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Electrooxidative α -hydroxymethylation of ketones with dimethylformamide as the carbon source†

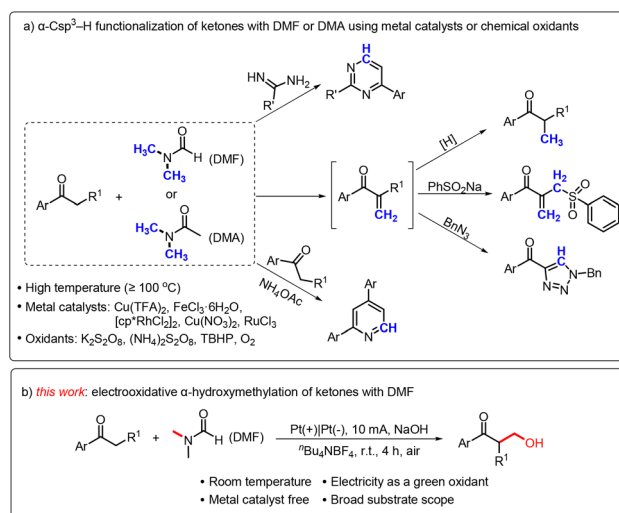
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An environmentally benign electrochemical approach has been developed for the α -hydroxymethylation of ketones using *N,N*-dimethylformamide as the carbon source for the construction of β -hydroxy ketones. This method does not require metal catalysts or chemical oxidants and proceeded smoothly at room temperature to demonstrate tolerance of a broad range of functional groups.

N,N-Dialkyl amides are common polar solvents, and are frequently used in variety of ways as cheap versatile synthons in synthetic organic chemistry to generate different functional groups.¹ Serving as reaction precursors, the use of *N,N*-dimethylformamide (DMF) and *N,N*-dimethylacetamide (DMA) as one carbon sources to realize the oxidative $\text{Csp}^3\text{-H}$ methylenation of ketones is well developed.^{2–7} The direct $\text{Csp}^3\text{-H}$ α -methylenation of ketones with DMF or DMA provides rapid and straightforward access to α,β -unsaturated carbonyl compounds *via* metal catalysis.² This process provides scope for further reduction with Rh–H for methylation of ketones,³ participation in cascade reactions with sodium sulfinates to provide β -acyl allylic sulfones under an iron-catalysed oxidative system,⁴ or further oxidative cycloaddition with BnN_3 to form 1,2,3-triazoles (Scheme 1a, middle).⁵ Some approaches have been disclosed for providing N-heterocyclic compounds, such as pyrimidines (Scheme 1a, upper)⁶ and pyridines (Scheme 1a, lower),⁷ by cascade cyclization with DMF, ketones, and nitrogen-containing reagents. Despite significant advances in the methylenation of ketones with *N,N*-dialkyl amides, these methods have several disadvantages, such as the accumulation of metallic wastes, the need for large amounts of chemical oxidizing agents, and the requirements of high temperature and harsh reaction conditions. As a result, the development of green methods that proceed under mild conditions to achieve

oxidative $\text{Csp}^3\text{-H}$ methylenation of ketones using *N,N*-dialkyl amides as the carbon source remains an important experimental challenge for researchers.

β -Hydroxy ketones are widely found in natural products and bioactive molecules,⁸ and serve as versatile synthetic intermediates and building blocks in organic synthesis.⁹ Several methods for the synthesis of β -hydroxy ketones have been developed, such as aldol reaction,^{10a} reduction of α,β -epoxy ketones,^{10b,c} oxy-Michael addition of α,β -unsaturated ketones,^{10d,e} photocatalytic oxygenation of cyclopropane derivatives,^{10f,g} hydration of propargyl alcohol derivatives,^{10h} and coupling reaction of vinylarenes and alcohols.¹⁰ⁱ Traditionally, formaldehyde has been utilized as a one carbon linkage to construct β -hydroxy ketones with methyl ketones in an aldol reaction.¹¹ Recently, Yang's group developed a visible-light-mediated α -hydroxymethylation of ketones using methanol as the hydroxymethylating reagent to afford β -hydroxy ketones in



Scheme 1 $\alpha\text{-Csp}^3\text{-H}$ functionalization of ketones with *N,N*-dialkyl amides.

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19%–76% yields by irradiation under 7 W white LEDs for 36 h.¹² However, the toxicity and the environmental impact of these reagents have hindered its further application. The identification of a simple, low-toxicity carbon source that is readily available for use under efficient, mild, and environmentally friendly conditions to give β -hydroxyl ketones is still of interest in contemporary organic synthesis. To the best of our knowledge, α -hydroxymethylation of ketones using *N,N*-dialkyl amides as one carbon source to generate β -hydroxy ketones has not been reported. The organic electrochemical synthesis represents an environmentally friendly method.¹³ Herein, we report the electrocatalytic α -hydroxymethylation of ketones using DMF as the carbon source with trace amounts of water at room temperature in air (Scheme 1b) in a conversion that proceeds without need for toxic and expensive chemical oxidants or metal catalysts.

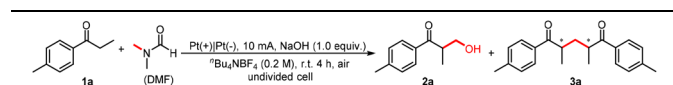
At the outset, we selected 1-(*p*-tolyl)propan-1-one (**1a**) and DMF as the model substrates. After screening the reaction conditions, we were pleased to find that the desired product β -hydroxy ketones (**2a**) could be obtained in 85% yield when the model reaction was performed at room temperature in air with platinum plates as anode and cathode, 0.2 M of ⁿBu₄NBF₄ as the electrolyte, and 1.0 equiv. of NaOH as base (Table 1, entry 1). The reaction was performed under a constant 10 mA current in an undivided cell (three-necked round-bottomed flask). In addition, no hydroxy-elimination product (2-methyl-1-(*p*-tolyl)prop-2-en-1-one) was detected. Control experiments showed that the reaction did not proceed in the absence of electric current (Table 1, entry 2). Exchanging DMF for DMA as solvent led to poor catalytic performance, delivering product **2a** in 32% yield (Table 1, entry 3), which indicating that the extended carbon atom was mainly ascribed to the *N,N*-dimethyl moiety rather than the carbonyl carbon from the

amides. The stoichiometric amounts of DMF in different solvents have been studied. The 10 equivalents of DMF in CH₃CN, CH₃OH or DMSO were inferior to DMF as solvent (Table S1 in ESI†). When using NaOAc instead of NaOH, the target product was obtained in 19% yield in addition to the further Michael addition product **3a** in 16% yield (Table 1, entry 4). Use of other bases such as NEt₃, DABCO, pyridine, NaOEt, ^tBuOK, Cs₂CO₃, or K₂CO₃ gave trace amounts of **2a** (Table 1, entry 5). Use of ⁿBu₄NClO₄, ⁿBu₄NPF₆, or ⁿBu₄NI as electrolyte afforded modest yields in the range of 11%–21% yields (Table 1, entries 6–8). When graphite rod was used as anode or cathode, only trace amounts of product were observed (Table 1, entries 9 and 10). Increasing the electric current to 15 mA or decreasing it to 5 mA led to lower yields than that observed with 10 mA (Table 1, entries 11 and 12).

To showcase the efficiency and green credentials of our electrolytic approach, some non-electrochemical methods were performed for comparison at room temperature. All of these methods previously achieved oxidative α -Csp³-H functionalization of arylketones with DMF or DMA using metal catalysts or chemical oxidants at high temperature to generate the corresponding 1-arylprop-2-en-1-one derivatives as intermediate or other desired products.^{2–7,14} However, as shown in Table 2, inferior results were observed at room temperature under non-electrochemical conditions. These results confirmed the green character and sustainability of our electrolytic approach for the α -hydroxymethylation of ketones using DMF as the carbon source.

With the optimized reaction conditions in hand, we investigated the substrate scope of this electrocatalytic α -hydroxymethylation of ketones using DMF as the carbon source. First, a wide range of propiophenone derivatives was examined. As shown in Scheme 2, a series of propiophenone derivatives reacted with DMF smoothly, producing a variety of β -hydroxy ketones in moderate to good yields (**2a–2q**). Propiophenone with electron-donating or electron-withdrawing substituents, such as methyl, ethyl, isopropyl, tertiary butyl, methoxy, -N(Ts)₂, halogen, trifluoromethyl, cyano and phenyl, at the *para*-position of the phenyl ring reacted with DMF successfully, leading to the corresponding products in

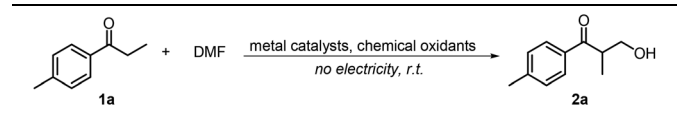
Table 1 Optimization of reaction conditions^a



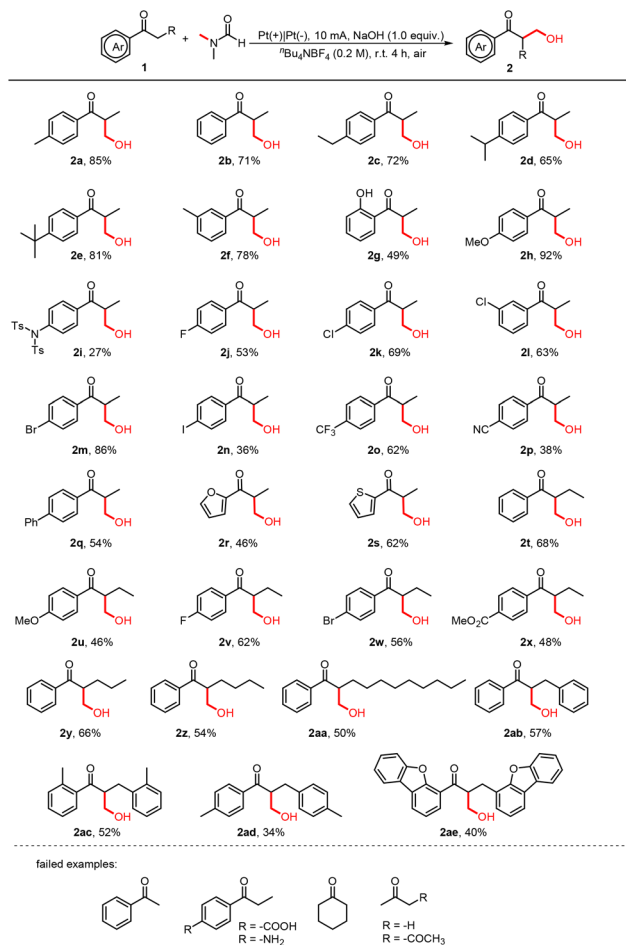
Entry	Variation from standard conditions	Yield ^b
1	None	85%
2	No electricity	N.R.
3	DMA instead of DMF	32%
4	NaOAc as the base	19% (16%) ^c
5	NEt ₃ , DABCO, pyridine, NaOEt, ^t BuOK, Cs ₂ CO ₃ or K ₂ CO ₃ as the base	Trace
6	ⁿ Bu ₄ NClO ₄ as the electrolyte	11%
7	ⁿ Bu ₄ NPF ₆ as the electrolyte	21%
8	ⁿ Bu ₄ NI as the electrolyte	15%
9	Pt(+) C(-), 10 mA	Trace
10	C(+) Pt(-), 10 mA	Trace
11	15 mA	70%
12	5 mA	28%

^a Standard conditions: **1a** (0.1 mmol), Pt(+) | Pt(-), 10 mA, NaOH (1.0 equiv.), ⁿBu₄NBF₄ (0.2 M), and DMF (5 mL), in an undivided cell, rt, 4 h, in air. ^b Yield of the isolated product **2a**. ^c Yield of the isolated product **3a**.

Table 2 α -Hydroxymethylation of ketones with DMF using metal catalysts or chemical oxidants at room temperature



Entry	Reaction conditions	Results
1 ^{2a}	Cu(TFA)·xH ₂ O (30 mol%), K ₂ S ₂ O ₈ (4.0 equiv.)	N.R.
2 ^{2b}	FeCl ₃ ·6H ₂ O (10 mol%), K ₂ S ₂ O ₈ (2.0 equiv.)	N.R.
3 ³	[Cp*RhCl ₂] ₂ (5 mol%), K ₂ S ₂ O ₈ (2.0 equiv.)	N.R.
4 ⁴	FeCl ₃ (10 mol%), K ₂ S ₂ O ₈ (3.5 equiv.), SDS (10 mol%)	N.R.
5 ⁵	70% TBHP (3.0 equiv.), Cs ₂ CO ₃ (2.0 equiv.)	Trace
6 ⁶	Cu(NO ₃) ₂ (20 mol%), K ₂ S ₂ O ₈ (3.0 equiv.)	N.R.
7 ⁷	RuCl ₃ ·3H ₂ O (5 mol%), O ₂ , NH ₄ OAc (1.5 equiv.)	N.R.
8 ¹⁴	Ru(cod)Cl ₂ (5 mol%), NaHSO ₃ (1.5 equiv.)	N.R.



Scheme 2 Scope of substrate. Reaction conditions: **1** (0.10 mmol), Pt (+)|Pt(-), 10 mA, NaOH (1.0 equiv.), ⁿBu₄NBF₄ (0.2 M), and DMF (5 mL), in an undivided cell, rt, 4 h, in air, yield of the isolated product.

moderate to excellent yields. *ortho*-OH-substituted propiophenone (**1g**) and *meta*-Me, and Cl-substituted propiophenone (**1f**, **1k**) also afforded the desired products. It is noteworthy that 1-(furan-2-yl)propan-1-one and 1-(thiophen-2-yl)propan-1-one were also compatible as substrate to give **2r** and **2s**. Furthermore, 1-phenylbutan-1-one with different substituents were all viable in this reaction, giving rise to the corresponding products in moderate yields (**2t–2x**). Moreover, 1-phenylpentan-1-one, 1-phenylhexan-1-one, and 1-phenylundecan-1-one, also participated in the reaction (**2y–2aa**). To our delight, dihydro-chalcone derivatives were also viable as substrates in this electrolysis to give the corresponding products (**2ab–2ae**) Propiophenone containing -COOH, -NH₂ substituents, acetophenone and aliphatic ketones were also screened, but the reaction failed to deliver the desired products.

To explore the possible mechanism of this reaction, a series of experiments were conducted. First, we monitored product formation during periodic electrolysis (Fig. 1a). As expected, the reaction was inactive without electrochemistry. Product **2a** was generated during periods of constant electrolysis, which showed that electricity is essential for the transformation to

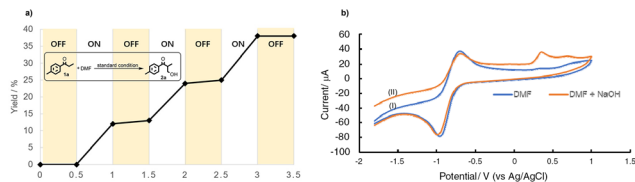
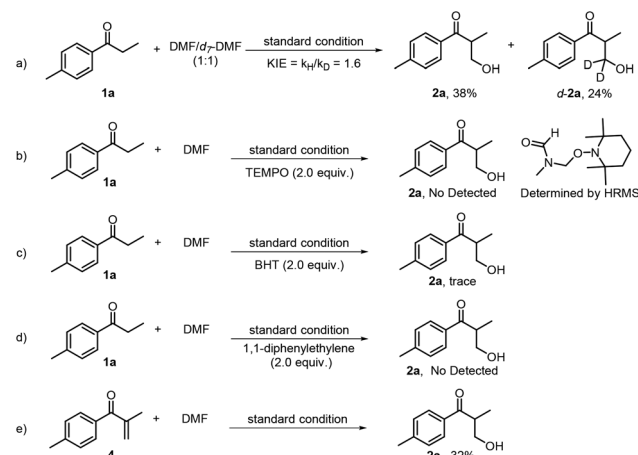


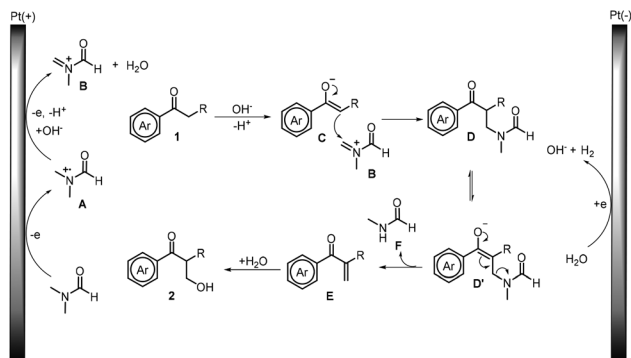
Fig. 1 (a) On/off experiment; (b) CV studies: (I) DMF, ⁿBu₄NBF₄ (0.2 M), and 100 mV s⁻¹ (II) DMF, ⁿBu₄NBF₄ (0.2 M), NaOH (0.04 M), and 100 mV s⁻¹.

proceed. Cyclic voltammetry (CV) experiments were also performed to gain insights into the mechanism (Fig. 1b). In the presence of ⁿBu₄NBF₄ electrolyte, DMF has two oxidation peaks at -0.69 V and 0.33 V, and has one reduction peak at -0.98 V. After the addition of NaOH, the intensity of the second anode peak was significantly increased, indicating that NaOH promotes the stepwise oxidation of DMF to form the iminium cation (Fig. S2 in ESI[†]). In the presence of ⁿBu₄NBF₄ electrolyte, DMA has two oxidation peaks at -0.80 V and 0.44 V (Fig. S3 in ESI[†]). The intensity of DMA first anode peak is weaker than DMF's, which possible led DMA to afford a lower yield than DMF (Table 1, entry 3).

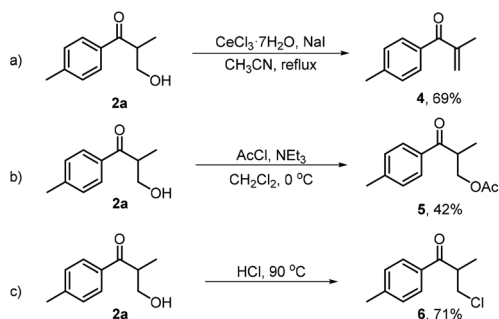
Several control experiments were performed to further clarify the reaction mechanism, as shown in Scheme 3. The intermolecular competitive reaction was carried out with DMF and *d*₇-DMF as the substrates to determine the kinetic isotopic effect (KIE); a value of $K_H/K_D = 1.6$ was obtained (Scheme 3a). This result suggests that the C-H cleavage of DMF was unlikely to be involved in the rate-determining step. The desired product **2a** could not be detected in TEMPO-exposed reaction mixture, in which TEMPO-DMF adduct was detected by HRMS analysis (Scheme 3b). When the reaction was carried out in the presence of other free-radical scavengers, such as butylated hydroxytoluene and 1,1-diphenylethene, **2a** was also not detected under standard conditions (Scheme 3c and d). This finding illustrated that the reaction proceeded *via* a radical



Scheme 3 Control experiments.



Scheme 4 Proposed mechanism.



Scheme 5 Transformations of 2a.

mechanism. Furthermore, 2-methyl-1-(*p*-tolyl)prop-2-en-1-one **4** was designated as the model substrate to explore the reaction mechanism. To our delight, the reaction worked smoothly under standard reaction conditions to give the desired product (Scheme 3e), which suggested enone **4** as the likely intermediate for this transformation.

Based on the observed experimental evidence and literature studies,^{2–7} a plausible reaction mechanism for the α -hydroxymethylation of ketones is illustrated in Scheme 4. Initially, the iminium species **B** is generated through stepwise oxidation of DMF at the anode. The *in situ* generated enol **C** attacks the iminium species **B** to form intermediate **D**, which then undergoes C–N bond cleavage to give intermediate **E**.^{2a,3} Michael-type addition of water to **E** then affords the desired product **2**. Meanwhile, water is reduced on the cathode, releasing OH^- and molecular hydrogen.

To illustrate the synthetic application of the products, further transformations of **2a** demonstrated its potential to serve as a versatile building block (Scheme 5). The **2a** was smoothly converted to enone **4**, ester **5**, and chloro derivative **6**, which are useful synthetic intermediates.

Conclusions

We have developed an electrooxidative α -hydroxymethylation of ketones that uses DMF as the carbon source. In the reaction

process, constant current is used to replace the external oxidant, thus avoiding the use of metal catalysts, chemical oxidants and high temperature. This proposed methodology features a broad substrate scope, good functional-group tolerance, mild reaction condition, and simple operation, and provides an alternative route to useful β -hydroxy ketones. Further investigations on the mechanistic pathway and the synthesis of other molecules through the use of a similar strategy are underway in our laboratory.

Conflicts of interest

There are no conflicts to declare.

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