Palladium-Catalyzed C(sp³)—H Oxygenation via Electrochemical Oxidation

Qi-Liang Yang,[†,‡] Yi-Qian Li,[†] Cong Ma,[†] Ping Fang,[†] Xiu-Jie Zhang,[†] and Tian-Sheng Mei[*,†]

†State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Lu, Shanghai 200032, China

‡Key Laboratory for Advanced Materials and Institute of Fine Chemicals, School of Chemistry & Molecular Engineering, East China University of Science and Technology, Meilong Road No. 130, Shanghai 200237, China

S Supporting Information

ABSTRACT: Palladium-catalyzed C—H activation/C—O bond-forming reactions have emerged as attractive tools for organic synthesis. Typically, these reactions require strong chemical oxidants, which convert organopalladium(II) intermediates into the Pd^{III} or Pd^{IV} oxidation state to promote otherwise challenging C—O reductive elimination. However, previously reported oxidants possess significant disadvantages, including poor atom economy, high cost, and the formation of undesired byproducts. To overcome these issues, we report an electrochemical strategy that takes advantage of anodic oxidation of Pd^{II} to induce selective C—O reductive elimination with a variety of oxyanion coupling partners.
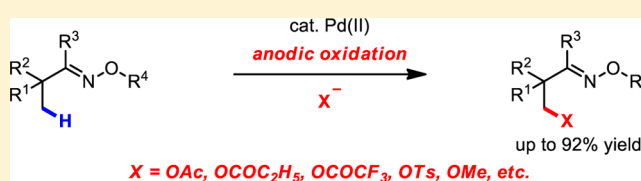
1. INTRODUCTION

The development of site-selective catalytic methods for the conversion of aliphatic carbon—hydrogen (C—H) bonds to carbon—oxygen (C—O) bonds remains a significant challenge in synthetic chemistry.[1] During the past decade, transition-metal-catalyzed site-selective C—H functionalization has emerged as a promising tool to construct carbon—carbon (C—C) and carbon—heteroatom (C—Y) bonds.[2,3] Pd(II)-catalyzed C—H oxygenation reactions, in particular, have received significant attention.[4−7] Previous studies have revealed that C—O reductive elimination, which is typically sluggish from Pd(II) centers, takes place under comparatively mild conditions from Pd^{III} or Pd^{IV} centers (Figure 1).[8,9] While these transformations hold great promise in offering new disconnections in retrosynthetic analysis, the need for an external chemical oxidant constitutes a practical disadvantage in these

systems (Figure 1).[10] The most typical oxidants in Pd-catalyzed C—H oxygenation include PhI(OAc)$_2$, t-BuOOAc, and K$_2$S$_2$O$_8$.[5−7] These oxidants have drawbacks in that they produce undesired byproducts, have poor atom economy, or are expensive. Recently, Sanford and co-workers elegantly developed aerobic oxygenation of C(sp³)—H bonds using catalytic amount of NaNO$_3$.[11] However, oxygen-mediated reactions on a large scale have been explicitly avoided by industry, owing to safety issues.[12] Thus, the development of novel oxidation systems represents a central challenge in the field of oxidative Pd(II)-catalyzed C—H functionalization.

Electrochemical oxidation has a rich history in synthetic chemistry and has become a promising alternative to traditional chemical oxidants because it obviates the use of dangerous and toxic reagents.[13,14]

The utilization of electric current as a potentially ideal oxidant for Pd(II)-catalyzed C—H functionalization is an attractive approach.[15−17] In this context, two major strategic approaches for aryl C(sp²)—H functionalization reactions have recently been investigated (Figure 2a,b). In mediated electron transfer, the anion (for example, a halide) is oxidized by the anode to produce the corresponding cation, which in turn oxidizes Pd(II) to high-valent Pd^{III} or Pd^{IV} species, triggering product formation via reductive elimination.[18,19] In contrast, in direct electron transfer, the Pd(II) species is oxidized by the anode directly to yield high-valent Pd^{III} or Pd^{IV} species in the presence of the spectator counteranion, which is then incorporated into the product through reductive elimination.[20,21] Following a seminal report by Kakiuchi and co-
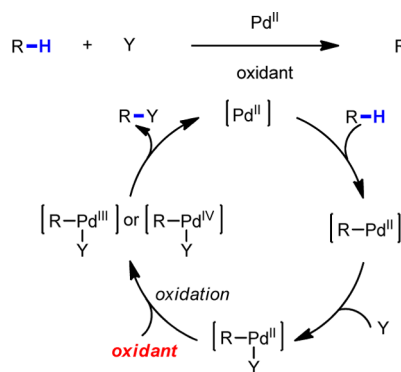

Figure 1. Pd^{II}/Pd^{IV} or Pd^{II}/Pd^{III} catalytic cycles.
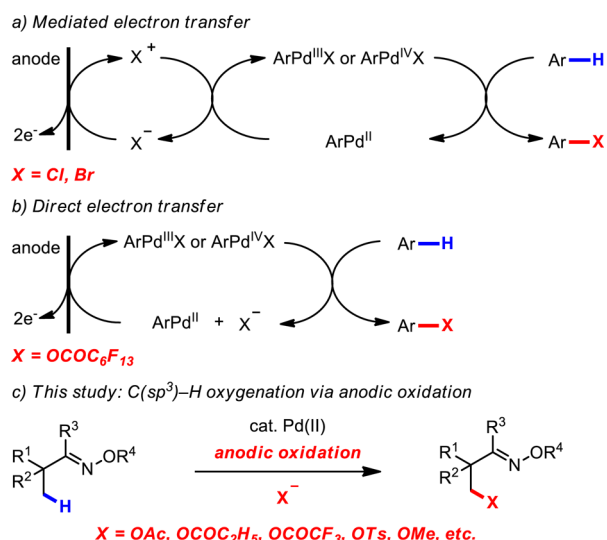
Figure 2. Approaches to Pd(II)-catalyzed C—H functionalization via electrochemical oxidation.

workers in 2009,[18] a number of examples of Pd-catalyzed aryl C(sp²)—H functionalization reactions using electrochemical oxidation have been reported.[19−21] To date, however, no examples of electrochemical Pd(II)-catalyzed oxidation of unactivated C(sp³)—H bonds, arguably the most challenging class of substrates, have been reported.

We reasoned that following C(sp³)—H cleavage, the anode could oxidize the resulting alkyl palladium(II) intermediate to a high-valent Pd^{III} or Pd^{IV} species.[22] In the presence of oxygen counteranions, we envisioned that ligand exchange would occur to set up a C—O reductive elimination step, giving the corresponding C(sp³)—H oxygenated product. We rationalized that this sequence of events would be viable if the oxidation potential of the counteranions was higher than that of Pd(II) (Figure 2b). Herein, we report the first example of

Pd(II)-catalyzed oxygenation of C(sp³)—H bonds with various oxyanions under electrochemical conditions (Figure 2c).
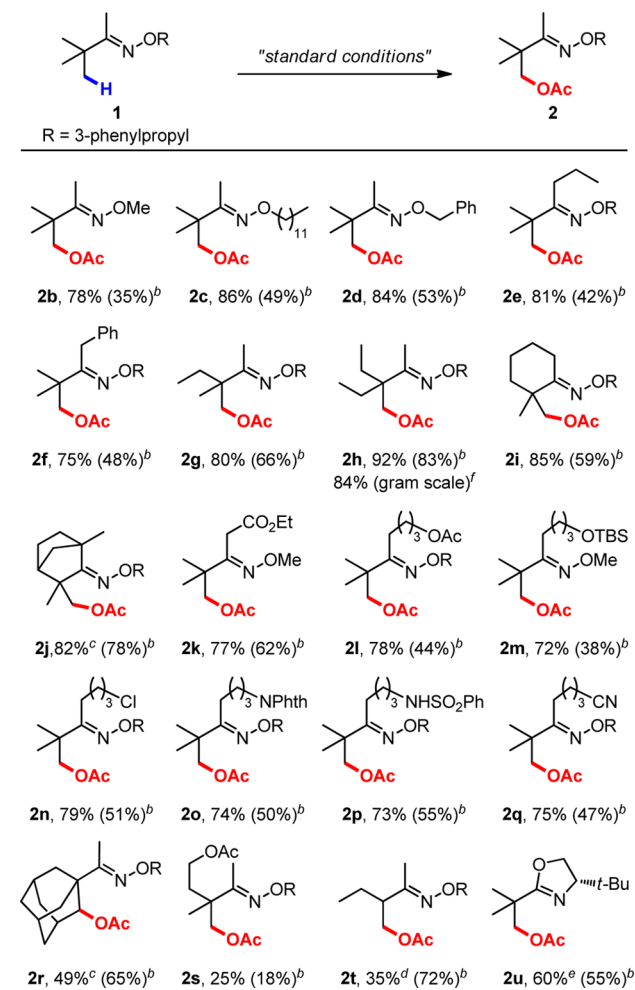
2. RESULTS

2.1. Initial Studies and Reaction Optimization. Our initial studies of electrochemical alkane oxidation focused on Pd-catalyzed β-oxygenation of pinacolone O-3-phenylpropyl oxime (**1a**). We were motivated to use this substrate because oxime moiety has previously been identified as a powerful directing group for C(sp³)—H functionalization reactions, and the resultant products can be subsequently transformed into useful products through standard functional group interconversion (Table 1).[5,11] Gratifyingly, the reaction of **1a** with 10 mol % Pd(OAc)$_2$ in the presence of sodium acetate (4 equiv) under constant-current electrolysis conditions at 1.5 mA (J = 0.75 mA·cm^{-2}) gave 82% monoacetoxylated product **2a** (entry 1). Decreasing the amount of palladium catalyst resulted in slightly lower yield (entry 2). Interestingly, approximately 10% chlorination product was formed when palladium chloride was used instead of palladium acetate (entry 3). Among the acetate sources that were tested, sodium acetate was found to be optimal (entries 4−6). Increase of electric current from 1.5 mA to 3 mA or 5 mA gave lower yields (entries 7 and 8). A control experiment revealed that no reaction was observed in the absence of electric current or Pd(OAc)$_2$ (entries 9 and 10). It is worth noting that the common chemical oxidants such as PhI(OAc)$_2$, t-BuOOAc, or NaNO$_3$/O$_2$[23] used as oxidants in lieu of electric current resulted in low yields due to the formation of corresponding di or triacetoxylated product (entries 11−13).

2.2. Substrate Scope for C(sp³)—H Oxygenation via Electrochemical Oxidation. Having optimized the reaction conditions, we next examined the scope of the Pd(II)-catalyzed C—H acetoxylation reaction by testing a series of oxime substrates containing different substitution patterns and various functional groups (Scheme 1). Several different oxime

Table 1. Reaction Optimization with Substrate 1a[a]

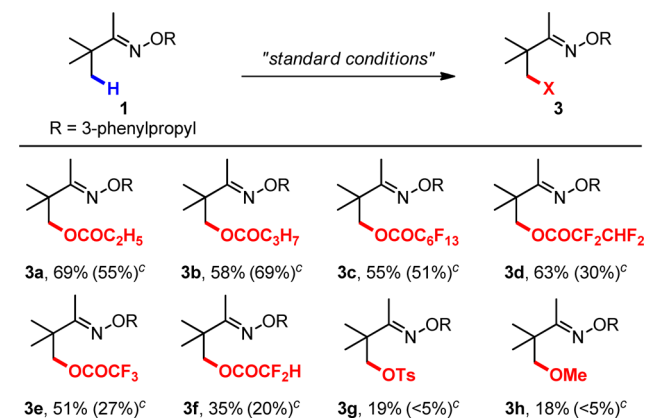| entry	deviation from above conditions	F/mol	2a	2aa
			yield (%)[b]	
1	none	2.2	84 (82)[c]	5
2	5 mol % Pd(OAc)$_2$ in lieu of 10 mol % Pd(OAc)$_2$	2.2	66	<5
3	10 mol % PdCl$_2$ in lieu of 10 mol % Pd(OAc)$_2$	2.2	66[d]	5
4	KOAc in lieu of NaOAc	2.2	68	8
5	LiOAc in lieu of NaOAc	2.2	74	10
6	CsOAc in lieu of NaOAc	2.2	75	12
7	5 mA in lieu of 1.5 mA (4 h)	2.5	35	<5
8	3 mA in lieu of 1.5 mA (6 h)	2.2	64	<5
9	no electric current		<5	<5
10	no Pd(OAc)$_2$	2.2	<5	<5
11	no electric current, PhI(OAc)$_2$ (2 equiv)		28	56
12	no electric current, t-BuOOAc (2 equiv)		46	26
13	no electric current, NaNO$_3$/O$_2$		62 (53)[c]	30

[a]Reaction conditions: **1a** (0.3 mmol), Pd(OAc)$_2$ (10 mol %), NaOAc (4 equiv), acetic acid (2 mL) [anode], and NaOAc (2 equiv), acetic acid (1 mL) [cathode] in an H-type divided cell with two platinum electrodes and a Nafion 117 membrane, 70 °C. [b]The yield was determined by GC with tridecane as the internal standard. [c]Isolated yield is in the parentheses. [d]Approximately 10% chlorination product was formed.

Scheme 1. Substrate Scope of Oximes[a]

2b, 78% (35%)[b] **2c**, 86% (49%)[b] **2d**, 84% (53%)[b] **2e**, 81% (42%)[b]

2f, 75% (48%)[b] **2g**, 80% (66%)[b] **2h**, 92% (83%)[b] 84% (gram scale)[f] **2i**, 85% (59%)[b]

2j, 82%[c] (78%)[b] **2k**, 77% (62%)[b] **2l**, 78% (44%)[b] **2m**, 72% (38%)[b]

2n, 79% (51%)[b] **2o**, 74% (50%)[b] **2p**, 73% (55%)[b] **2q**, 75% (47%)[b]

2r, 49%[c] (65%)[b] **2s**, 25% (18%)[b] **2t**, 35%[d] (72%)[b] **2u**, 60%[e] (55%)[b]

[a]Isolated yield. [b]The yields in the parentheses use $NaNO_3/O_2$ as an oxidant. [c]The reaction temperature is 90 °C. [d]The reaction temperature is 100 °C. [e]The reaction temperature is 50 °C. [f]1.04 g (4.0 mmol) **1h** is used under electrochemical oxidation.

directing groups were found to be effective in this acetoxylation reaction (**2b–d**). To our satisfaction, a variety of functional groups, including ester, acetoxy, OTBS, chloro, amino, and cyano substituents, were well tolerated in the reaction system (**2k–q**). However, the substrate containing the acetoxy group in the hindered side of the oxime substrates (**2s**) resulted in low yield. In addition, substrates containing an α-hydrogen atom reacted more slowly, giving lower yields (**2t**). Encouragingly, our standard conditions also proved to be effective for C—H acetoxylation of oxazoline,[6b] although a slightly lower yield was obtained (**2u**). Furthermore, electrolysis of 1.04 g (4.0 mmol) **1h** produced **2h** in 84% yield, which demonstrated the synthetic potential of this protocol. Among the chemical oxidants that we tried, the $NaNO_3/O_2$ oxidation system (entry 13, Table 1) developed by Sanford and co-workers produced the best results.[11] Thus, we have also included the yields of every substrate where a chemical oxidant ($NaNO_3/O_2$) was used for a direct comparison. This clearly demonstrates the advantage of anodic oxidation over chemical oxidation to achieve monoacetoxylation products, although chemical oxidation resulted in better yields with the substrates containing the α-H (**2t**) and other (**2r**).

On the basis of the proposed reaction pathway (Figure 2b), we reasoned that it should be possible to incorporate other functional groups under anodic oxidation conditions through the utilization of different oxyanion nucleophiles in solution. To test this idea, we employed several different oxygen anions in the reaction system and were pleased to find that they also competently participated in the reaction (Scheme 2). The

Scheme 2. Scope of Oxygen Nucleophiles[a,b]

3a, 69% (55%)[c] **3b**, 58% (69%)[c] **3c**, 55% (51%)[c] **3d**, 63% (30%)[c]

**3e**, 51% (27%)[c] **3f**, 35% (20%)[c] **3g**, 19% (<5%)[c] **3h**, 18% (<5%)[c]

[a]Isolated yield. [b]The corresponding carboxylic acids or sodium salts were used in lieu of HOAc and NaOAc in the anode. [c]The yields in the parentheses use $NaNO_3/O_2$ as an oxidant.

lower yields in these examples (**3e–h**) mainly stem from the formation of acetoxylation product in the reaction conditions. Nevertheless, the success of these transformations clearly demonstrates the potential generality of this electrochemical oxidation approach for enabling $C(sp^3)$—H functionalization with different reaction partners. Similarly, compared to chemical oxidation ($NaNO_3/O_2$), anodic oxidation gave superior yields in all substrates except **3b** (Scheme 2).

2.3. Mechanistic Considerations and Catalytic Cycle. To gain insight into the reaction mechanism, kinetic isotope effect (KIE) experiments were carried out, and a large KIE was measured in both a parallel single-component experiment ($k_H/k_D = 3.7$) and a competition experiment ($k_H/k_D = 5.0$) (Scheme 3).[24] This indicates that the C—H bond cleavage step is the turnover-limiting step in the catalytic cycle.

Scheme 3. Kinetic Isotope Effect Studies
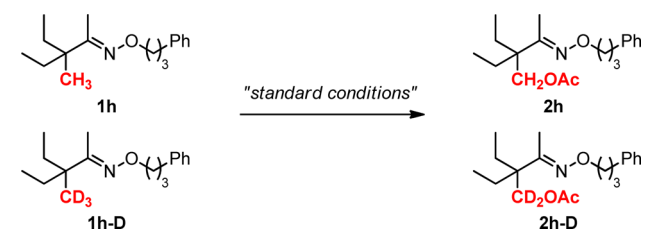
Furthermore, a cyclic voltammogram of cyclometalated Pd(II) complex **4**,[6b,25] a plausible intermediate in the catalytic cycle, in Ac_2O reveals two oxidation waves: one at 1.05 V, and one at 1.54 V Vs Ag/AgCl (**c**, Figure 3). Since the oxazoline ligand is not redox active within this potential range (**a, b**, Figure 3). This provides evidence that the anode could oxidize the alkyl palladium(II) intermediate to a high-valent Pd^{III} or
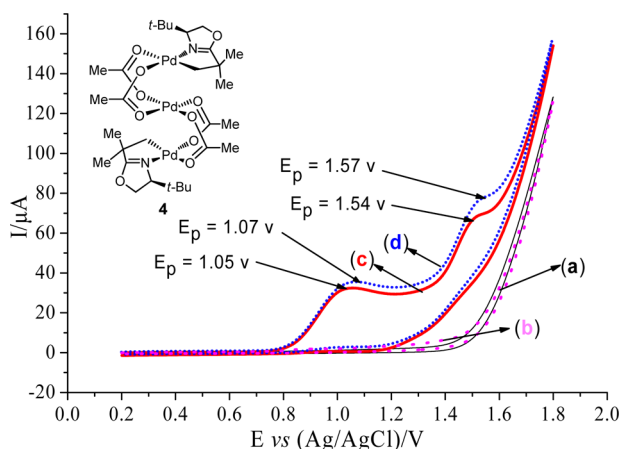
Figure 3. Cyclic voltammograms recorded on a glassy carbon electrode (area =7.1 cm^2) at 100 mVs^{-1} in (a) Ac$_2$O containing 0.1 M of n-Bu$_4$NOAc; (b) solution (a) with 10 mM of **1u**; (c) solution (a) with 7 mM of complex **4**; (d) as (c) in the presence of 10 mM of **1u**.

Pd^{IV} species, which induces selective C—O reductive elimination.[21,22]

A plausible mechanism for this Pd(II)-catalyzed C—H oxygenation via electrochemical oxidation is proposed in Scheme 4. Initially, the palladium catalyst coordinates with a

Scheme 4. Proposed Reaction Mechanism
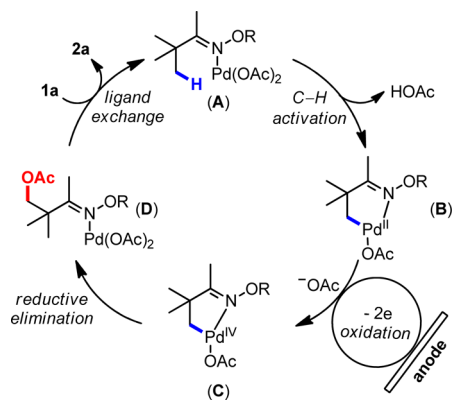
nitrogen atom in the substrate **1a**, which brings it in close proximity to the β-C—H bond. Next, C—H activation takes place to give palladacycle **B**,[26] which constitutes the rate-limiting step in the catalytic cycle. The resulting complex **B** is directly oxidized at the anode to form a Pd(III) or Pd(IV) species **C**.[9] Finally, reductive elimination from the high-valent palladium center gives the palladium(II)−product complex **D**, which can undergo ligand exchange with a new substrate molecule, releasing the product and closing the catalytic cycle. Alternatively, complex **D** can cause another C—H activation/ C—O bond formation sequence to occur, resulting in a di or triacetoxylation product.

3. CONCLUSIONS

We have demonstrated the first example of Pd(II)-catalyzed C(sp^3)—H oxygenation via anodic oxidation. This process offers an alternative to conventional methods that require harsh chemical oxidants and represents an environmentally benign tool for coupling various oxygen anions, including acetate, toslyate, and alkoxides, with C(sp^3)—H bonds. Investigations

aimed at understanding the reaction mechanism and further increasing the scope of these reactions are currently underway in our laboratory.

4. EXPERIMENTAL SECTION

4.1. General Information. All the electrochemical oxidations were performed in an H-type divided cell equipped with two platinum electrodes (1.0 × 1.0 cm^2) unless otherwise noted. The two compartments were separated by a DuPont Nafion PFSA membrane N-117. Solvents and commercially available reagents were used without purification. All commercial reagents were purchased from TCI, Sigma-Aldrich, Adamas-beta, 9-Ding chemistry, and Energy Chemical of the highest purity grade. They were used without further purification unless specified. ^{1}H NMR and ^{13}C NMR spectra were recorded on Agilent AV 400, Varian Inova 400 (400 and 100 MHz, respectively). ^{19}F NMR spectra were recorded on Agilent AV 400, Varian Inova 400 (376 MHz) instrument and are reported relative to the CFCl$_3$ as the internal standard. The peaks were internally referenced to TMS (0.00 ppm) or residual undeuterated solvent signal. Infrared spectra were obtained on a Bio-Rad FTS-185 instrument. High resolution mass spectra were recorded at the Center for Mass Spectrometry, Shanghai Institute of Organic Chemistry.

4.2. General Procedure for the Preparation of Oxime Substrates. Substrates **1a**, **1c−1j**, **1l**, and **1n−1t** were prepared according to a literature procedure.[27] To a 250 mL RB flask equipped with a stirring bar were added hydroxylamine hydrochloride (15 mmol, 1.5 equiv), NaOAc (25 mmol, 2.5 equiv), solvent (100 mL, H$_2$O:EtOH = 2:3), and ketone (10 mmol, 1.0 equiv). The reaction was allowed to heat to 100 °C and refluxed for overnight. After cooling to room temperature, the reaction was diluted with H$_2$O (20 mL) and extracted with ethyl acetate (100 mL, ×3). The combined organic layer was dried by MgSO$_4$ and evaporated. The crude oxime was used directly for next step without further purification. To a 100 mL RB flask equipped with a stirring bar were added resulting oxime (5.0 mmol, 1.0 equiv), alkyl bromide (7.5 mmol, 1.5 equiv), tetrabuty-lammonium iodide (0.25 mmol, 0.05 equiv), NaI (0.75 mmol. 0.15 equiv), KOH (6.0 mmol, 1.2 equiv), and THF (30 mL). The reaction was stirred at room temperature for 16 h. The reaction mixture was concentrated under reduced pressure and the residue was made alkaline with saturated NaHCO$_3$, and extracted with ethyl acetate. The organic layer was washed with brine, dried, and evaporated. Further purification was carried out by flash chromatography.

Substrates **1b**, **1k**, and **1m** were prepared according to a literature procedure.[28] To a 50 mL RB flask equipped with a stirring bar were added methoxyammonium chloride (7.5 mmol, 1.5 equiv), NaOAc (12.5 mmol, 2.5 equiv), solvent (15 mL, H$_2$O:MeOH = 2:1), and ketone (5.0 mmol, 1.0 equiv). The reaction was allowed to heat to 100 °C and refluxed for 5 h. After cooled to room temperature, the reaction was diluted with H$_2$O (10 mL) and extracted with dichloromethane (50 mL, ×3). The combined organic layer was dried by MgSO$_4$, filtered, and concentrated under reduced pressure. Further purification was carried out by flash chromatography.

4.3. General Procedure for C(sp^3)—H Oxygenation via Electrochemical Oxidation. The electrochemical oxidation was carried out in an H-type divided cell equipped with two platinum electrodes (1.0 × 1.0 cm^2). The two compartments were separated by a DuPont Nafion PFSA membrane N-117. The anodic chamber was charged with a solution of NaOAc (2 mL, 0.6 M in HOAc), an oxime compound (0.3 mmol) and Pd(OAc)$_2$ (0.03 mmol). The cathodic chamber was charged with a solution of NaOAc (1 mL, 0.6 M in HOAc) and a certain amount of silica sand. Then the mixture in the anodic chamber was stirred at a constant current of 1.5 mA at 70 °C for 12 h. At the end of the reaction, the reaction mixture from both chambers was transferred to a flask through a funnel. The electrodes and silica sand were washed with EtOAc (20 mL). Then the solvent was evaporated under the reduced pressure and further purification was carried out by flash chromatography.

ASSOCIATED CONTENT

S Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.7b01232.

Detailed experimental procedures and characterization of new compounds (PDF)

AUTHOR INFORMATION

Corresponding Author

*mei7900@sioc.ac.cn

ORCID

Qi-Liang Yang: 0000-0003-4734-5391
Yi-Qian Li: 0000-0002-3794-2355
Cong Ma: 0000-0001-7568-1347
Ping Fang: 0000-0002-3421-2613
Xiu-Jie Zhang: 0000-0003-1600-595X
Tian-Sheng Mei: 0000-0002-4985-1071

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

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