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The intramolecular  $C(sp^3)-H/C(sp^2)-H$  cross-coupling of 1,3-dicarbonyl compounds has been achieved through Cp<sub>2</sub>Fe-catalyzed electrochemical oxidation. The key to the success of these dehydrogenative cyclization reactions is the selective activation of the acidic  $\alpha$ -C-H bond of the 1,3-dicarbonyl moiety to generate a carbon-centered radical.

Carbon-centered radicals derived from 1,3-dicarbonyl compounds are useful synthetic intermediates and have been applied for synthesis of several natural products and bioactive compounds.<sup>1</sup> These electrophilic C-centered radicals can be generated through the oxidative cleavage of the acidic  $\alpha$ -C-H bond of the 1,3-dicarbonyl compounds using stoichiometric metal or organic oxidants<sup>2</sup> or *via* transition-metal catalyzed aerobic oxidation (Scheme 1a).<sup>3</sup> Alternatively, they can be accessed from  $\alpha$ -brominated precursors *via* reductive cleavage of the C-Br bond (Scheme 1a).<sup>4</sup> The intramolecular cyclization reactions of these C-centered radicals with arenes have been employed for the synthesis of various cyclic structures including oxindoles and 3,4-dihydro-1*H*-quinolin-2ones.<sup>3,5</sup>

To reduce the use of chemical oxidants in the oxidative radical chemistry of active methylene compounds, electrochemical recycling of  $Mn(OAc)_3$  in a divided cell has been investigated.<sup>6</sup> We have been involved in the development of electrochemical methods<sup>7</sup> for the generation of synthetically useful organic radical intermediates from R-H (R = C or heteroatom) precursors<sup>8</sup> and recently reported radical-mediated dehydrogenative cyclization reactions of  $\alpha$ -fluoromalonate amides for the synthesis of 3-fluorooxindoles.<sup>8a</sup> Herein we report the electrochemical generation of C-centered radicals from  $\alpha$ -alkyl substituted 1,3-dicarbonyl compounds and their cyclization reactions with arenes (Scheme 1b).

# Electrochemical dehydrogenative cyclization of 1,3-dicarbonyl compounds<sup>†</sup>

Zheng-Jian Wu,‡ Shi-Rui Li,‡ Hao Long and Hai-Chao Xu 🕑 \*

a) Generation of carbon-centered radicals from 1,3-dicarbonyl compounds



b) Electrochemical dehydrogenative cyclization of 1,3-dicarbonyl compounds (this work)





Our investigation was started by optimizing the electrolysis conditions for the cyclization of  $\alpha$ -methyl-substituted malonate amide 1. Our previously established conditions for the cyclization of  $\alpha$ -fluoromalonate amides were not effective in promoting the reaction of 1 probably because of the reduced acidity of 1 compared with its fluoro analogue. After some screening of the reaction parameters, the optimal electrolysis conditions were determined to utilize THF/MeOH (2:1) under reflux in the presence of 10 mol% of Cp<sub>2</sub>Fe,<sup>9</sup> 10 mol% of Y(OTf)<sub>3</sub>, and 50 mol% of LiOMe (Table 1). The electrolysis employed a constant current of 7.5 mA and an undivided cell (a three-necked round bottomed flask) equipped with a reticulated vitreous carbon (RVC) anode and a platinum plate cathode. Under these reaction conditions, the desired oxindole product 2 was isolated in 85% yield after the consumption of 2.5 F mol<sup>-1</sup> of charge (entry 1). The reaction could be scaled up to decagram scale without reduction in the yield (entry 2). A dramatic decrease in yield was observed when the reaction was carried out at RT (entry 3) or in the absence of Cp<sub>2</sub>Fe (entry 4) or Y(OTf)<sub>3</sub> (entry 5). The use of LiOMe as the base was critical for the success of the reaction as the use of weaker bases such as Cs<sub>2</sub>CO<sub>3</sub> (entry 6),

State Key Laboratory of Physical Chemistry of Solid Surfaces, Key Laboratory of Chemical Biology of Fujian Province, Innovative Collaboration Center of Chemistry for Energy Materials, and College of Chemistry and Chemical Engineering, Xiamen University, Xiamen 361005, P. R. China. E-mail: haichao.xu@xmu.edu.cn

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<sup>‡</sup> These authors contributed equally to this work.



	н	Me	THF/MeOH (2:1), reflux	Ме
		1		2
Entry	y	Deviati	on from the standard conditions	Yield <sup>b</sup> [%]
1		None		85 <sup>c</sup>
2		Decagr	am scale	84 (8.47 g) <sup>c</sup>
3		Reactio	on at RT	33 (38)
4		No Cp <sub>2</sub>	Fe	5 (48)
5		No Y(C	/Tf) <sub>3</sub>	26 (47)
6		Replac	ing LiOMe with Cs <sub>2</sub> CO <sub>3</sub>	23 (70)
7		Replac	ing LiOMe with Na <sub>2</sub> CO <sub>3</sub>	0 (95)
8		Replac	ing LiOMe with K <sub>3</sub> PO <sub>4</sub>	15 (46)
9		Replac	ing LiOMe with K <sub>2</sub> HPO <sub>4</sub>	0 (82)
10		Replac	ing $Y(OTf)_3$ with $Zn(OTf)_2$	45 (12)
11		Replac	ing $Y(OTf)_3$ with $Sc(OTf)_3$	63 (18)
12		Replac	ing $Y(OTf)_3$ with $Sm(OTf)_3$	42 (28)
13		Replac	ing $Y(OTf)_3$ with $ln(OTf)_3$	66 (12)
14		Replac	ing $Y(OTf)_3$ with $Yb(OTf)_3$	75 (14)
15		Replac	ing $Y(OTf)_3$ with $La(OTf)_3$	65 (7)

Me

CO<sub>2</sub>Me

:0

<sup>*a*</sup> Undivided cell, RVC anode (100 PPI, 1 cm  $\times$  1 cm  $\times$  1.2 cm), Pt plate cathode (1 cm  $\times$  1 cm), constant current = 7.5 mA, 1 (0.3 mmol), solvent (6 mL), argon, 2.8 h (2.5 F mol<sup>-1</sup>). <sup>*b*</sup> Determined by <sup>1</sup>H NMR analysis using 1,3,5-trimethoxybenzene as the internal standard. Recovered 1 is given in brackets. <sup>*c*</sup> Isolated yield.

 $K_2CO_3$  (entry 7),  $K_3PO_4$  (entry 8), or  $K_2HPO_4$  (entry 9) led to either low yield or no product at all. In addition, other metal triflates such as  $Zn(OTf)_2$  (entry 10),  $Sc(OTf)_3$  (entry 11),  $Sm(OTf)_3$  (entry 12),  $In(OTf)_3$  (entry 13),  $Yb(OTf)_3$  (entry 14) or  $La(OTf)_3$  (entry 15) were less effective in promoting the product formation than  $Y(OTf)_3$ .

The substrate scope for the synthesis of oxindoles was then explored (Scheme 2). First, the N-phenyl ring could be substituted at the para-position with electron donating OMe (3), halogens such as F (4), Cl (5), and Br (6), and electron-withdrawing substituents such as  $CF_3$  (7),  $OCF_3$  (8), and  $CO_2Me$  (9), but not the highly electron-accepting CN (10) or  $NO_2$  (11). The decreased reaction efficiency for the electron-deficient substrates was probably caused by the difficulty in cyclizing the electrophilic C-radical onto the N-phenyl ring. An alkynyl group at the paraposition was tolerated (12). The reaction was also compatible with substitution at the ortho position of the N-phenyl ring with OMe (13) or a fused ring (14-16). The  $\alpha$ -methyl group in the substrate could be replaced by functionalized alkyl chains bearing alkenyl (17, 18), alkynyl (19) or phenyl (20) groups. The N-substituent also tolerated variation and was compatible with *n*Pr (21), Bn (22), allyl (23), and aryl (24, 25) groups. While the tert-butyl ester (26) cyclized efficiently, the bisamide failed to afford the expected product 27 probably because of its reduced acidity.

Further investigations revealed that the electrochemical reaction could also be employed for the synthesis of the 3,4-dihydro-1*H*-quinolin-2-ones (Scheme 3). The  $\alpha$ -alkyl malonic esters are more acidic than the malonate amides and the former cyclized efficiently in the presence of 5 mol% of Cp<sub>2</sub>Fe and 30 mol% of Na<sub>2</sub>CO<sub>3</sub> without the need for a Lewis acid or a strong base. Once again, the *N*-phenyl ring could accommodate *para*-substituents with diverse



Scheme 2 Scope of oxindole synthesis. Reaction conditions: undivided cell, substrate (0.3 mmol), THF (4 mL), MeOH (2 mL), argon, constant current = 7.5 mA, 2.8–3 h. <sup>a</sup>Yield of isolated product. <sup>b</sup>Methyl *tert*-butyl ether/MeOH (2:1) were used as solvent. PMP = *para*-methoxyphenyl.

electronic properties (28–34). Introduction of a *meta*-bromo group led to the formation of two regioisomers (35 and 35'). The 3-aminopyridine derived substrate cyclized regioselectively at the *ortho* position of the pyridyl nitrogen atom to give 36. *tert*-Butyl ester (37) and  $\beta$ -keto ester (38) were also suitable for the cyclization reaction. Substitution at the  $\alpha$ -position of the amide with a methyl group did not affect the electrolysis reaction (39). Lastly, the electrochemical conditions could also be employed to promote the intramolecular dehydrogenative cross-coupling of a malonic ester with a pyrrole ring to form the 2,3-dihydro-1*H*pyrrolizine 40, which could be converted to the drug ketorolac through saponification followed by decarboxylation.<sup>1</sup>*e* 

Based on the studies in this work and previous investigations by  $us^{8a}$  and others,<sup>10</sup> a possible mechanism for the electrochemical dehydrogenative cyclization reactions was proposed using malonate amide **1** as the substrate (Scheme 4). When electricity is passed through the cell, Cp<sub>2</sub>Fe gets oxidized at the anode to give Cp<sub>2</sub>Fe<sup>+</sup>. Meanwhile, methoxide is generated at the cathode through reduction of methanol solvent. The base methoxide deprotonates the malonate amide **1** to give its conjugate base **I** with the equilibrium probably lying far to the side of **1**.



**Scheme 3** Scope of 3,4-dihydro-1*H*-quinolin-2-one synthesis. Reaction conditions: undivided cell, constant current = 10 mA, substrate (0.3 mmol), THF (3 mL), MeOH (3 mL), argon, reflux, 2 h (2.5 F mol<sup>-1</sup>). <sup>a</sup> Isolated yield. <sup>b</sup>Na<sub>2</sub>CO<sub>3</sub> (0.3 mmol), *n*Bu<sub>4</sub>NBF<sub>4</sub> (0.9 mmol), THF (5 mL), MeOH (1 mL).



The carbanion **I** is then oxidized by the anodically generated  $Cp_2Fe^+$  through single electron transfer (SET) to afford the C-radical **II** and regenerate  $Cp_2Fe^{.8a,10}$  The cyclization and rearomatization of **II** led to the final oxindole **2**. Considering that only the carbanion **I** but not the neutral **1** can be oxidized by  $Cp_2Fe^+$ , the role of the added Lewis acid Y(OTf)<sub>3</sub> and LiOMe is most likely to help drive the acid–base equilibrium to the side of **I**. In comparison, these additives are not necessary for  $\alpha$ -alkyl malonic esters (p $K_a = 13.1$  in H<sub>2</sub>O), which is more acidic than the malonate amides such as **1** as well as methanol (p $K_a = 15.5$  in H<sub>2</sub>O).

In summary, we have developed Cp<sub>2</sub>Fe-catalyzed electrochemical methods for the generation of C-centered radicals from the  $\alpha$ -alkyl-substituted 1,3-dicarbonyl compounds *via* C-H bond cleavage. This radical generation protocol enables the development of intramolecular C-H/Ar-H cross-coupling reactions. This work was supported by Ministry of Science and Technology (2016YFA0204100), National Natural Science Foundation of China (21672178), "Thousand Youth Talents Plan", and Fundamental Research Funds for the Central Universities.

### Conflicts of interest

There are no conflicts to declare.

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