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Direct Electrosynthesis of Ketones from Benzylic Methylenes by Electrooxidative C−H Activation

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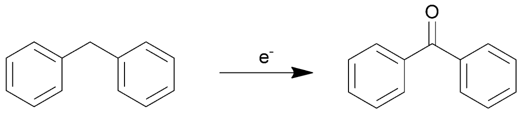
Direct oxidative activation of benzylic C−H bonds under mild conditions is of importance due to its wide applications, especially in organic synthesis. Many chemists have made great contributions to this important transformation.[1] The generated ketones can not only act as building blocks for the synthesis of pharmaceuticals and agrochemicals, but can also form important intermediates in natural products.[2] Traditionally, benzylic oxidation usually required oxidants based on heavy metals in stoichiometric amounts, such as potassium permanganate, potassium dichromate, or ammonium cerium nitrate.[3] Recently, great progress has been made in terms of catalysts or oxidants, such as metal catalysts[4] involving Cr, Mn, Co, Bi, Ru, Rh, Fe, and Au and metal-free oxidants[5] including 2-Iodoxybenzoic acid (IBX), NaClO/TBHP, and HBr/H_2O_2. Although these methods afford good results, the toxicity of expensive metal catalysts, harsh reaction conditions, and tedious work-up procedures limits their application in organic synthesis. Therefore, simple and efficient methods for the benzylic C−H oxidation are highly desirable.

As for electrochemical oxidation, our group has made some progress, such as the one-pot synthesis of homoallylic alcohols[6] and electrosynthesis imidines from aliphatic amines and sulfonyl azides.[7] Previously, we employed iodine–pyridine–*tert*-butylhydroperoxide (I_2-Py-TBHP)[5f] as a catalytic system to achieve benzylic oxidation. Intrigued by the electrochemical redox catalysts[8] and electroredox integrated with chemical oxidation,[9] we realized direct electrosynthesis of ketones from benzylic methylenes through an electrooxidative C−H activation. This method features a green oxidant of mass-free electrons, wide substrate scope, and mild conditions.

Initially, we chose the oxidation of diphenylmethane as a model reaction. To the best of our knowledge, smooth platinum can stand the large overpotential for oxygen and hydrogen evolution in solution.[10] Therefore, in the presence of two platinum electrodes, various different solvents were tested (Table 1, entries 1–7). It was obvious that water could promote the reaction to some extent (entry 2). On the other hand, no product was obtained when the reaction was performed in net water. Among all tested solvents, CH_3CN/H_2O was the best choice (entries 2–7). Afterwards, the electrolytes, such as Bu_4NBF_4, Bu_4NClO_4, Bu_4NHSO_4, and $LiClO_4$ were examined in this reaction. It was found that $LiClO_4$ was the most efficient in the electrochemical reaction (entries 2 and 8–10). Under these conditions, various combinations of the electrodes were attempted and plati-

Table 1. Optimization for the oxidation of diphenylmethane into benzophenone.[a]



Entry	Electrode (anode/cathode)	Electrolyte	Current [mA]	Solvent [mL]	Yield [%][b]
1	Pt/Pt	Bu_4NBF_4	20	CH_3CN	–
2	Pt/Pt	Bu_4NBF_4	20	CH_3CN/H_2O	24
3	Pt/Pt	Bu_4NBF_4	20	CH_2Cl_2/H_2O	trace
4	Pt/Pt	Bu_4NBF_4	20	$MeOH/H_2O$	trace
5	Pt/Pt	Bu_4NBF_4	20	$EtOH/H_2O$	trace
6	Pt/Pt	Bu_4NBF_4	20	THF/H_2O	trace
7[c]	Pt/Pt	Bu_4NBF_4	20	H_2O	–
8	Pt/Pt	Bu_4NClO_4	20	CH_3CN/H_2O	65
9	Pt/Pt	Bu_4NHSO_4	20	CH_3CN/H_2O	79
10[d]	Pt/Pt	$LiClO_4$	20	CH_3CN/H_2O	84
11	Pt/Pt	$LiClO_4$	30	CH_3CN/H_2O	72
12	Pt/Pt	$LiClO_4$	10	CH_3CN/H_2O	62
13	Pt/C	$LiClO_4$	20	CH_3CN/H_2O	82
14	C/Pt	$LiClO_4$	20	CH_3CN/H_2O	62
15	C/C	$LiClO_4$	20	CH_3CN/H_2O	55

[a] Reaction conditions: diphenylmethane (0.5 mmol), electrolyte (1 mmol), solvent/H_2O = 18:1 (9.5 mL); the electrolysis was conducted at a constant current for 5 h in an undivided cell. [b] Yields of the isolated products. [c] KNO_3 (1 mmol) was added. [d] **Caution!** lithium perchlorate is a potential explosive.

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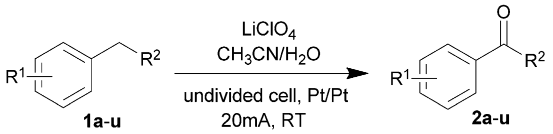
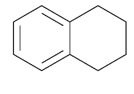
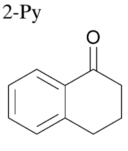
num proved to be the best one for the electrochemical oxidation. Moreover, the current of the oxidation was also optimized. Below 20 mA of the current the reaction proceeded slowly in a low yield, while no improvement was observed beyond the 20 mA (entries 10–12). Therefore, we chose 20 mA as the current of electrolysis in the reaction. Eventually, the optimal conditions were obtained as below: $LiClO_4$ (1 mmol) as the electrolyte, CH_3CN/H_2O (9/0.5 mL) as the solvent, platinum as both the anode and the cathode. All the reactions were electrolyzed at a constant current of 20 mA.

Under the optimized reaction conditions, various benzylic methylenes were investigated and the results are summarized in Table 2. Diarylmethane (**1a**) was efficiently oxidized to benzophenone (**2a**) in 84 % yield (Table 2, entry 1). The oxidation of diarylalkanes can be carried out well regardless of the electron-withdrawing or -donating ability of R^1 on the phenyl ring (entries 2–10). However, a steric effect could be observed since *ortho* substitution gave a lower yield relative to *meta* and *para* substitution (entry 14 vs. 11 and 2; entry 15 vs. 12 and 3; entry 16 vs. 13 and 10). When R^2 was alternated from an aromatic group to an aliphatic group, the reaction could still be carried out smoothly to afford the corresponding ketones with moderate to good yields (entries 18, 19). Moreover, tetralin (**1u**), bearing a cyclic aliphatic group, also led to a medium yield (entry 20). When R^2 was an electron-deficient substituent, the reaction hardly occurred, as shown in entry 20. More importantly, the reaction conditions were so mild that the nitro group could survive the reaction even when the electrolysis time was 7 h (entry 6).

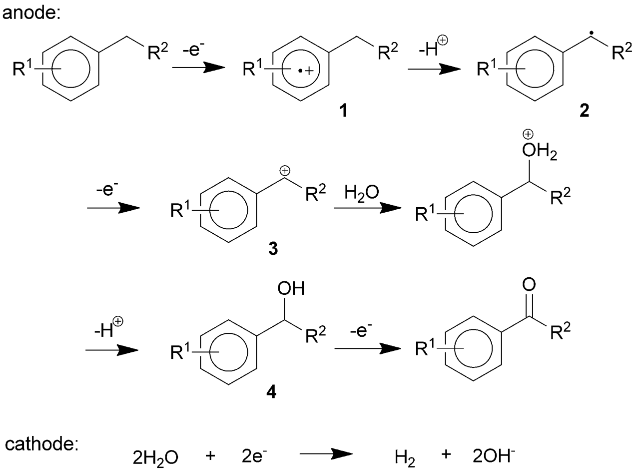
Table 2. Scope of the electrosynthesis of ketones from benzylic methylenes.[a]



Entry	R^1	R^2	Faradaic yield [%]	Yield [%][b]
1	H	Ph	62	84
2	4-F	Ph	56	87
3	4-Cl	Ph	56	86
4	4-Br	Ph	51	83
5	$4\text{-}CF_3$	Ph	54	84
6	$4\text{-}NO_2$	Ph	54	48
7	4-Ph	Ph	43	42
8	4-OAc	Ph	56	82
9	$4\text{-}OCH_3$	Ph	65	63
10	$4\text{-}CH_3$	Ph	65	83
11	3-F	Ph	51	83
12	3-Cl	Ph	54	71
13	$3\text{-}CH_3$	Ph	54	75
14	2-F	Ph	69	66
15	2-Cl	Ph	51	67
16	$2\text{-}CH_3$	Ph	65	64
17	$4\text{-}CH_3$	$4\text{-}CH_3Ph$	65	56
18	H	CH_3	54	49
19	H	$CH_2CH_2CH_3$	54	42
20	H	2-Py	–	–
21			65	72

[a] The reactions were carried out on a 0.5 mmol scale. [b] Yields of the isolated products.

From the cyclic voltammogram curves, we observed that the oxidation potentials for diphenylmethanol and diphenylmethane were about 1.23 and 1.18 V, respectively, as shown in Figure S1 of the Supporting Information. To gain more insight into the reaction mechanism, reaction progress was investigated by ESR spectroscopy. The ESR spectrum of the diphenylmethane radical[11] (**2** in Scheme 1) was observed, as shown in Figure 1. The two-band hyperfine structure in the spectrum centered at the calibrated $g_{iso} \approx 2.004$ indicates that in the radical there is a strong magnetic-coupled nucleus possessing the $I = 1/2$ nuclear spin leading to the $2I+1=2$ hyperfine peaks. This nucleus is assigned to the proton ($I = 1/2$) on the methyl group, that is, the unpaired electron is localized in the methyl carbon atom. In the meantime, the weaker hyperfine interactions between the electron and the protons (2,6,2′,6′-position of the phenyl rings) is not resolved in the 150 K ESR spectrum relative to those measured at room temperature. With the simulation, the hyperfine coupling constant for the proton on the methyl is 16.5 G, and those for the four equivalent protons (2,6,2′,6′-position of the phenyl rings) ≈4 G. Besides, when we added 1,1-diphenylethylene to the reaction mixture and performed the reaction for 2 h, the radical coupling product of 1,1,3,3-tetraphenyl-1-propene was observed by GCMS analysis.[12] In contrast, we didn't find the signal of any radical in the absence of diphenylmethane under the same conditions.[12] Also, a stable intermediate, diphenylmethanol, was detected by GCMS analysis.[12] Moreover, under the same conditions, diphenylmethanol was also electrolyzed and the desired product was obtained with a yield of 90 %.



Scheme 1. Proposed mechanism for the oxidation of methylenes.

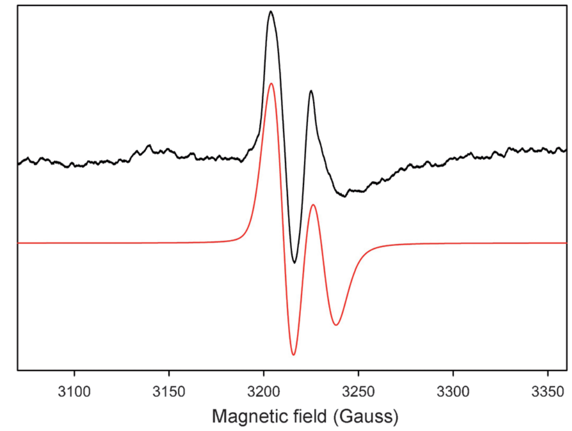


Figure 1. ESR spectrum obtained for the diphenylmethane radical (black) and the simulation (red) measured at 150 K. In the simulation, the calibrated isotropic g-value for the radical is $g_{iso} \approx 2.004$, the principal isotropic hyperfine constants of the methyl proton and of the four equivalent protons (2,6,2′,6′-position of the phenyl rings) are 16.5 and 4 G, respectively, and the molecular correlation time of 10^{-9} s is included to show the known increasing asymmetry of the spectrum when the molecular motion is significantly slowed at liquid nitrogen temperature. Standard conditions: diphenylmethane (0.5 mmol), $LiClO_4$ (1 mmol), and Bu_4NClO_4 (0.5 mmol) in CH_2Cl_2 (10 mL) were electrolyzed for 20 min at a current of 20 mA between Pt/Pt electrodes; thereafter, the electrolyte was transferred with a cooled syringe at 150 K to the ESR tube.

Based on the experimental results above and the related literature,[8a,9,13] we proposed a tentative reaction mechanism, as shown in Scheme 1. First of all, diphenylmethane is oxidized to give radical cation **1** on the surface of the anode. The initially formed radical cation deprotonates into the benzyl radical **2**, which undergoes subsequent oxidation to afford a diarylcarbenium ion, intermediate **3**. Intermediate **3** is attacked by H_2O following deprotonation to generate a substituted benzyl alcohol **4**, which is further oxidized to give the desired product. Water is electrolyzed to release hydrogen gas as a result of cathodic reduction.

In conclusion, an electrochemical method was developed that converts the benzyl group into a keto group under mild conditions. By virtue of electrochemistry, an environmental friendly and metal-free C–H activation was realized with a wide scope of the reaction substrates. More importantly, this transformation mechanism was investigated in detail. A key intermediate **2** was detected by ESR spectroscopy. We will continue to work on the study of electrochemical oxidation of hydrocarbons and broaden the application of electrochemistry in organic synthesis.

Experimental Section

General procedure: A mixture of benzylic methylenes (0.5 mmol), $LiClO_4$ (1 mmol), and CH_3CN (9 mL)/H_2O (0.5 mL) were added to an undivided cell. The cell was equipped with platinum (1.0×1.0 cm^2) as the anode and cathode. The electrolyte was allowed to stir and electrolyzed at a constant current of 20 mA. Upon completion of the reaction, CH_3CN was removed with a rotary evaporator and added to H_2O (10 mL). The resulting mixture was extracted with ethyl acetate (3×15 mL). The combined organic phase was dried with Na_2SO_4. The solvent was removed with a rotary evaporator. The residue was purified by column chromatography on silica gel and the product was dried under high vacuum before it was weighed and characterized by NMR spectroscopy.

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Keywords: C–H activation · electrochemistry · ketones · oxidation · synthetic methods

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[12] Details are provided in the Supporting Information.

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