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Fe Catalyzed Intramolecular Cross-Dehydrogenative-Arylation (CDA), Efficient Synthesis of 1-Aryl Naphthalenes and 4-Aryl Coumarins

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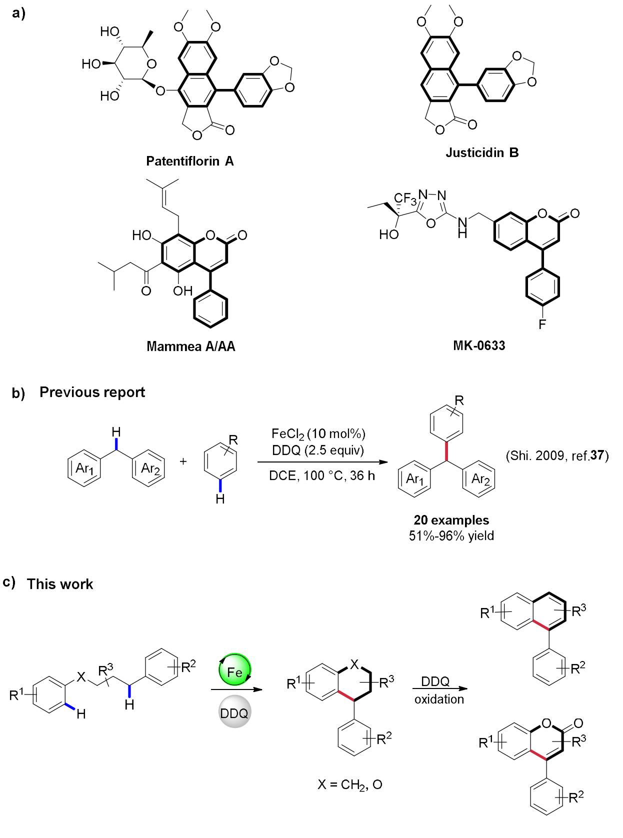
Dedication to Professor Peter Kündig on the occasion of his 75th birthday.

Direct cross dehydrogenative coupling of different inert C-H bonds is the most straightforward and environmentally benign method to construct C-C bonds. In this paper, we developed an iron-catalyzed intramolecular Cross-Dehydrogenative-Arylation (CDA) between benzylic $C(sp^3)H$ bond and aromatic $C(sp^2)H$ bond. From the readily available linear substrates, 1-aryl naphthalenes and 4-aryl coumarins can be quickly constructed with moderate to good yield (18 examples, up to 73% yield) in one step. Both symmetrical and unsymmetrical substrates with different functional groups could tolerate this system well to form the anticipated products. A radical initiated dehydrogenative cyclization-dehydrogenation tandem process was proposed

Keywords: Cross-dehydrogenative-arylation, Fe-catalysed, radical, 1- aryl naphthalenes, 4- aryl coumarins.

Introduction

Naphthalenes[1,2] and coumarins[3-6] are ubiquitous structural units in many natural products, pharmaceutical synthetic intermediates, as well as functional materials.[7,8] For example, Patentiflorin A[9] is a potent inhibitor of drug-resistant HIV-1 strains identified from the medicinal plant Justicia gendarussa. Justicidin B[10] exhibits a wide array of biological properties ranges from piscicidal to antifungal, antiviral and antibacterial activities. Mammea- A/AA[11] is the active compound of Mammea Africana stem bark extract, exhibiting anticancer, antimicrobial, and antioxidant properties. and MK-0633,[12] is a promising 5-lipoxygenase inhibitor (Scheme 1a). Over the past decades, many efforts have been made to construct such motifs[13-18,5,6,19-21]. However, the development of general and efficient methodologies remains challenging and is still highly desired. Transition-metal-catalyzed C-H bond functionalization could provide a green and economical solution to synthesize valuable products from simple molecules, has been employed as a powerful warhead in the pharmaceutical and chemical industry.[22–34] C–H/C–H coupling reactions, which were well-featured as cross-dehydrogenative-coupling reactions (CDC), offered a complementary strategy to construct C–C bonds from two simple C–H bonds directly.[35–52] Among all of the reported transition metals, Fe was brought into focus because of its low toxicity, popular price, and environmentally benign features.[53–60] Many excellent works of iron-catalyzed CDC reactions involve $C(sp^3)H$ bond activation have been reported.[36,61–71] In 2009, we developed a Fe catalyzed cross dehydrogenation coupling reaction of electron-rich aromatic hydrocarbons and diphenylmethane.[36] (Scheme 1b). Based on our continuous research on the field of transition-metal-catalyzed oxidative coupling of unactivated C-H bonds,[36,72,73] we here developed an inexpensive, readily available $FeCl_3$/DDQ system to efficiently catalyze the tandem cross-dehydrogenative arylation/oxidation reaction of 1, 4-diphenylbutane and (3-phenoxypropyl) benzene towards the synthesis of 1-aryl naphthalenes and 4-aryl coumarins (Scheme 1c).



Scheme 1. a) Naphthalenes and coumarins in pharmaceuticals. b) Fe/DDQ catalyzed cross dehydrogenative arylation. c) This work.

Results and Discussion

To initiate our study, 1, 4-diphenylbutane **1a** was synthesized follow the reported peocedure[74] as the model substrate (Table 1). At the beginning of the reaction condition optimization, we found that DDQ (3.0 equiv) could promote the oxidative coupling in the absence of metal catalyst in DCE at

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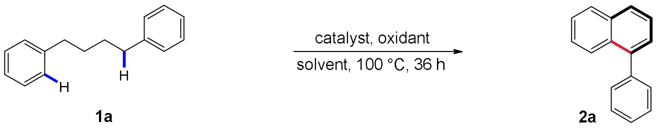
100 °C, to form **2a** with 26 % yield (Table 1, entry 1). Different metal salts were then screened, and $FeCl_3$ gave a relatively high result (Table 1, entries 2-10. Table s1 and s2). The catalyst loading was then identified to 2.5 mol% (Table 1, entry 12). Other solvents like CH_3CN, 1,4-Dioxane, and $MeNO_2$ still works in this system but not as effective as DCE (Table 1, entries 14-16). DDQ is essential to this oxidative coupling. No desired product was monitored in the absence of DDQ, even large amount excess of $FeCl_3$ was used (Table 1, entry 17). Subsequently, we increased DDQ to 5 equivalents to give **2a** in 77 % yield (Table 1, entry 19).

Table 1. Screening conditions.



Entry	Catalyst (mol%)	Oxidant (equiv)	Solvent	Yield of **2a**[b]
1	/	DDQ (3)	DCE	26
2	$PdCl_2$ (5.0)	DDQ (3)	DCE	27
3	CuBr (5.0)	DDQ (3)	DCE	28
4	$CoBr_2 \cdot xH_2O$	DDQ (3)	DCE	28
5	$RhCl_3$ (5.0)	DDQ (3)	DCE	29
6	$FeBr_2$ (5.0)	DDQ (3)	DCE	57
7	$FeCl_2$ (5.0)	DDQ (3)	DCE	60
8	$FeCl_3$ (5.0)	DDQ (3)	DCE	61
9	$FeBr_3$ (5.0)	DDQ (3)	DCE	32
10	$Fe(OAc)_2$ (5.0)	DDQ (3)	DCE	55
11	$FeCl_3$ (1.25)	DDQ (3)	DCE	56
12	$FeCl_3$ (2.5)	DDQ (3)	DCE	63
13	$FeCl_3$ (10.0)	DDQ (3)	DCE	26
14	$FeCl_3$ (2.5)	DDQ (3)	CH_3CN	50
15	$FeCl_3$ (2.5)	DDQ (3)	1,4-Dioxane	41
16	$FeCl_3$ (2.5)	DDQ (3)	$MeNO_2$	49
17	$FeCl_3$ (300.0)	/	DCE	0[c]
18	$FeCl_3$ (2.5)	DDQ (4)	DCE	70
19	**$FeCl_3$ (2.5)**	**DDQ (5)**	**DCE**	**77/73[d]**
20	$FeCl_3$ (2.5)	DDQ (6)	DCE	73

[a] Conditions: **1a** (0.2 mmol, 1.0 equiv), catalyst, oxidant, solvent (2.0 mL), 100 °C for 36 hours, under N_2 atmosphere. [b] Yield of **2a** was determined by ^{1}H-NMR using 1,3,5-trimethoxylbenzene as the internal standard. [c] No **2a** was produced even 3.0 eq. of $FeCl_3$ was used. [d] Isolated yield. [e] More details about the condition optimization could be found in the SI.

With the optimized reaction condition in hand, we then begin to explore the substrate scope. Firstly, several symmetric 1,4-diphenylbutanes[74,75] were investigated in this reaction system. While 1,4-di-p-tolylbutane **1b** was used as the starting material, we have to reduce the DDQ loading to 4 equiv. to inhibit the over-oxidative by-product. To our delight, we still could get **2b** in good yield (66 %). Then different functional groups like -F (**2c**), -Cl (**2d**), -CO_2Me (**2e**), and -phenyl (**2f**) were introduced to 1,4-diphenylbutanes and all could tolerate well to give corresponding 1-phenyl naphthalenes in medium to good yield. For the electron-withdrawing-group-containing substances like **1c**-**1e**, a higher temperature (120 °C) was needed. As to **1c** and **1d**, 4.5 equiv. of DDQ could give better results, form **2c** and **2d** with 68 % and 59% yield. The yield of 1,4-di-o-tolylbutane **1g** was slightly lower (45% isolated yield) than its para analog **1b**, while they all met the same over-oxidize issue. Then two asymmetric 1,4-diphenylbutane substrates **1h** and **1i** were synthesized[76,77] and introduced to this system. For the reaction of 1-(tert-butyl)-4-(2-methyl-4-phenylbutyl)benzene **1h**, fascinating, good regio selectively was conducted. This may derive from the highly steric hindrance of the *t*-Bu group, which makes the ortho position hardly be approached, to inhibiting the formation of another product. As to 1-methyl-2-(4-phenylbutyl)benzene **1i**, a 1:3 regio-selectivity was obtained to get **2i** and **2i'**. The results of the above two asymmetric substances **1h** and **1i**, revealed that the cross-coupling between the benzylic C-H bond of the alkyl-substituted benzene and the C(sp^2)H bond of the unsubstituted benzene was favored.

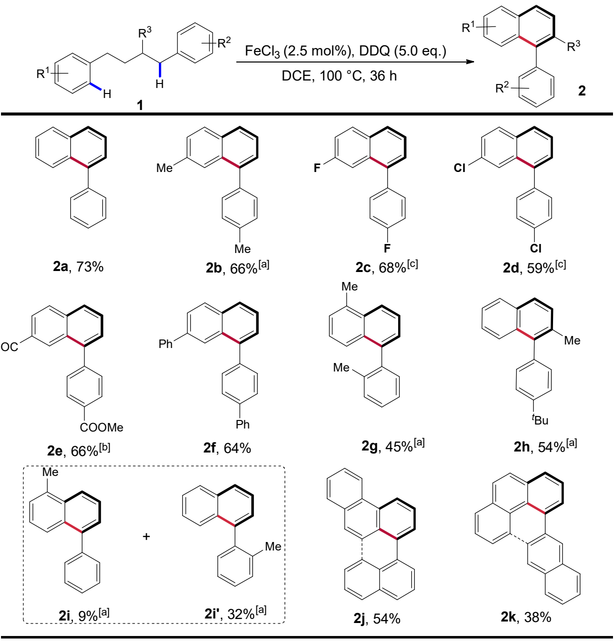


Figure 1. Substrate scope for construction of 1-aryl naphthalenes. Reaction conditions: **1** (0.2 mmol, 1.0 equiv), $FeCl_3$ (2.5 mol%), DDQ (5.0 equiv), DCE (2.0 mL), 100 °C for 36 hours, under N_2 atmosphere. [a] with 4.0 equiv DDQ. [b] 120 °C. [c] **1** (0.5 mmol, 1.0 equiv), 120 °C, DDQ (4.5 equiv). [d] Yield of 2i and 2i' was calculated by ^{1}H-NMR.

The cross oxidative coupling of 1,4-di(naphthalene-1-yl)butane **1j** and 1,4-di(naphthalene-2-yl)butane **1k** ran well to form the corresponding fused ring compound **2j**, **2k**. These two products could easily undergo a further dehydrogenative coupling,[79–81] to form benzo[b]perylene and dibenzo[de,qr]tetracene, which exhibited intriguingly photoelectric performance in the functional materials.[82]

We further extended this reaction system to the (3-phenoxypropyl) benzene derivatives **3**. To our delight, 4-aryl coumarins **4** could be obtained with moderate yield under the standard reaction condition (Figure 2), accompany with a 3-phenylpropanal by-product, which was produeced from the phenolic C-O bond cleavage and alcohol oxidation. Halogens like F (**4b**, 35%), Cl (**4c**, 44%), Br (**4d**, 40%), and phenyl (**4e**, 51%), tert-butyl (**4f**, 44%) groups could tolerate the oxidative condition to form corresponding 4-aryl coumarins in one step. The first cross-dehydrogenative-couping step of 1,2,3-trifluoro-5-(3-phenylpropoxy)benzene **3g** ran smoothly, but the following tandem oxidative process didn't work well, even under higher temperature (120 °C). Only 15% yield of **4g** was formed, with 55% of **4g'**.

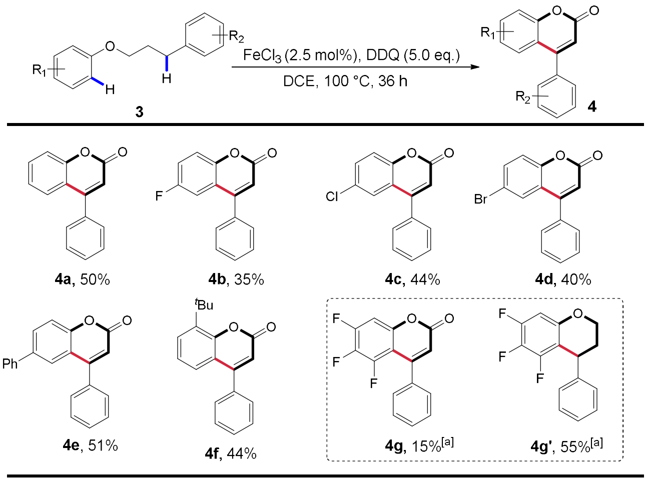
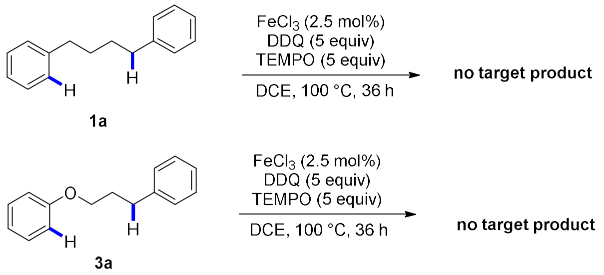


Figure 2. 4-aryl coumarins obtained by the iron-catalyzed intramolecular cross-dehydrogenative coupling of **3**. Reaction conditions: 1 (0.2 mmol, 1.0 equiv), $FeCl_3$ (2.5 mol%), DDQ (5.0 equiv), DCE (2.0 mL), 100 °C for 36 hours, under N_2 atmosphere. [a] 120 °C.

To get more insight of the mechanism, a model reaction was performed with 5.0 equiv of TEMPO, and the formation of **2a** and **4a** were completely inhibited, which implies that a radical species may be involved in this reaction (Scheme 2).



Scheme 2. Radical quenching experiment.

Based on the above experimental results and the literature reports,[36,61,83,84] we proposed a plausible mechanism for the intramolecular CDA reaction *(Fig. 3)*. Firstly, the benzylic C(sp^3)-H bond of **1** or **3** is activated to generate benzylic radical species **A** and the complex **B**; 2) an intramolecular radical addition occurred to form the radical intermediate **C**; 3) **C** is quickly captured by **B** to form intermediate **D** and released $DDQH_2$ and $FeCl_3$. 4) Finally, **D** is further oxidized by DDQ to obtain the target product **2 (X = CH₂)** or **4 (X = O)**[85-88].

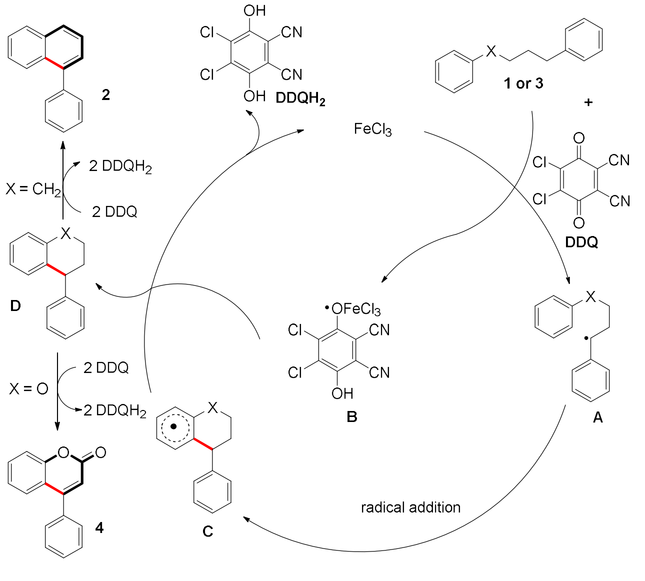


Figure 3. Proposed mechanism for the intramolecular CDC reaction.

Conclusions

In summary, an iron-catalyzed tandem intramolecular CDA/oxidation process for the synthesis of biologically and synthetically important 1-aryl naphthalenes and 4-aryl coumarins was explored. In this system, DDQ was essential for this tandem protocol. Polycyclic aromatic hydrocarbons, which exhibits significant photoelectric performance, could also be synthesized from this protocol. Further mechanistic exploration and application investigation was underway in our lab.

Experimental Section

General information

All chemicals were purchased from commercial suppliers and were used without further purification Melting points were determined with an X-4 apparatus. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker 400 spectrometer operating at 400 MHz for ^1H NMR, 101 MHz for ^{13}C NMR with $CDCl_3$ as the solvent. Chemical shifts are reported relative to $CDCl_3$ as an internal standard. The ^1H NMR data are reported as the chemical shift in parts per million, multiplicity (*s, singlet; d, doublet; dd, doublet of doublet; dq, doublet of quartet; dt, doublet of quartet; t, triplet; m, multiplet; brs, broad singlet.*), coupling constant in Hertz (Hz), and number of protons. HRMS (EI, FI, DART) were performed by the State-authorized Analytical Center in Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences. All reported yields are isolated yields, unless otherwise noted.

General Procedures

To a 25 mL oven-dried Schlenk tube with magnetic stir bar, $FeCl_3$ (2.5 mol%), DDQ (5.0 equiv) was added, then the substrate (0.2 mmol, 1.0 equiv) and 2.0 mL DCE were added to the reaction mixture successively. Subsequently the tube was pumped 3 times on the vacuum line with nitrogen. The tube was sealed and stirred at 100 °C for 36 hours. The reaction mixture was cooled to room temperature, diluted with 10 mL DCM, filtered, and rinse with an appropriate amount of DCM. The filtrate was concentrated and purified by flash column chromatography on silica gel.

See **supporting information** for specific experimental operations and structural characterization.

Acknowledgments

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Author Contribution Statement

Dr. Feng Liu and Prof. Zhangjie Shi led this project. Haiyan Diao did most of the experiments. Thanks to Changcheng Wang for discovering this subject and giving suggestions. Zhen Zhang helped expanding the substrate scope and repeat the experiment.

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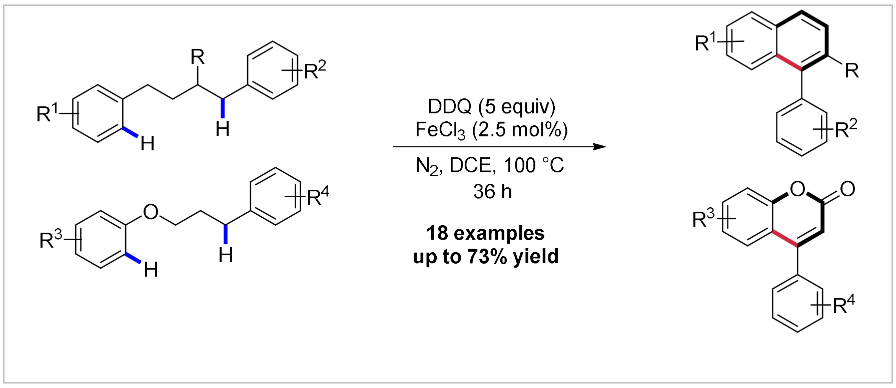
Fe Catalyzed Intramolecular Cross-Dehydrogenative-Arylation (CDA), Efficient Synthesis of 1-Aryl Naphthalenes and 4-Aryl Coumarins



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From the easily available linear substrates, we developed an iron-catalyzed intramolecular Cross-Dehydrogenative-Arylation (CDA) between benzylic C(sp^3)H and aromatic C(sp^2)H, which could easily construct 1-aryl naphthalenes and 4-aryl coumarins in one pot.