VIP Cross-Coupling Very Important Paper

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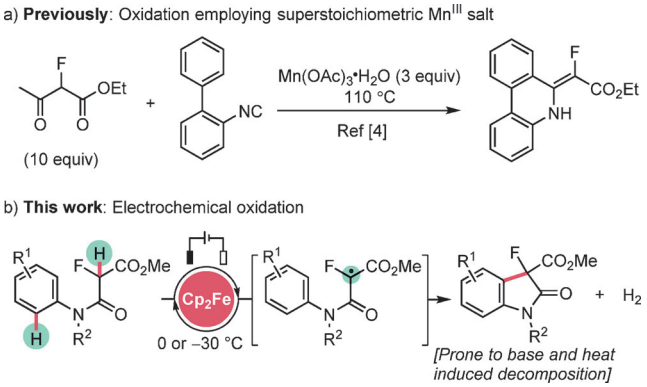
Synthesis of C3-Fluorinated Oxindoles Through Reagent-Free Cross-Dehydrogenative Coupling

*Zheng-Jian Wu and Hai-Chao Xu**

Abstract: *Reported herein is an unprecedented synthesis of C3-fluorinated oxindoles through cross-dehydrogenative coupling of C(sp^3)-H and C(sp^2)-H bonds from malonate amides. Under the unique and mild electrochemical conditions, the requisite oxidant and base are generated in a continuous fashion, allowing the formation of the base- and heat-sensitive 3-fluorooxindoles in high efficiency with broad substrate scope. The synthetic usefulness of the electrochemical method is further highlighted by its easy scalability and the diverse transformations of the electrolysis product.*

Organofluorine compounds have attracted broad interest from chemists due to their wide application in pharmaceutical and agrochemical industries.[1] Although trifluoromethyl- and difluoroalkyl-bearing compounds can be prepared via radical fluoroalkylation with relatively satisfactory efficiency, the lack of convenient precursors and initiating systems for the generation of monofluoroalkyl radicals has limited their utility in the synthetic applications.[2] The few isolated examples on formation of monofluoroalkyl radicals generally rely on activation of a C-heteroatom bond.[3] Nonetheless, Wang and Ji[4] have recently reported the oxidative radical reactions of 2-fluoro-1,3-dicarbonyl compounds, although a high temperature and an excess of Mn^{III} salt[5] are needed (Scheme 1 a).

On the other hand, the promising therapeutic potentials of 3-fluorooxindoles have stimulated synthetic efforts toward their preparation,[6] which are achieved through derivatization of existing oxindoles,[7a–c] Pd-catalyzed cross-coupling using arylbromide,[7d] or fluoroarylation of diazoacetamides.[7e] Although these methods provide very useful access to 3-fluorooxindoles, they require functionalized or even hazardous precursors. The groups of Kündig[8a] and Taylor[8b] independently reported the synthesis of 3,3-disubstituted oxindoles through straightforward cross-dehydrogenative coupling[9] of *N*-aryl amides using stoichiometric amounts of Cu^{II} salt and Na(K)O*t*Bu. Following these pioneering studies, other oxidizers including Ag_2O, I_2, and DDQ were reported.[10] Aerobic oxidation using copper catalysis at temperatures of above 100 °C was also found to promote similar reactions.[11] Despite these progresses, it is still highly desirable and yet challenging to develop mild catalytic conditions for the synthesis of 3,3-disubstituted oxindoles through cross-coupling of C–H bonds, especially in a reagent-free fashion. We[12] have developed electrosynthesis of several classes of heterocycles through radical-mediated cross-coupling of C–H and N–H bonds.[13] Herein we report a new strategy for the generation of functionalized monofluoroalkyl radicals through electrochemical activation of C–H bonds[14] and its application in the unprecedented synthesis of 3-fluorooxindoles through cross-coupling of C(sp^3)-H and C-(sp^2)-H bonds (Scheme 1 b).[15]



Scheme 1. Oxidative formation and reaction of monofluoroalkyl radicals.

The cost-effective organometallic compound ferrocene (Cp_2Fe) was employed as a redox catalyst for the electrochemical cyclization of the model substrate **1** because Cp_2Fe^+ is known to promote oxidative radical reactions (Table 1).[12a,b,16] After some experiments, the optimal reaction conditions were defined as electrolyzing **1** at 0 °C in a mixed solvent of MeOH/THF (1:2) using 10 mol % of Cp_2Fe as the catalyst and 30 mol % of LiCp as additive. The constant current electrolysis was conducted in an undivided cell equipped with a reticulated vitreous carbon (RVC) anode and a Pt plate cathode. Under these mild conditions, the desired 3-fluorooxindole **2** was isolated in 82 % yield after the consumption of 2.5 F of charge. Running the reaction without Cp_2Fe (entry 2) or in the presence of triarylamine-type redox catalysts (entry 3–4) led to substrate decomposition and either no or low yield of **2**. The basic additive LiCp was also important for optimal yield as its absence (entry 5) or replacing it with $NaHCO_3$ (entry 6), or Na_2CO_3 (entry 7) or LiOMe (entry 8) all led to inferior results.[17] The proper anode material was critical for success as the use of platinum

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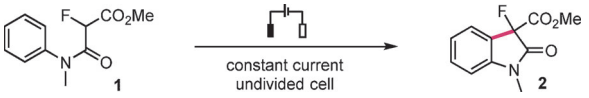
Table 1: Optimization of reaction conditions.[a]



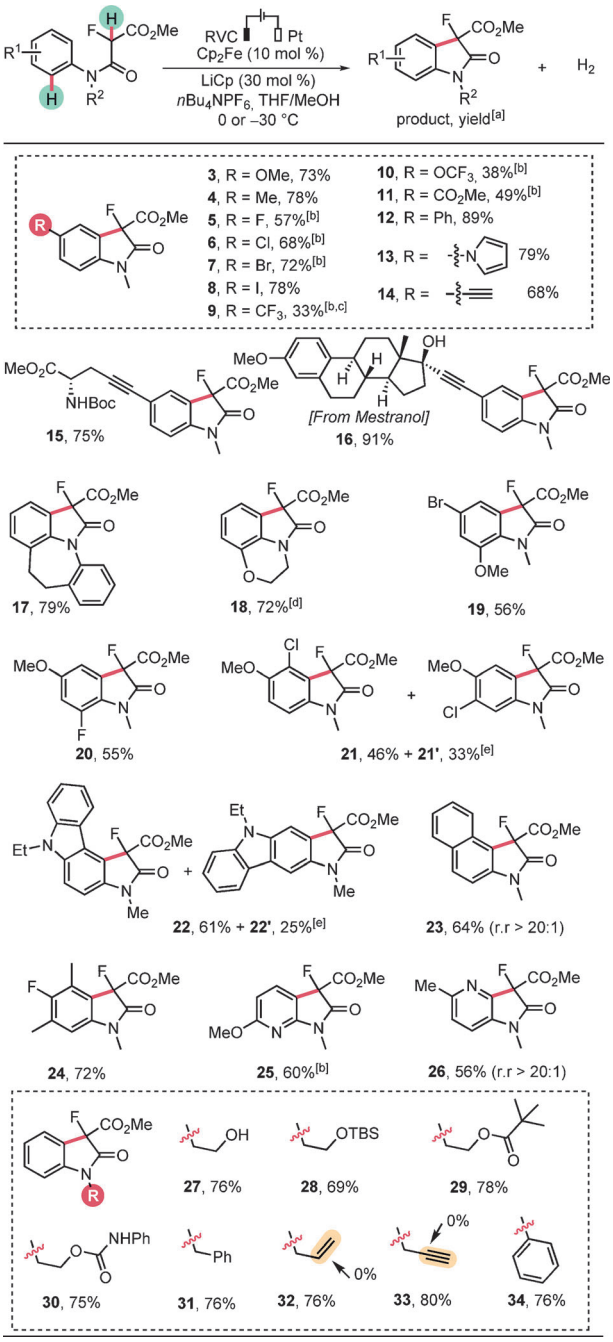
Entry	Conditions	Yield [%][b] 1	2
1	Cp_2Fe (10 mol%), MeOH/THF (1:2), LiCp (30 mol%), 4 Å MS, nBu_4NPF_6, 0°C, 7.5 mA	0	86(82)
2	entry 1 but no Cp_2Fe	35	0
3	entry 1 but $(4\text{-BrPh})_3N$ as mediator	75	9
4	entry 1 but $(4\text{-MePh})_3N$ as mediator	70	9
5	entry 1 but no LiCp	43	33
6	entry 1 but replacing LiCp with $NaHCO_3$	37	39
7	entry 1 but replacing LiCp with Na_2CO_3	30	41
8	entry 1 but replacing LiCp with LiOMe	0	64
9	entry 1 but Pt or graphite plate anode (1 cm×1 cm)	61–80	trace
10[c]	entry 1 but 15 mA	0	79

[a] Reaction conditions: RVC anode (100 PPI, 1.2 cm×1.2 cm×0.6 cm), Pt plate cathode (1 cm×1 cm), **1** (0.3 mmol), nBu_4NPF_6 (0.6 mmol), solvent (6 mL), argon, 2.7 h (2.5 F). [b] Yield determined by ^1H NMR analysis using 1,3,5-trimethoxybenzene as the internal standard. Isolated yield in parenthesis. [c] Reaction time = 1.3 h.

or graphite plate as the anode led to only trace amount of product formation (entry 9). The reaction may be conducted using higher current of 15 mA to reduce the reaction time with small yield loss (entry 10).

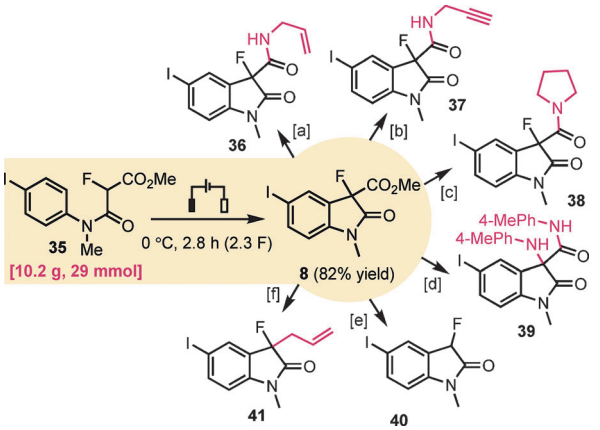
Subsequent investigation of the reaction scope revealed a broad tolerance of substituents with diverse electronic properties at all positions on the *N*-aryl group of the amide substrate (Scheme 2). Highly functionalized oxindoles could be conveniently prepared from substrates bearing a multi-substituted *N*-aryl group (**19**–**24**). Meta-substitution resulted in the formation of two separable regioisomers (**21**, **22**). On the other hand, oxindoles bearing diverse *N*-substituents including functionalized alkyl groups (**27**–**33**) and an aryl group (**34**) could be accessed. The electrochemical oxidation process showed satisfactory compatibility with a multitude of functional groups, including the full range of halogens (**5**–**8**), alkyne (**14**–**16**), aminoester (**15**), alcohol (**16**, **27**), pyridine (**25**, **26**), silylether (**28**), ester (**29**), and redox sensitive pyrrole (**13**), carbozole (**22**), and *N*-phenyl carbamate (**30**). However, it should be noted that the oxindole products bearing electron-withdrawing groups (**5**–**7**, **9**–**11**, **25**) were prone to base-induced decomposition even at 0°C. Thus, the reaction temperature needed to be lowered to −30°C to obtain optimal yields (Table S1, the Supporting Information).

In the cases of synthesis of **32** and **33**, the intended oxindole products were obtained in high yields despite the presence of better radical acceptors, that is, a C–C double or triple bond, to compete with the phenyl group. Tertiary amides bearing a phenyl group and an unhindered alkyl group on the amidyl nitrogen existed predominately in the *cis* form (as illustrated for amide **1** in Table 1).[18] The activation energy for the *cis*/*trans* isomerization of amide is usually higher than that of radical cyclization.[19] As a result, the regioselectivity was dictated by the conformational preference of the starting amide.



Scheme 2. Scope of 3-fluorooxindole synthesis. Reaction conditions: Table 1, entry 1. [a] Yield of isolated product. [b] Reaction at −30°C. [c] The reaction time was 4 h (3.7 F). [d] Reaction at reflux. [e] Two separable isomers.

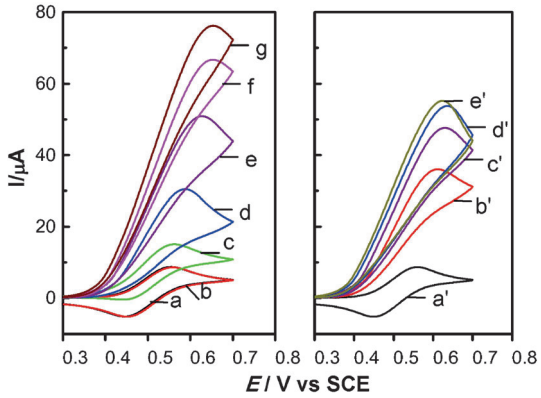
The electrolytically driven C3-fluorinated oxindole synthesis could also be performed on a larger scale (Scheme 3). The electrolysis of 10.2 grams (29 mmol) of **35** proceeded smoothly to furnish the desired product **8** in 82% yield in less than 3 h, with similar yield and current efficiency to the same reaction on a smaller scale (see Figure S1 in the Supporting Information for reaction setup). The ester group in **8** was activated by the neighboring fluoro and amide substituents, which greatly facilitated its aminolysis by a primary or secondary amine to afford amides **36**–**38**. In the presence of



Scheme 3. Gram-scale synthesis and product transformations. [a] Allylamine, MeOH, 50 °C, 94 %. [b] Propargylamine, MeOH, 50 °C, 96 %. [c] Pyrrolidine, $ZnCl_2$, THF, 0 °C, 60 %. [d] 4-$MePhNH_2$, $AlMe_3$, toluene, 0 °C-RT, 39 %. [e] Propargyl alcohol, $(iPr)_2NEt$, RT, 93 %. [f] Allylbromide, Cs_2CO_3, MeOH, RT, 71 %.

p-toluidine and $AlMe_3$,[20] both of the ester group and the C–F bond underwent aminolysis to generate 3-aminooxindole **39**. In addition, the ester group could be removed (**40**) or replaced in a single step by an allyl substituent (**41**). These diverse transformations highlighted the potential of the current electrochemical method in medicinal chemistry.

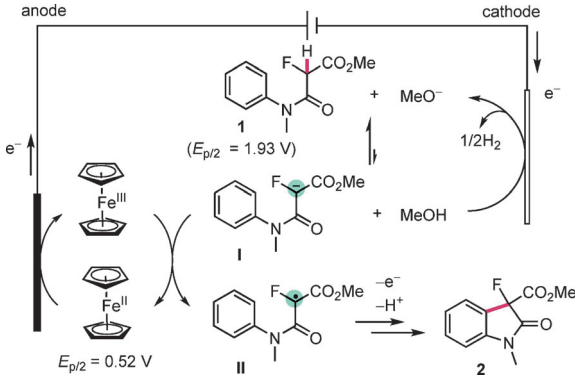
To investigate the reaction mechanism, we first compared the cyclic voltammograms of Cp_2Fe in the absence or presence of **1** (Scheme 4). The absence of any detectable changes between the two voltammograms (traces a vs. b) suggested that there was no electron transfer between the electrochemically generated Cp_2Fe^+ and the starting substrate, which could be rationalized by the large potential difference between the two species ($E_{p/2} = 0.52$ V and 1.93 V vs. SCE for Cp_2Fe and **1**, respectively). However, a catalytic current was observed when a base such as LiCp (trace c) or LiOMe (trace e) was included. The intensity of the current



Scheme 4. Cyclic voltammograms of Cp_2Fe (3 mM) in 2:1 THF/MeOH (0.1 M nBu_4NBF_4). a) Cp_2Fe. b) Cp_2Fe, **1** (36 mM). c) b + LiCp (36 mM). d) b + LiOMe (18 mM). e) b + LiOMe (36 mM). f) b + LiOMe (72 mM). g) b + LiOMe (108 mM). a′) Cp_2Fe. b′) Cp_2Fe, LiOMe (36 mM), **1** (18 mM). c′) Cp_2Fe, LiOMe (36 mM), **1** (36 mM). d′) Cp_2Fe, LiOMe (36 mM), **1** (72 mM). e′) Cp_2Fe, LiOMe (36 mM), **1** (108 mM).

was shown to increase with the strength (trace c vs. e) and concentration (traces d–g) of the base. In fact, this trend continued even after the concentration of LiOMe exceeded that of **1** (traces f–g), suggesting that **1** did not undergo substantial deprotonation by methoxide.[21] On the other hand, we discovered that the catalytic current also gained in strength when a higher concentration of **1** was used while the amount of base (LiOMe) remained unchanged (traces b′–e′). Taken together, these results suggested that **1** was oxidized by Cp_2Fe^+ through a rate-limiting deprotonation step followed by a quick electron transfer.[22]

Based on the above-mentioned findings, a possible mechanism for the electrochemical dehydrogenative cross-coupling reaction was proposed (Scheme 5). As a start, the



Scheme 5. Mechanistic proposal.

application of a potential difference across the electrolysis cell triggers the anodic oxidation of Cp_2Fe and the cathodic reduction of MeOH. The resultant MeO^- or added LiCp[23] then abstracts the malonyl proton from **1** to give rise to its conjugate base **I** with equilibrium lying far to the side of **1**.[24] This unfavorable deprotonation is driven forward by the following reaction of **I**, which involves facile electron transfer with Cp_2Fe^+ to form the key carbon radical intermediate **II** and regenerate the redox catalyst Cp_2Fe followed by radical cyclization and rearomatization to furnish the final oxindole **2**.

In summary, we have developed an efficient and highly chemoselective electrochemical cross-coupling reaction of $C(sp^3)$-H and $C(sp^2)$-H bonds employing Cp_2Fe as the redox catalyst, leading to a straightforward, modular and efficient synthesis of functionalized 3-fluorooxindoles. The in situ generation of the requisite oxidant and base at relatively low temperature and in a continuous fashion allow the base- and heat-sensitive fluorinated oxindoles to be formed with high efficiency. Importantly, we have demonstrated that electrochemical oxidation using redox catalysis can provide an effective entry into functionalized monofluoroalkyl radicals through activation of C–H bonds. Application of these fluorinated C-radicals to the development of new fluoroalkylation reactions are currently underway in our laboratory.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: cyclization · electrochemistry · ferrocene · radicals · redox chemistry

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Communications

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Cross-Coupling

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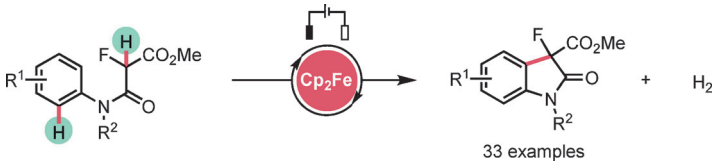
Synthesis of C3-Fluorinated Oxindoles Through Reagent-Free Cross-Dehydrogenative Coupling



C–H functionalization: A ferrocene-catalyzed electrochemical cross-coupling reaction of C(sp^3)-H and C(sp^2)-H centers has been developed to give access to C3-fluorinated oxindoles using fluorinated malonate amides. The electrosynthetic method is characterized by mild reaction conditions, broad substrate scope, high functional group tolerance, and easy scalability.