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Substrate-Dependent Electrochemical Dimethoxylation of Olefins

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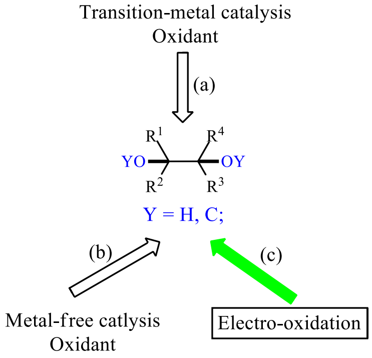
Abstract: A general and direct electrochemical dimethoxylation of olefins is reported, which enables a divergent route to different products depending on the structure of olefins. The present protocol features mild conditions and broad substrate scope (49 examples) obviating the usage of transtion-metals and external oxidants. More importantly, to rationalize the divergent route of the transformation, an ionic-like pathway involving carbocation intermediate is proposed and the diverse products is attributed to the different stability of carbocations.

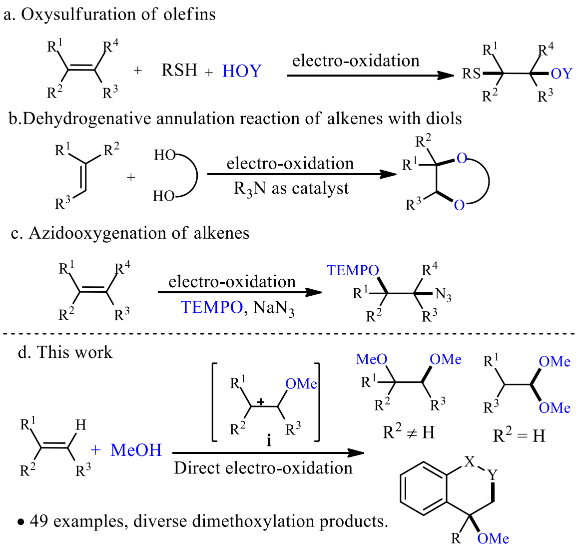
Keywords: Electrochemistry; Oxidation; Dimethoxylation; Olefins;

Olefins as one of the most accessible and abundant chemical feedstocks are considered as appealing substrates in organic synthesis from an academic and industrial perspective. Particularly, direct dioxygenation of olefins has received tremendous attention since the pioneering work of Sharpless.[1],[2] The classical Sharpless asymmetric dihydroxylation involves the usage of toxic osmium together with oxidants, which provides the impetus to develop alternative environmentally benign methods. For instance, some alternative transition metals, including ruthenium, manganese, palladium, have been reported for the dioxygenation of olefins (Scheme 1, process a).[3] To further improve the process, some metal-free strategies have also been achieved by using stoichiometric peroxides, hypervalent iodine and selenium (Scheme 1, process b).[4] Despite the tremendous progress, a greener and more practical dioxygenation method is still highly demanded. Organic electrochemistry represented as an ideal synthetic technology has experienced a renaissance,[5] owning to the reason that electrons can be directly manipulated via the electrochemical oxidation and reduction. As our ongoing work on organic electrosynthesis,[6] we envisaged that direct electrochemical oxidation might be an appealing strategy towards dioxygenation of olefins (Scheme 1, process c), which could obviate the participation of transition-metals and external oxidant.



Scheme 1. Approaches toward the dioxygenation of olefins

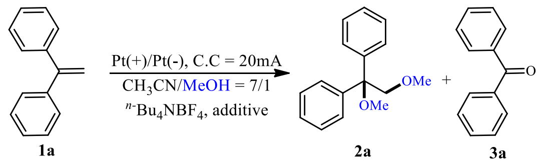
Recently, electro-oxidation has proved to be a powerful tool in difunctionalization of alkenes,[7] especially for the formation of C-O bonds. Very recently, an efficient electrochemical oxidative radical oxysulfuration was independently reported by Lei and Han (Scheme 2a).[8] Notably, a remarkable breakthrough in the electrocatalytic synthesis of 1,4-dioxane and 1,4-dioxepane was achieved by Xu *et al* (Scheme 2b).[9] Lin also unveiled a prominent work of electrochemical azidooxygenation of alkenes (Scheme 2c).[10] Nevertheless, the dimethoxylation of olefins was still considered as an illusive issue due to the undesired olefin dimerization.[7],[11] In this context, a direct electro-oxidation was selected as a strategy to solve the dimethoxylation of olefins (Scheme 2d). More importantly, we found that the electrochemical dimethoxylation delivered different products largely dependent on the stability of the carbocation intermediate **i** (Scheme 2d). It also demonstrated that the reaction proceed through an ionic-like pathway. Furthermore, the utility of this efficient protocol could readily expand to the synthesis of lactones, lactams and indolines via an intramolecular difunctionalization of olefins.



Scheme 2. Electrooxidative C-O bonds formation of alkenes

Initially, 1,1-diphenylethylene was selected as a pilot substrate in the electrochemical dimethoxylation using platinum plate as electrodes in an undivided cell under constant current conditions (Table 1). Increasing reaction temperature could afford the product **2a** with higher yield, albeit with a higher yield of byproduct **3a** (Entry 1-3). To further improve the reaction performance, the byproduct **3a** had to be suppressed. Interestingly, the generation of **3a** was attributed to water residue in the solvent according to result of Entry 4. Subsequently, anhydrous solvent was tested and the dimethoxylated product **2a** was exclusively obtained with a satisfactory yield (Entry 5). Further evaluation on additives showed that DBU as a base had little effect on the yield of the reaction, while guanidine and tetramethylguanidine (TMG) resulted in much lower yields (Entry 6-8). Replacing the platinum electrodes with graphite electrodes caused significant erosion on the yield (Entry 9).

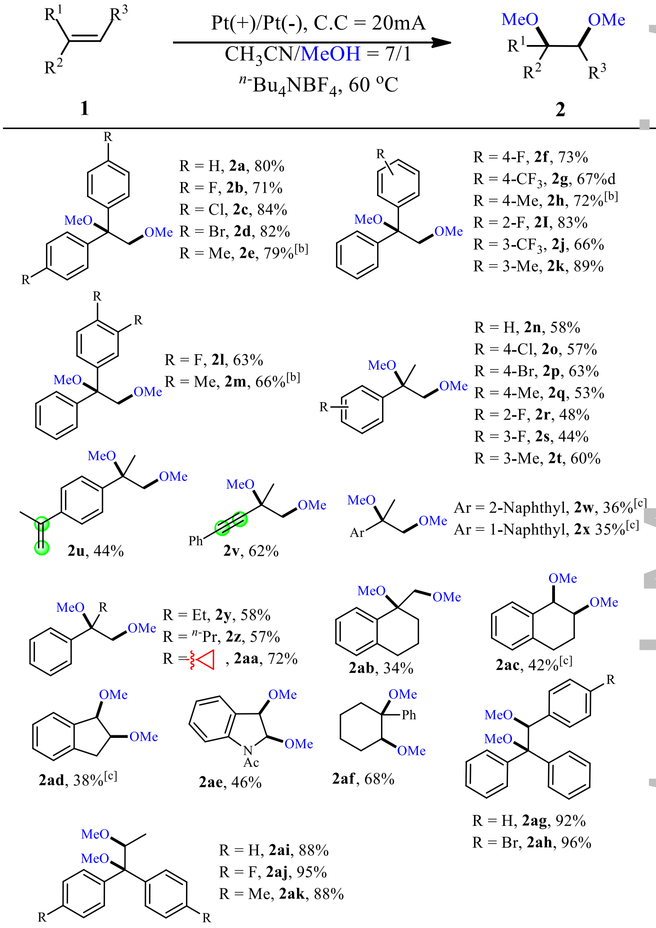
Table 1. Optimization of electrochemical dimethoxylation of olefins [a]



Entry	T/°C	Additive	Yield (**2a**/**3a**)[b]
1	30	-	46/n.d.
2	50	-	63/n.d.
3	60	-	65/16
4[c]	60	H_2O	trace/76
5[d]	60	-	80/trace
6 [d,e]	60	DBU	79/trace
7 [d,e]	60	guanidine	66/ trace
8[d,e]	60	TMG	69/trace
9[d,f]	60	-	68/trace

[a] Reaction conditions: undivided cell, platium electrodes (1.5 × 1.5 cm^2), J = 8.9 mA/cm^2), **1a** (0.5 mmol), CH_3CN/MeOH (7/1 mL, v/v), ^{n}-Bu_4NBF_4 (0.8 mmol) under argon for 2 h, 3.0 F. [b] Isolated yield. [c] 0.5mL H_2O was added as an additive. [d] Anhydrous solvent was used. [e] DBU (0.1 mmol) was added as an additive. [f] Graphite electrodes were used.

Table 2. Substrate scope of olefins in the dimethoxylation of olefins [a]



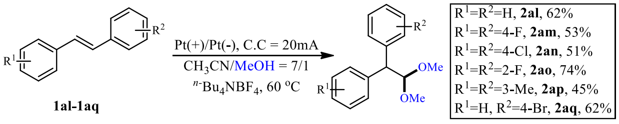
[a] Reaction conditions: undivided cell, platium electrodes (1.5 × 1.5 cm^2, J = 8.9 mA/cm^2), **1** (0.5 mmol), CH_3CN/MeOH (7/1 mL, v/v), ^{n}-Bu_4NBF_4 (0.8 mmol) at 60 °C under argon for 2 h, 3.0 F. [b] Lower current density (J = 4.4 mA/cm^2) and prolonged reaction time (3h, 2.2 F) were required. [c] DBU (0.1 mmol) was added as an additive.

Having identified the optimal conditions, a broad spectrum of olefin was investigated (Table 2). It was found that the electronic property and the substitution pattern of 1,1-diphenylethylenes marginally affected the reaction performance resulting in the corresponding products (**2a-2m**) with good yields (63-89%). Next, 2-substituted propenes were subjected to the optimal conditions and relative lower yields were observed (**2n-2x**), which were partially due to the volatility of the products. Remarkably, the

10.1002/adsc.201801173

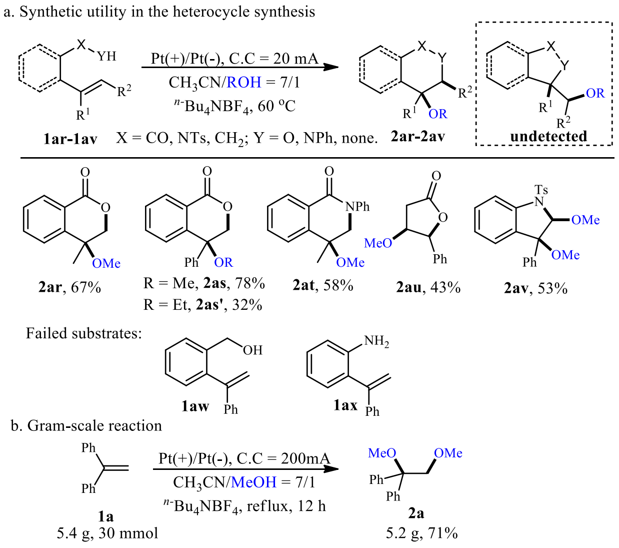
substrates **1u** and **1v** containing multiple reactive sites were well tolerated in this electrochemical method, thereby giving the products (**2u-2v**) with good selectivity. In the case of substrates containing fused ring, DBU was added to facilitate the nucleophilic addition of methanol. Additionally, other alkyl and cyclo-alkenes were also tested and proved to be amenable in the reaction (**2y-2ae**). It was particularly noteworthy that a radical-clock substrate [12] **1aa** proceeded smoothly in this reaction (**2aa**) without giving any ring-expansion products. This result clearly suggests an ionic-like pathway involving in the reaction. Finally, we found that trisubstituted olefins were favoured substrates in this transformation furnishing the dimethoxylated products with up to 96% yield (**2af-2ak**).

To further verify the ionic-like pathway, 1,2-substituted olefins, which could form less stable carbocations, were explored (Scheme 3). Surprisingly, the carbocation-initiated semipinacol rearrangement was observed, thereby giving access to the acetals (**2al-2aq**) with moderate yields (45-74%). It showed that this electrochemical dimethoxylation delivered different products largely independent of the substitution pattern of olefins, due to the different stability of the carbocations.



Scheme 3. Semipinacol rearrangement in the electrochemical dimethoxylation

To demonstrate the synthetic utility of the electrochemical approach, some specific substrates and the gram-scale reaction were studied. As shown in the Scheme 4, the olefins (**1ar-1av**) bearing nucleophilic reactive sites (COOH, CONHPh, NHTs) were employed in the reaction. To our delight, a different regioselectivity compared with the radical type reactions[8b] (**2ar-2av**) was achieved, which made this protocol a complementary method to construct lactones, lactams and indolines. Notably, ethanol proved to be a compatible nucleophile as well, although only 32% yield was observed (**2as'**). Nevertheless, the substrates bearing hydroxyl (**1aw**) and amino groups (**1ax**) failed to give the desired product. Furthermore, the gram-scale dimethoxylation of olefins were achieved with a modified condition delivering the products **2a** with 71% yield.



Scheme 4. Synthetic utility of the electrochemical approach

Next, we turned our attention to the mechanism of the reaction. To elucidate the reaction process, cyclic voltammetry of the reactants was explored. As shown in the Figure 1, no significant oxidation peak of MeOH was observed (curve b) in the potential window of interest. In contrast, an obvious peak was observed in the CV of substrate **1a** and **1al** (curve c, d). The comparison indicated that olefin can be oxidized more easily than MeOH under the optimized conditions, which further excluded the possibility to generate methoxyl radicals in the presence of olefins. Further kinetic isotope effect studies verified that the nucleophilic addition of MeOH might not be the rate-determining step (for details see SI).

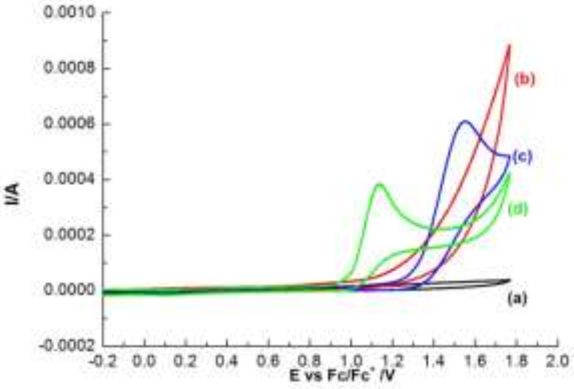
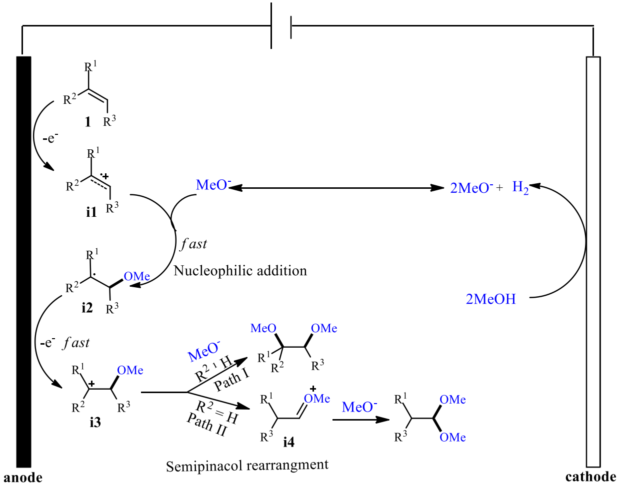


Figure 1. Cyclic voltammograms of substrates: (a) background ($LiClO_4$ 0.1M in CH_3CN), (b) MeOH (10 mmol/L), (c) **1a** (5 mmol/L), (d) **1al** (5 mmol/L).

On the basis of the observation in the reaction and the CV experiment, a plausible mechanism was proposed as shown in the Scheme 5. Firstly, anodic oxidation of alkene produces a radical cation intermediate (**i1**), which subsequently undergoes a nucleophilic addition affording the radical **i2**. Secondly, a further oxidation of transient species **i2** leads to the generation of carbocation **i3**, which can be considered as the major intermediate in the process due to the fast steps of nucleophilic addition and radical oxidation. Ultimately, the *in-situ* generated carbocation **i3** can experience two different pathways, depending on the stability nature of **i3**. The more stable cation bearing multiple substituents proceeds through a direct nucleophilic addition (path I), whereas the less stable one proceeds a semipinacol rearrangement (path II) delivering the acetal product.

In conclusion, an electrochemical dimethoxylation of olefins is unveiled, which is compatible with a wide range of alkenes. In this efficient transformation, an ionic-like pathway involves in the reaction, which provides a complementary method compared with the radical pathway. More importantly, the two types of products can be obtained depending on the substitution pattern of alkenes.



Scheme 5. Proposed mechanism

Experimental Section

Electrochemical dimethoxylation of olefins (**1a** as example) : An undivided cell was equipped with a magnet stirrer, platinum plate (1.5×1.5 cm^2) electrode, as the working electrode and counter electrode. The substrate 1,1-diphenylethylene **1a** (90 mg, 0.5 mmol) and electrolyte *n*-Bu$_4$NBF$_4$ (263 mg, 0.8 mmol) was added to the anhydrous solvent CH$_3$CN/MeOH (7/1 mL) under argon atmosphere. The resulting mixture was allowed to stir and electrolyze at constant current conditions (J = 8.9 mA/cm^2) at 60 °C for 2 hours. Then the solvent was removed with a rotary evaporator and the residue was purified by column chromatography (EA/PE = 1/50-1/30) on silica gel to afford the desired product (1,2-dimethoxyethane-1,1-diyl)dibenzene **2a** with 80 % yield.

Acknowledgements

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Adv. Synth. Catal. **Year**, *Volume*, Page – Page

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