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Electrocatalytic Generation of Amidyl Radicals for Olefin Hydroamidation: Use of Solvent Effects to Enable Anilide Oxidation

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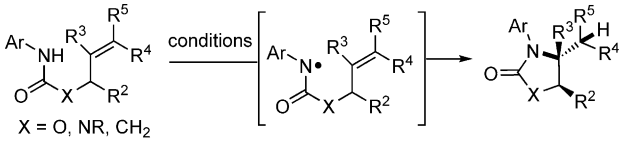
Abstract: *Oxidative generation of synthetically important amidyl radicals from N–H amides is an appealing and yet challenging task. Previous methods require a stoichiometric amount of a strong oxidant and/or a costly noble-metal catalyst. We report herein the first electrocatalytic method that employs ferrocene (Fc), a cheap organometallic reagent, as the redox catalyst to produce amidyl radicals from N-aryl amides. Based on this radical-generating method, an efficient intramolecular olefin hydroamidation reaction has been developed.*

Nitrogen-centered radicals are versatile intermediates for the construction of nitrogen-containing compounds. Unfortunately, their use in synthesis is limited because of the difficulty associated with their preparation.[1] Recently, the oxidative activation of the N–H bond has emerged as an appealing, yet challenging method for the generation of amidyl radicals.[2] One of the pioneering methods in this field was developed by Nicolaou[2a] using readily available *N*-aryl amide substrates and 2-iodoxybenzoic acid (IBX) as oxidant to achieve facile hydroamidation[3] of a wide range of functionalized olefins (Scheme 1). Subsequently, catalytic activation of the N–H bond to generate nitrogen radicals was applied by the groups of Chiba,[2c] Zheng,[2d] Li,[2e] Xiao,[2f] and Knowles[2g] in various C–N bond-forming reactions. While this manuscript was in preparation, Knowles disclosed an efficient photoredox olefin hydroamidation reaction catalyzed by an Ir complex (Scheme 1).[2h] Despite these advances, a common disadvantage of the abovementioned N–H activation approaches consists in their requirement for a stoichiometric chemical oxidant[4] and/or expensive noble-metal reagent.[5] To address these limitations, we report herein the first electrocatalytic method for the generation of amidyl radicals from *N*-aryl amides using the inexpensive ferrocene (Fc or Cp_2Fe)[6] as a highly reactive and yet chemoselective redox catalyst. With this method, we have developed an intramolecular olefin hydroamidation reaction that tolerates a host of sensitive functional groups (Scheme 1).[7]



Nicolaou: **4 equiv. IBX**, THF/DMSO, 90 °C.
Knowles: **2 mol% [Ir]**, *hv*, H-atom donor (cat.), CH_2Cl_2, rt.
This work: **5 mol% Cp_2Fe**, electricity, MeOH/THF, 1,4-CHD (5 equiv.), reflux.

Scheme 1. Intramolecular olefin hydroamidation using amidyl radicals.

Electro-oxidation of the amide N–H bond can be accomplished either through direct electrolysis or indirectly with the help of an electron-relaying redox catalyst.[8,9] An example of the direct electrolysis method was reported by Moeller as an environmentally friendly approach to generate nitrogen radicals.[10] In comparison, indirect electrolysis can usually avoid electrode passivation, eliminate kinetic inhibition, and achieve better selectivity.[8b] In this regard, we have recently developed the first electrochemical aminooxygenation of unactivated alkenes, in which 2,2,6,6-tetramethylpiperidine-*N*-oxyl radical (TEMPO) was used as both a mediator to generate amidyl radicals and an oxygen-atom donor for the carbon radical generated from the cyclization.[9h] While the excellent reactivity of TEMPO towards carbon radicals is beneficial for their oxygenation, it precludes their participation in other types of bond-forming reactions. Hence, we embarked on the quest for a non-interfering redox catalyst in the hope of expanding the application scope of the electrochemically generated amidyl radicals.

Allylic carbamate **1a**, which bears an electron-deficient *N*-aryl group that makes it difficult to be oxidized, was chosen as the model substrate and studied for its redox properties in cyclic voltammetry experiments along with Fc. The electrode potential of **1a** ($E_{p/2} = +0.83$ V vs. saturated calomel electrode; SCE) in basic MeOH solution[11] was much higher than that of Fc ($E_{p/2} = +0.37$ V vs. SCE). Consequently, the cathodic curve of Fc remained unaffected by the addition of **1a** (Figure 1, left), suggesting the absence of electron transfer between **1a** and Fc^+. In contrast, the adoption of a mixed solvent of THF/MeOH (5:1) lowered the electrode potential of **1a** and simultaneously increased that of Fc so that their $E_{p/2}$ were much closer, differing by only 60 mV (**1a**: $E_{p/2} = +0.61$ V;[11] Fc: $E_{p/2} = +0.55$ V, vs. SCE), which enabled efficient electron transfer as evidenced by the disappearance of the back-scan curve (Figure 1, right). These results suggested

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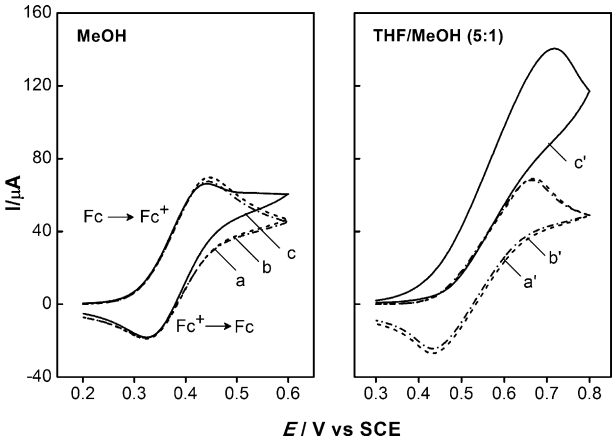
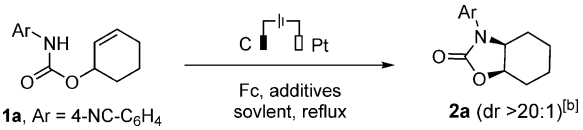


Figure 1. Cyclic voltammograms in 0.1 M nBu_4NBF_4/MeOH (left) or 5:1 THF/MeOH (right). a and a′: Fc (3 mM). b and b′: Fc (3 mM), **1a** (7.5 mM). c and c′: Fc (3 mM), **1a** (7.5 mM), NaOMe (7.5 mM).

the possibility of oxidizing anilides using electrochemically generated Fc^+ in a non-polar solvent.[12,13]

As a proof of concept, a pilot electrocatalytic hydroamidation reaction of **1a** was carried out in an undivided cell with 10 mol% Fc using a mixed solvent of THF/MeOH (5:1) under reflux conditions (Table 1). To our delight, the product

Table 1: Optimization of electrolysis conditions for hydroamidation.[a]



1a, Ar = 4-NC-C_6H_4 — **2a** (dr >20:1)[b]

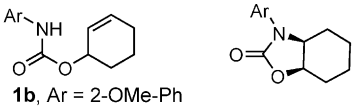
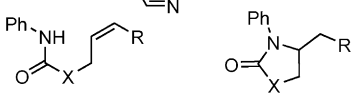
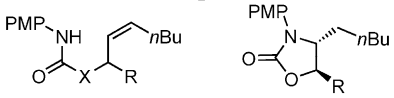
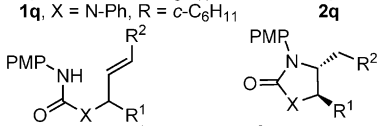
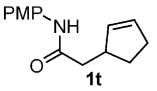
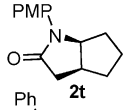
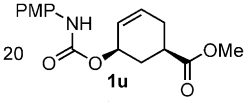
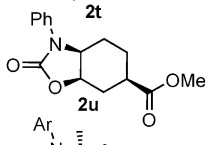
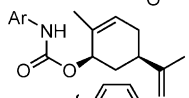
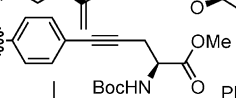
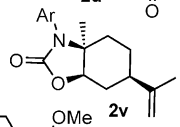
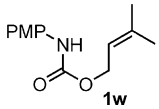
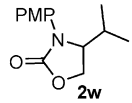
Entry	Electrolysis conditions	Electricity [F mol^{-1}]	Yield [%][c]
1	THF/MeOH (5:1), Fc (10 mol%)	3.4	80
2	THF/MeOH (5:1), Fc (5 mol%), 1,4-CHD (5 equiv), Na_2CO_3 (1 equiv) "standard conditions"	3.5	90
3	entry 2 but THF/MeOH (1:1)	2.5	66
4	entry 2 but reaction at RT	2.5	7(72)
5	entry 2 but no THF, or Fc, or electricity	2.5	NR
6	entry 2 but in air	4.4	92
7	entry 2 but using 1.0 g of **1a**	4.0	71

[a] Carbon anode, Pt cathode, constant current = 5 mA, **1a** (0.3 mmol), solvent (9 mL), nBu_4NBF_4 (0.9 mmol), reflux, argon. [b] Determined by ^{1}H NMR analysis of the crude reaction mixture. [c] Isolated yield. Recovered starting material in parenthesis. NR = no reaction.

2a was isolated in 80% yield (entry 1). Subsequent reaction optimization improved the yield to 90% by adopting a reaction system that consisted of 5 mol% Fc, 1 equiv of Na_2CO_3 and 5 equiv of 1,4-cyclohexadiene (1,4-CHD) in an electrolyte of nBu_4BF_4 in THF/MeOH (5:1) (entry 2). The formation of **2a** was supressed by lowering the concentration of THF (entry 3) or performing the reaction at RT (entry 4), and could be completely abolished by withholding Fc or THF, or by not supplying electricity (entry 5). It should be emphasized that the reaction could be conducted under atmospheric conditions (entry 6) or on gram scale (entry 7).

Screening a panel of functionally diverse carbamates, ureas, and amides revealed a broad substrate scope for the electrocatalytic hydroamidation reaction (Table 2; for additional scope, see Table S1 in the Supporting Information). First, the *N*-aryl group could accommodate a wide variety of substituents with different electronic and/or steric properties (entries 1–9).[14] Second, the substitution pattern and configuration of the alkene C=C bond did not have a negative

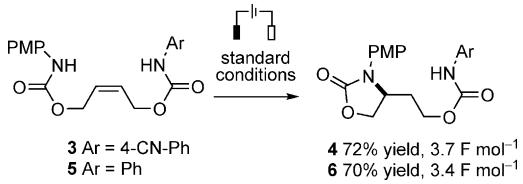
Table 2: Substrate Scope.[a]

Entry	Substrate	Product	Electricity [F mol^{-1}]	Yield [%],[b] dr[c]
				
1	**1b**, Ar = 2-OMe-Ph		4.2	87, >20:1
2	**1c**, Ar = 4-Me-Ph		2.2	77, >20:1
3	**1d**, Ar = Ph		2.3	78, >20:1
4	**1e**, Ar = 3-F-Ph		2.8	88, >20:1
5	**1f**, Ar = 4-Br-Ph		2.9	94, >20:1
6	**1g**, Ar = 4-CF_3-Ph		3.1	76, >20:1
7	**1h**, Ar = 4-MeCO-Ph		2.7	85, >20:1
8	**1i**, Ar = 2,6-Cl_2-Ph		2.2	78, >20:1
9	**1j**, Ar = 		3.7	71, >20:1
				
10	**1k**, X = N-allyl, R = H	**2k**	2.2	95, NA
11	**1l**, X = O, R = $CH_2OCONHBn$	**2l**	3.7	64, NA
12	**1m**, X = O, R = CH_2OTBS	**2m**	2.5	92, NA
				
13	**1n**, X = O, R = CH_2CH_2OH	**2n**	2.5	79, >20:1
14	**1o**, X = O, R = CH_2CH_2NHTs	**2o**	2.5	82, >20:1
15	**1p**, X = O, R = *c*-C_6H_{11}	**2p**	2.0	64, >20:1
16	**1q**, X = N-Ph, R = *c*-C_6H_{11}	**2q**	5.3	89, >20:1
				
17	**1r**, X = N-*n*Bu, R^1 = *c*-C_6H_{11}, R^2 = *n*Bu	**2r**	3.1	83, >20:1
18	**1s**, X = O, R^1 = *i*Pr, R^2 = Et	**2s**	3.8	96, 2:1
19	 **1t**	 **2t**	2.2	81, >20:1
20	 **1u**	 **2u**	2.6	88, >20:1
21	 **1v** Ar = 	 **2v**	5.3	71, >20:1
22	 **1w**	 **2w**	2.1	67, NA

[a] C anode, Pt cathode, 5 mA, **1** (0.3 mmol), Fc (0.015 mmol), 1,4-CHD (1.5 mmol), nBu_4NBF_4 (0.9 mmol), Na_2CO_3 (0.3 mmol), THF (7.5 mL), MeOH (1.5 mL), reflux, 3–9 h. [b] Isolated yield. [c] Determined by ^{1}H NMR analysis of the crude reaction mixture. dr = diastereomeric ratio. TBS = *tert*-butyldimethylsilyl. PMP = 4-methoxyphenyl.

impact on the cyclization efficiency. As a result, substrates bearing mono- (entry 10), di- (entries 11–20), and trisubstituted olefins (21–22) with an acyclic or cyclic structure are well-tolerated. Branched allylic carbamates (entries 13–15) and ureas (entries 16–17) cyclized to give the desired products in excellent diastereoselectivity except the allylic carbamate with a *trans*-alkene (entry 18).[15]

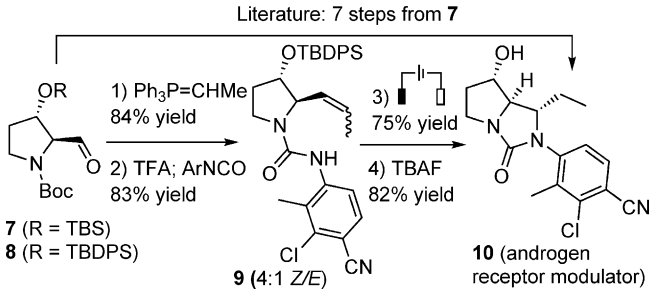
The electrocatalytic hydroamidation detailed in this study offers two key advantages. On the one hand, the process exhibits excellent compatibility with various functionalities including base/acid-labile groups, such as chiral esters (entry 20) and Boc-protected amino esters (21; Boc = *tert*-butyloxycarbonyl), and oxidation-sensitive groups, such as free alcohols (entry 13), sulfonamides (entry 14), and *N*-aryl carbamates (Scheme 2). On the other hand, the current



Scheme 2. Chemoselectivity of the electrocatalytic hydroamidation reaction.

method simultaneously afforded broad reactivity with anilides and outstanding chemoselectivity. For example, while the carbamate groups of **3** and **5** are all oxidation-active, the electrocatalytic reaction was observed only on the relatively electron-rich PMP-substituted carbamate moiety (Scheme 2).

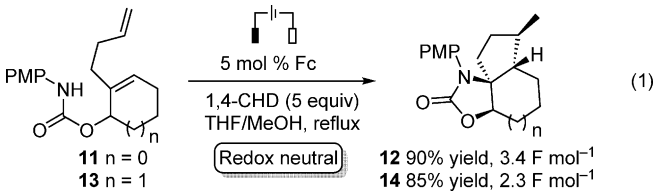
The synthetic utility of the hydroamidation reaction was further demonstrated. The synthesis of the androgen receptor modulator **10** was previously achieved through a 7-step route that started with aldehyde **7** (Scheme 3).[16] In comparison,

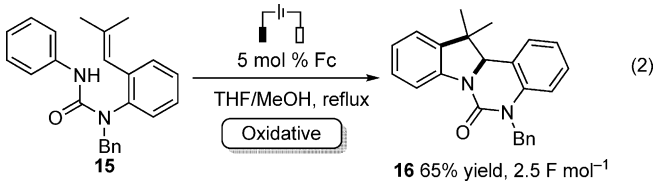


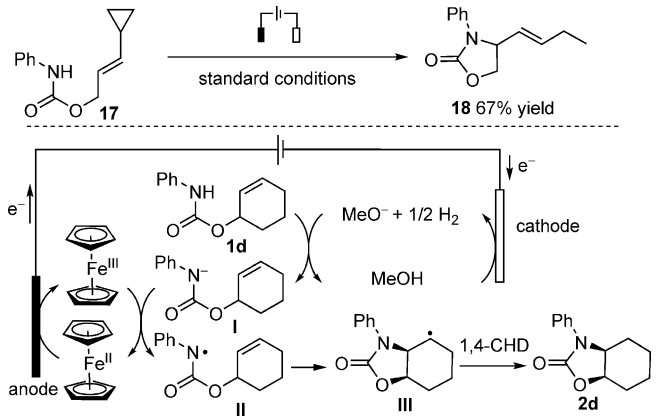
Scheme 3. Synthesis of androgen receptor modulator **10**.

our method, which involved a key hydroamidation step to form the cyclic urea moiety, was able to complete the synthesis in 4 steps from aldehyde **8**. Moreover, the electrochemically generated nitrogen radical intermediate can trigger tandem cyclizations to construct polycyclic *N*-heterocycles.[17] For example, diene substrate **11** and **13** reacted smoothly to afford the tricyclic products **12** and **14**, respectively, as a single diastereomer [Eq. (1)]. Interestingly, cyclization of **15** in the absence of the H-atom donor 1,4-CHD afforded indoline **16** following an oxidative termination [Eq. (2)].

The radical nature of the hydroamidation reaction was investigated by electrolyzing substrate **17** bearing a cyclopropyl group as the radical clock (Scheme 4, top). The







Scheme 4. Mechanistic studies and rationale.

formation of the ring-opening product provides compelling evidence for a radical-type mechanism.

Based on the results elucidated in this and our earlier study,[9h] a plausible mechanism is proposed using **1d** as a model substrate (Scheme 4, bottom). Application of electric current first causes the anodic oxidation of Fc to Fc^+ and cathodic reduction of MeOH to H_2 and MeO^-. The latter deprotonates **1d** to give its conjugate base **I**. Instead of being reduced at the cathode, the ferric catalyst Fc^+ rapidly oxidizes **I** via single-electron-transfer to furnish the key amidyl radical intermediate **II** and to regenerate Fc. This electron transfer step is facilitated in less polar media because of reduced solvation of the ionic species. The electrochemically generated MeO^- is thought to be critical for the reaction as no electron transfer was detected when no base was added (cf. Figure 1) or when Na_2CO_3 was used as the base (Figure S1). The final prodcut **2d** is formed by cyclization of amidyl radical **II** onto the tethered olefin, followed by H-atom abstraction of

the resulting carbon radical **III** from 1,4-CHD or a solvent molecule.

In conclusion, we have developed an unprecedented electrocatalytic method in which an assortment of functionalized, olefin-bearing amidyl radicals can be efficiently prepared through the use of Fc as the redox catalyst and subjected to intramolecular hydroamidation to synthesize valuable lactams and cyclic carbamates and ureas. The success of this transformation relies on the use of a non-polar solvent to lower the oxidation potential of anilides relative to that of Fc, which facilitate the electron transfer between the substrate and Fc^+. Efforts are underway in our laboratory to extend the application of this method to other aminative functionalization reactions.

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