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Intramolecular oxidative coupling of 3-indolylarylketones with Pd(II)-catalysis under air: convenient access to indenoindolones

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ABSTRACT

A Pd-catalyzed method has been developed for the intramolecular oxidative coupling of 3-indolylarylketones under open air as terminal oxidant toward the synthesis of indeno[1,2-*b*]indol-10(5*H*)-ones. This reaction represents an intramolecular coupling with dual activation of C–H bonds for electron-deficient arenes, while such reactions are common for electron-rich arenes. Pd(II)-catalysis with pivalic acid as co-catalyst has been found to be crucial. The reaction undergoes without indole N–H-protection.

Direct arylation of (hetero)arene has recently emerged as an appealing strategy in organic synthesis.[1] In contrast to conventional cross-coupling reactions,[2] this approach obviates the necessity of additional pre-functionalization of arenes. In this direction, oxidative C–C coupling with dual activation of C–H bonds is most valuable.[3] The intramolecular variant provides convenient access to polyheterocycles.[4–7] Diaryl-amine or ether, and *N*-arylenamine in Pd(II)-catalyzed oxidative coupling reactions construct carbazole, dibenzofuran, and indole scaffolds, respectively.[7,8] However, these substrates represent a common class of structural motifs in which two coupling moieties (tethered arenes) are connected through a heteroatom. This makes the tethered arenes nucleophilic and undergo electrophilic palladation. These oxidative couplings are strongly influenced by electron supply from the tethering group to arenes and the electron-releasing/withdrawing effects of substitutions on arenes.[5b,7b,9] Decrease in electron density on tethered arenes reduces the rate of oxidative coupling and increases the relative amount of palladium acetate (even upto 2 equiv) required for the reaction. In fact, there are rare reported examples of intramolecular oxidative C_{aryl}–C_{aryl} coupling for electro-deficient arenes.[10,11] Herein, we report a Pd(II)-catalyzed intramolecular oxidative coupling of 3-indolylarylketone which is an electron-deficient arene. This affords convenient access to diversely substituted indeno[1,2-*b*]indol-10(5*H*)-ones. Also importantly, this method employs an open air atomosphere as terminal oxidant.[5a,11]

Indenoindolones and their derivatives possess a wide range of pharmaceutical activities.[12] The common methods for the synthesis of indeno[1,2-*b*]-indol-10(5*H*)-ones involve several reaction steps, limit the generation of substitution-diversity in product, and/-or require harsh reaction conditions.[12a,b,13] Recently, we have developed an approach of Friedel–Crafts 3-(2-bromo)benzoylation of indoles and intramolecular direct arylation toward the synthesis of indenoindolones.[14a] These compounds have been found to exhibit potent apoptotic anticancer activities.[14b] The synthesis is a two-step method, but the requirement of 2-bromo-functionality in aroyl moiety limits considerably the substitution-diversity in indenone-arene. In this aspect, the intramolecular oxidative coupling of 3-aroylindoles, which with diverse substitutions are readily accessible, is indeed of advantage.

Acidic reaction conditions enhance electrophilicity of cationic $[PdX]^+$ species and thus favor electrophilic palladation of arenes.[5b] Therefore, for the initial experiment, we carried out the oxidative coupling of 3-benzoylindole with $Pd(OAc)_2$-catalysis in acetic acid solvent under open air as terminal oxidant. It provided indole C2-dehydrogenative homo-coupling product as major but not indeno[1,2-*b*]indol-10(5*H*)-one (Table 1, entry 1). This indicated that electrophilic palladation for two C–H activation steps took place at indole C2 with two different 3-benzoylindole molecules. The intramolecular benzene C2-electrophilic palladation with indole-C2-PdX in the second C–H activation step was not favored. Plausible reasons may be that benzoyl-benzene lacks nucleophilicity at C2 and arylpalladium acetate, which would be the active species in the second C–H activation, is less electron deficient than palladium acetate. For direct arylation of electron-deficient arenes,

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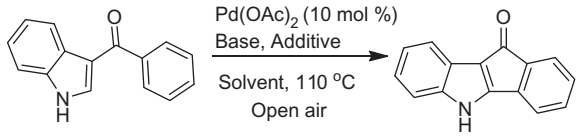
Table 1
Evaluation of $Pd(OAc)_2$, base, additive, and solvent in intramolecular oxidative coupling of 3-benzoylindole[a]



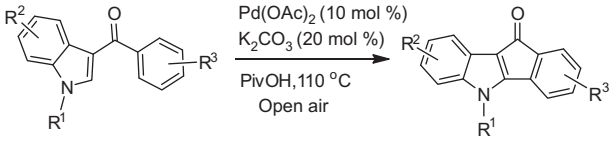
S. No.	Base (mol %)	Additive (mol %)	Solvent	Time (h)	Yield[b] (%)
1	K_2CO_3 (20)	—	AcOH	18	0[c]
2	K_2CO_3 (100)	—	PivOH	36	34
3	K_2CO_3 (100)	PivOH (50)	Toluene	36	12
4	K_2CO_3 (100)	PivOH (50)	DMF	36	14
5	K_2CO_3 (100)	PivOH (50)	DMSO	36	9
6	K_2CO_3 (100)	PivOH (50)	PEG 400	36	13
7	K_2CO_3 (200)	—	PivOH	36	16
8	K_2CO_3 (50)	—	PivOH	30	51
9	K_2CO_3 (20)	—	PivOH	21	85
10	Cs_2CO_3 (20)	—	PivOH	24	62
11	—	—	PivOH	48	24
12	K_2CO_3 (20)	$Cu(OAc)_2$ (20)	PivOH	30	86

[a] Reaction conditions: 3-benzoylindole (0.5 mmol), $Pd(OAc)_2$ (10 mol %) base (20 mol %), additive (20–50 mol %), solvent (0.75 mL), 110 °C,18–48 h.
[b] Isolated yields.
[c] It formed indole C2-dehydrogenative homo-coupling product.

2,2-dimethylpropionic acid (pivalic acid, PivOH) is known to play a role as co-catalyst with Pd-catalysis.[15] It promotes concerted metalation deprotonation (CMD) at acidic C–H rather than nucleophilic site of arene. Considering arene C2-H acidity of 3-aroylindole, we speculated that the CMD process might induce the arene C2-palladation in the second C–H activation step. Accordingly, the reaction was performed with $Pd(OAc)_2$ in PivOH as solvent in place of AcOH. To our delight, it afforded indeno[1,2-*b*]indol-10(5*H*)-one in 34% yield. No other product including dimer or oxidative dimer of 3-aroylindole formed, but the reaction was incomplete. The use of PivOH in substoichiometric quantity with other solvents such as toluene, DMF, DMSO, PEG 400 lowered the yield (Table 1, entries 3–6). Variation in equivalence of K_2CO_3 was then investigated (Table 1, entries 7–9). Gratifyingly, 20 mol % of K_2CO_3 afforded indeno[1,2-*b*]indol-10(5*H*)-one in 85% yield. Cs_2CO_3 in place of K_2CO_3 was found to be less efficient (Table 1, entry 10 vs 9). The use of $Cu(OAc)_2$ as co-oxidant provided similar yield of product (Table 1, entry 12).

With the optimized protocol in hand, we next set out to explore its scope. Various 3-aroylindoles with diverse substitutions were easily prepared by Friedel–Crafts arylation of indole.[16] They underwent the oxidative coupling in the present method and produced corresponding indeno[1,2-*b*]indol-10(5*H*)-ones in moderate to high yields (Table 2). The oxidative couplings of indole-containing compounds generally require the protection of indole-N–H functionality such as N-alkylation, acylation, or tosylation.[3c,d,4] The free N–H indole is prone toward dimerization in acidic condition.[16] In the present method, 3-aroyl derivatives of both N–H-unprotected and protected indoles underwent smooth intramolecular oxidative coupling. The tolerance of functionalities such as indole-N–H,

Table 2
Intramolecular oxidative coupling of 3-indolylarylketones toward synthesis of indenoindolones[17]



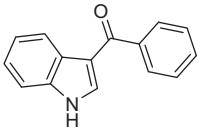
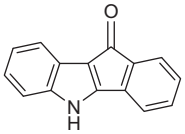
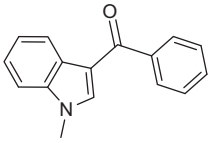
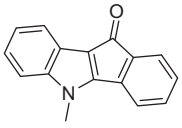
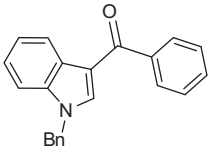
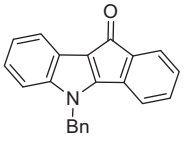
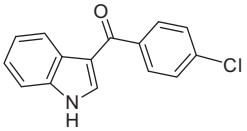
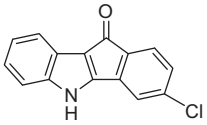
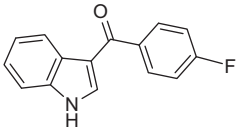
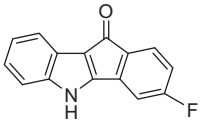
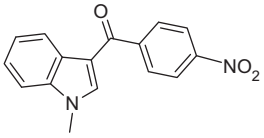
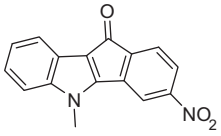
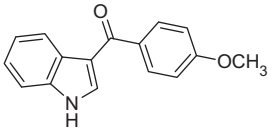
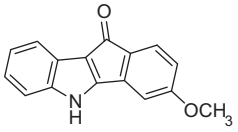
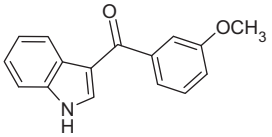
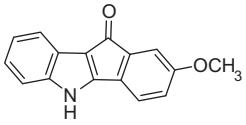
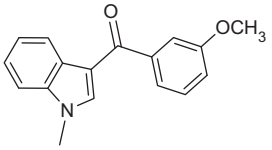
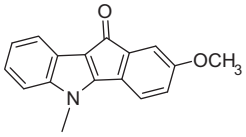
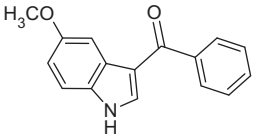
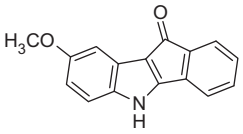
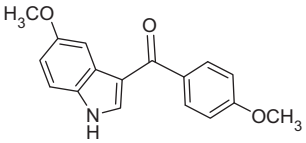
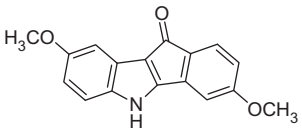
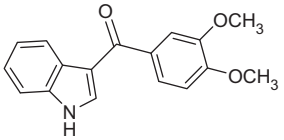
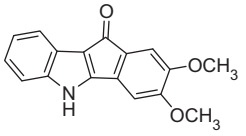
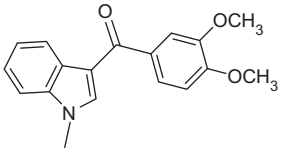
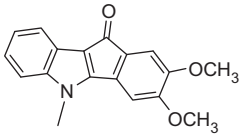
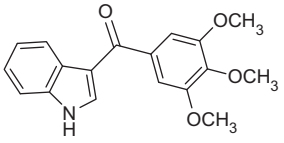
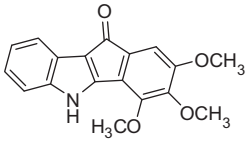
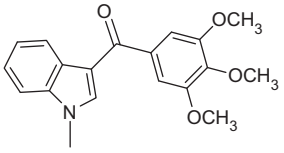
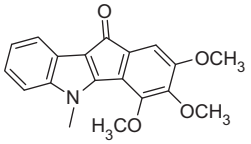
Entry	3-Indolylaryl-ketone	Indenoindolone	Time (h)	Yield[a] (%)
1			21	85
2			26	92
3			30	54
4			60	38
5			72	46

Table 2 (*continued*)

Entry	3-Indolylaryl-ketone	Indenoindolone	Time (h)	Yield[a] (%)
6			40	69
7			30	76
8			30	70
9			30	74
10			36	82
11			36	61
12			30	56
13			30	71
14			30	67
15			30	65

[a] Isolated yields.

chloro, nitro, methoxy in this protocol provides the opportunity of their various further chemical manipulations in products. The presence of electron-withdrawing functionalities in 3-aroylindoles lowered the rate of reactions, conversions, and isolated yield of products. This is in accordance with the literature reports that the reactivity of diaryl-amine or ether for the oxidative biaryl coupling is strongly reduced by the presence of the electron-withdrawing group.

In conclusion, we have developed a method for intramolecular oxidative coupling of 3-indolylarylketones with Pd(II)-catalysis in PivOH under open air as the terminal oxidant. The reaction does not require indole N–H-protection unlike common oxidative

couplings of indole-containing compounds. Intramolecular oxidative couplings for electron-rich arenes are common in the literature. However, this method has rendered electron-deficient 3-indolylarylketones as valid substrates for such coupling. The method has led to a convenient preparation of indeno[1,2-*b*]indol-10(5*H*)-ones, which may find its potential application.

Acknowledgments

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10. For intramolecular oxidative coupling of benzophenone to fluorenone (one example only), see Ref. 5b
11. For oxidative cyclization of *N*-benzoylindole and *N*-3-methoxybenzoylindole, see Ref. 5a and Dwight, T. A.; Rue, N. R.; Charyk, D.; Josselyn, R.; DeBoef, B. *Org. Lett.* **2007**, *9*, 3137.
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17. *Representative procedure for synthesis of indeno[1,2-b]indol-10(5H)-one from 3-benzoylindole (Table 2, entry 1):*
3-Benzoylindole (110 mg, 0.5 mmol), $Pd(OAc)_2$ (11 mg, 10 mol %) and K_2CO_3 (13 mg, 20 mol %) were taken in a round-bottomed flask. Pivalic acid (0.75 mL) was added to the mixture. The reaction mixture was stirred at 110 °C (silicon oil bath temperature) under open air. After completion of the reaction as indicated by TLC (21 h), the resultant mixture was cooled to room temperature, extracted with EtOAc and washed with saturated aqueous solution of Na_2CO_3. The organic solution was dried over anhyd Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (60–120 mesh) eluting with EtOAc–hexane. It afforded indeno[1,2-*b*]indol-10(5*H*)-one (93 mg, 85% yield). Reddish solid; mp >250 °C; IR(KBr): 3230, 2959, 1728, 1599, 1217 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 7.57–7.55 (m, 1H), 7.47–7.45 (m, 1H), 7.39 (t, J = 7.3 Hz, 1H), 7.34–7.24 (m, 3H), 7.17–7.15 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 185.0, 159.1, 142.2, 140.8, 135.0, 133.1, 130.3, 123.6, 123.4, 122.9, 122.8, 119.8, 119.5, 114.5, 114.1; MS (APCI) m/z: 220 (MH^+).
All oxidative couplings (Table 2) were performed following this experimental procedure.
The structures of all products were characterized by ^1H and ^{13}C NMR, IR, and Mass (APCI) (for known compounds) or HRMS (ESI) (for unknown compounds) spectroscopies. The data for known compounds are in accordance with the literature values.