4z**). Alkyls, halogens, Bpin-, TBSO-, Naph- remained intact under the standard conditions, demonstrating good functional group compatibility (**4k** to **4s**). Besides α-methyl styrene, other alkyl groups such as Bn, Bu, and cyclopentyl also proceeded well in the transformation with only small amounts of elimination isomers (**4t** to **4w**). Trisubstituted 1-aryl-1-alkyl olefins smoothly converted into the desired products (**4x** to **4y**), including a derivative of sertraline (**4z**). However, the presence of electron-withdrawing groups (EWGs) completely suppressed the reaction, resulting in no desired products. Notably, 1,2,2,2-tetrakis(4-methoxyphenyl)ethan-1-one (**5a**), formed by pinacol rearrangement following the reductive coupling of ketone **3a**, was obtained in nearly quantitative yield in above reactions, demonstrating the high efficiency of this electroreductive process.

Inspired by these results, we further extended this transformation to *p*-methylphenol derivatives to achieve new kinds of adducts of alkenes and benzylic radicals (Scheme 3). A range of substrates proved amenable to this transformation. Several styrenes were tested and proceeded well in the transformation with BHT (**7a** to **7c**). However, for 1-aryl-1-alkyl olefin such as α-methyl styrene, the regioselectivity is not good (**7d** and **7d'**), in contract, another α-cyclopentyl styrene, only gave one elimination isomer due to kinetically controlled elimination process (**7e**). Internal alkenes like *1H*-indene could also work well in this reaction (**7f**). Notably, this oxidative alkylation process was successfully applied to synthesize estrone derivative **7g**, which shows anti-tumor activity against A549 and Huh7 (see SI). Furthermore, other *p*-methylphenol



Scheme 2 Substrate scope for the oxidative coupling of styrenes with THF.[ab] [a]isolated yield. [b]NMR yield of another elimination product.

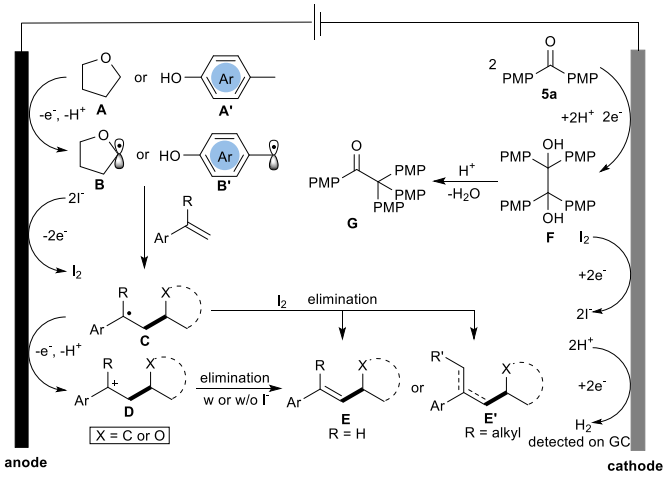


Scheme 3 Substrate scope for the oxidative coupling of styrenes with *p*-methylphenols.

derivatives such as 2-bromo-4,6-dimethylphenol and 3,5-dimethyl-[1,1'-biphenyl]-2-ol were treated under standard conditions and produced the desired oxidative alkylation product in moderate yields (**7h** and **7i**).

To gain insight into the mechanism of this transformation, several mechanistic experiments were conducted. To clarify the possible radical mechanism, radical-trapping experiment was performed using TEMPO and BHT (Figure S3). The formation of the desired product was completely suppressed, meanwhile the radical trapping product **6a** was isolated in 54% yield (also see Scheme 3), indicating that the radical process is most likely involved in C–H cleavage of ethers and *p*-methylphenols. When substrate **3a** was directly treated under the standard reaction conditions without **1a**, pinacol rearrangement product **5a** was obtained in 62% yield (Figure S3), demonstrating that Csp^3 carbon-centred radicals generated by anodic oxidation was cross-coupled with reduction of **3a** on the cathode. However, using only 0.8 equivalents of ketone 3a was insufficient to complete the entire electron transfer in this transformation. Therefore, there must be other species being reduced at the cathode. Further GC analysis detected the generation of H_2 under standard conditions (Figure S6), demonstrating that proton reduction was involved at the cathode to balance the electron transfer of the entire reaction. Lastly, CV test showed

that redox potential of TBAI 0.3 V vs SCE (Figure S5), the direct oxidation and reduction of TBAI was involved on anode and cathode, both I_2 and I^- anion may promote the elimination of benzylic radical or cation intermediates.[4c]



Scheme 4 Plausible reaction mechanisms

Based on above studies and previous reports,[4] a plausible paired electrocatalysis mechanism was proposed (Scheme 4). Initially, THF (**A**) or *p*-methylphenol derivatives (**A'**) undergo anodic oxidation resulting in the formation of a Csp^3 radical intermediate **B** or **B'**,[7c,10] which is subsequently intercepted by olefins to yield the benzylic radical intermediate **C**. Radical **C** is further subjected to anodic oxidation, leading to the formation of its carbocation intermediate **D**. Following the elimination with I^- or w/o I^- anion, carbocation intermediate **D** generates final product **E** or **E'**. In another path way, benzylic radical intermediate **C** might generate benzylic iodide species with assistant of I_2 oxidated on anode, then followed by elimination of HI to deliver the final products **E** or **E'**. On the cathode, reduction of three species were involved based on experiments: a) Reductive coupling of **5a** to deliver pinacol Intermediate **F**, following by pinacol rearrangement to deliver the ketone **G**, this process was proved to be paired with oxidation of THF or *p*-methylphenol derivatives on anode; b) The reduction of I_2 to I- facilitated the catalytic cycle of TBAI, which was a key factor in improving the efficiency of the entire transformation. c) Lastly, proton reduction to generate H_2 was proven to be involved.

Conclusions

In conclusion, a paired electrocatalysis strategy for oxidative coupling of styrenes with alkyl radicals generated from oxidation of ethers or *p*-methylphenol derivatives using ketone as mild oxidant was developed. The aforementioned protocol function as efficient synthesis tools capable of generating valuable desaturated alkanes with good regio- and chemo-selectivity, ultimately opening a new pathway for the development of paired electrochemical reactions.

Author contributions

Dong, Li: Methodology, Data curation, Investigation, Formal analysis, Writing – original draft. Ling Zhang: Investigation, Formal analysis. Daixi Li: Investigation, Writing – review & editing, Funding acquisition. Peng Yu: Writing – review & editing, Supervision. Tao Shen: Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Project administration, Funding acquisition, Data curation, Conceptualization.

Acknowledgements

This project was supported by the financial support provided by National Science Foundation (22301179), Fundamental Research Funds for the Central Universities (24X010301678, 23X010301599), Excellent Young Scientists Fund Program (overseas), and Shanghai jiao Tong University 2030 Initiative, Fujian Province Natural Science Foundation (2021J05280) and Fujian Province Talent Introduction Program Foundation (01102801). TS is a Xiaomi Young Scholar and are grateful for financial support from Xiaomi Corporation.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article have been included as part of the ESI.

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Data Availability Statement

The data supporting this article “Paired electrocatalysis enabled oxidative coupling of styrenes with alkyl radicals” have been included as part of the Supplementary Information.

Signature: 申涛 Date: July 31, 2024