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KO^{t}Bu-Mediated Aerobic Transition-Metal-Free Regioselective β-Arylation of Indoles: Synthesis of β-(2-/4-Nitroaryl)-indoles

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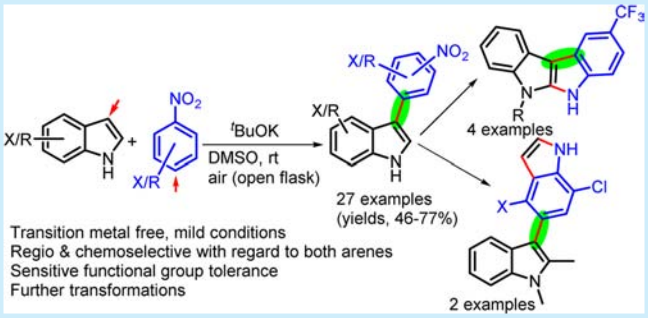
S *Supporting Information*

ABSTRACT: A KO^{t}Bu-mediated intermolecular oxidative C−C coupling of nitroarenes with indoles is presented in DMSO at room temperature in an open flask. By using this mild and economical methodology, syntheses of β-(2/4-nitroaryl)-indoles with sensitive functionalities such as bromo, iodo, cyano, and nitro were achieved chemo- and regioselectively. Synthesized β-(2/4-nitroaryl) indoles were transformed into densely functionalized biindoles, indoloindoles, and (4-aminoaryl)-indoles which demonstrate post-transformation utility of the developed methodology.

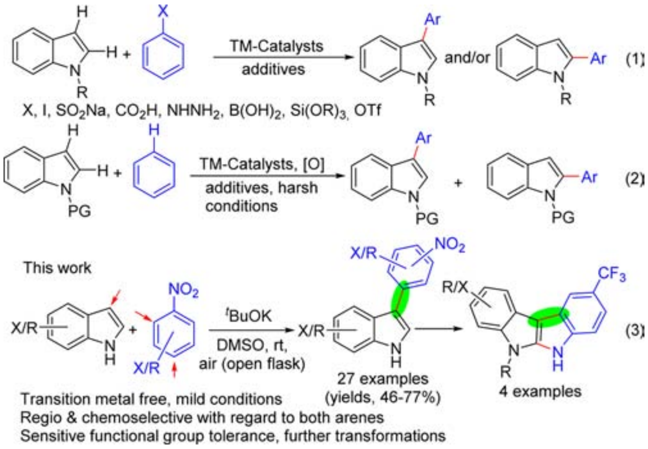


Transition metal free, mild conditions
Regio & chemoselective with regard to both arenes
Sensitive functional group tolerance
Further transformations

The direct transition-metal-free cross-coupling of two C−H bonds to C−C bond is an effective strategy for the synthesis of organic molecules. This approach exhibits several interesting features: a highly atom economic process, avoidance of expensive transition-metal-catalysts, particularly, palladium, mild reaction conditions, and generation of environmentally friendly side products.

Aryl-indoles and their analogues constitute a large number of biologically important pharmaceuticals, fragrances, agrochemicals, conducting polymers, and ligands.[1,2] As a result, several methodologies have been developed to construct aryl-indoles (Scheme 1).[3−5] Transition-metal-catalyzed coupling of aryl halides with indoles under heating conditions is one of the conventional routes to access aryl-indoles.[3a,b] Apart from aryl halides, benign coupling partners such as boronic acids, sodium sulfinates, acids, silanes, phenylhydrazine hydrate, and [Ph-I-Ph]BF$_4$ have been used for the synthesis of α-/β-aryl-indoles under palladium- or copper-catalyzed methodologies (eq 1).[3,4] Transition-metal-catalyzed approaches to the direct C-(β)-arylation of protected indoles using arenes have also been reported under harsh reaction conditions (eq 2).[5] Nonetheless, these reactions provide a mixture of α-, β-, and α,β-diaryl-indoles and are only suitable for the nonsubstituted and symmetrically substituted arenes, as regioselective coupling of arenes has not been achieved.[5] Deng and Liao et al. have meticulously achieved regioselective synthesis of β-aryl-indoles from cyclohexanone coupling partners utilizing a Pd(TFA)$_2$ and DPEphos catalytic system at 140 °C for 30 h.[5e] Most of the developed methodologies require costly transition-metal-catalysts, even more costly additives/ligands, and harsh reaction conditions to obtain aryl-indoles.

Scheme 1. Synthetic Routes to Aryl-Indoles



Transition metal free, mild conditions
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Transition-metal-free approaches for C−C coupling reactions have attracted considerable interest recently.[6−10] Itami and coworkers reported a transition-metal-free KO^{t}Bu-mediated C−C coupling of heteroarenes with aryl iodides.[6] Later Kwong, Lei et al., Shi et al., and others have presented KO^{t}Bu-mediated C−C coupling of unreactive arenes with aryl halides.[7,8a−d,f,h,k,l,9] Pioneering work on ^{t}BuO$^-$-mediated aerobic oxidative C−C coupling has been reported by Ess and Kürti et al. for the synthesis of α-arylated ketones.[10i] Our group has also studied KO^{t}Bu-mediated C−C coupling in phenols and benzamides using aryl halide coupling partners.[9]

Here for the first time, a transition-metal-free synthesis of β-aryl-indoles via intermolecular oxidative coupling of indole with inexpensive nitroarenes[10] is presented at rt (eq 3). Further, new

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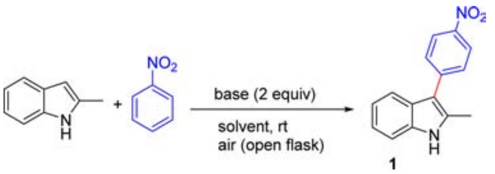
synthetic routes have been established to construct indoloindoles and biindoles which are difficult or inaccessible by existing methodologies.

For the optimization of reaction, we began with 2-methylindole and nitrobenzene coupling partners for screening of various solvents, bases, and additives to obtain β-aryl-indole **1** (Table 1). Bases such as K_2CO_3, Cs_2CO_3 and even LiO^{t}Bu did not provide any β-aryl-indole **1** and reactants 2-methylindole and nitrobenzene recovered quantitatively from the reaction (entries 1–3, Table 1). Interestingly, potassium and sodium *tert*-butoxides provided 74 and 68% yields, respectively, of oxidative coupled product **1** (entries 4 and 6, Table 1). Potassium and sodium hydride were also effective for the promotion of C–C coupling reaction (entries 10–11). Other strong bases KOH, and NaOH noticed to be less effective for the oxidative C–C coupling as poor yields of **1** was noticed. Next solvents such as DMF, DME, CH_3CN, EtOH, and benzene were screened in the reaction (entries 12–16), unfortunately, none of the solvents gave better yield of product **1**.

Table 1. Optimization of Reaction Conditions[a]



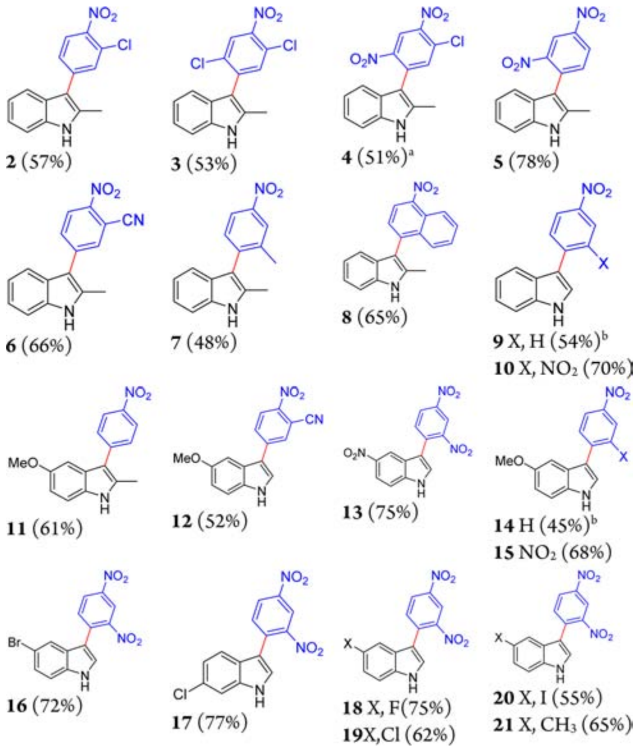
entry	base	solvent	time (h)	yield (%)
1	K_2CO_3	DMSO	12	NR
2	Cs_2CO_3	DMSO	12	NR
3	LiO^{t}Bu	DMSO	12	NR
4	**KO^{t}Bu**	**DMSO**	**3**	**74**
5	KO^{t}Bu (3 equiv)	DMSO	3	48
6	NaO^{t}Bu	DMSO	3	68
7	KO^{t}Bu + CuI	DMSO	3	68
8	KOH	DMSO	12	18
9	NaOH	DMSO	12	14
10	KH	DMSO	3	72
11	NaH	DMSO	3	65
12	KO^{t}Bu	DMF	3	40[b]
13	KO^{t}Bu	DME	12	trace
14	KO^{t}Bu	CH_3CN	12	<10
15	KO^{t}Bu	EtOH	12	NR
16	KO^{t}Bu/L[c]	benzene	12	20

[a]Reactions were carried out using 2-methylindole (1 mmol) and nitrobenzene (2 mmol) and base (2 mmol) in an open flask for indicated time. [b]Side products were also observed. [c]L, 1,10-phenanthroline.

After screening of bases and solvents, we studied the substrate scope of coupling partners utilizing two equiv of KO^{t}Bu in DMSO and results are presented in Scheme 2. 2-Chloronitrobenzene and 1,4-dichloro-2-nitrobenzene coupled with indole successfully to give respective β-aryl-indoles **2** and **3**. Interestingly, S_NAr C–C coupled product or dechlorination was not observed under the reaction conditions. Structure of β-(3-chloro-4-nitrophenyl)-2-methylindole **2** is also established by X-ray single crystal structure study, Figure 1 (*vide infra*).[11]

Next, 1-chloro-2,4-dinitrobenzene was coupled with indole which furnished β-aryl-indole **4** in 51% yield and formation of S_NAr product **5** by dehydrochlorination was also observed. Alternatively, β-aryl-indole **5** was prepared by the oxidative coupling of indole with 1,3-dinitrobenzene in 78% yield. Further, 2-nitrobenzonitrile, 1-methyl-3-nitrobenzene, and 1-nitronaphthalene reacted smoothly with indole under optimized conditions, leading to cyano-substituted-4-nitrophenyl-, methyl-substituted-, and 4-nitro-naphthyl indoles (**6**–**8**) in 48–66% yields. After variation of substitution in nitrobenzene, the substrate scope with respect to indole was studied. Unsubstituted indoles underwent oxidative coupling at the β-position leading various aryl-indoles **9**–**10** and **12**–**21** chemo- and regioselectively in 45–77% yields, and formation of α-aryl-indoles was not observed under the reaction conditions. However, oxidative C–N coupled products, 1-(4-nitrophenyl)-indoles, were also noticed along with the formation of β-aryl-indoles **9** and **14** (for detail information, see SI pp S7–S9). The desired β-aryl-indoles **9** and **14** were obtained as major products by carrying out the reaction at 100 °C.[12] Also electron-donating groups such as methyl, methoxy or withdrawing groups such as nitro, bromo, chloro at various positions in the benzene ring of indole could be tolerated under the reaction conditions and gave phenyl substituted β-aryl-indoles **11**–**21** in moderate to good yields.

Scheme 2. Synthesis of β-(4-Nitrophenyl)-1H-indoles



[a]Aryl-indole **5** (25%) was also formed by the coupling of C–Cl and C–H bonds via S_NAr pathway. [b] Reaction was carried at 100 °C; formation of respective C–N coupled product was observed at rt (see SI, pp S-7, S-9).

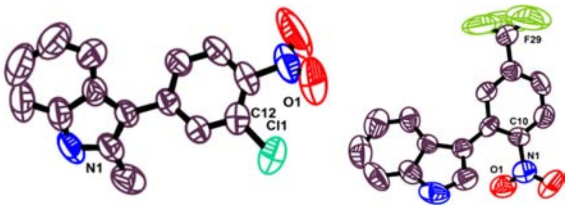
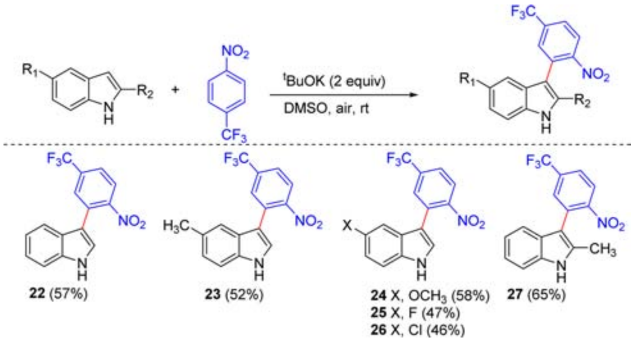


Figure 1. Crystal structures of β-(4/2-nitrophenyl)-indoles **2** and **22**.

On the other hand, electron-donating 2-ethyl, 3-amino, 3-methyl, and 4-methoxy-nitrobenzenes were observed to be unreactive, as only 3-methyl-nitrobenzene coupled with indole to form *β*-arylindole **7** in 48% yield.

β-(2-Nitroaryl)-indoles could be useful intermediates for the preparation of indoloindoles (*vide infra*). We envisaged the synthesis of *β*-(2-nitroaryl)-indoles by *ortho*-C−H coupling in nitrobenzenes with indoles. For this purpose, *para*-substituted 4-trifluoromethylnitrobenzene was reacted with indole under the optimized reaction conditions (Scheme 3). To our delight, 4-trifluoromethyl substituted nitrobenzene underwent *ortho*-C−H oxidative coupling with indole leading to *β*-(2-nitrophenyl)-indole **22** in moderate yield (57%).Oxidative *ortho*-C−H coupling in 4-trifluoromethylnitrobenzene was also confirmed by the single crystal study of *β*-aryl-indole **22** (Figure 1).[11]

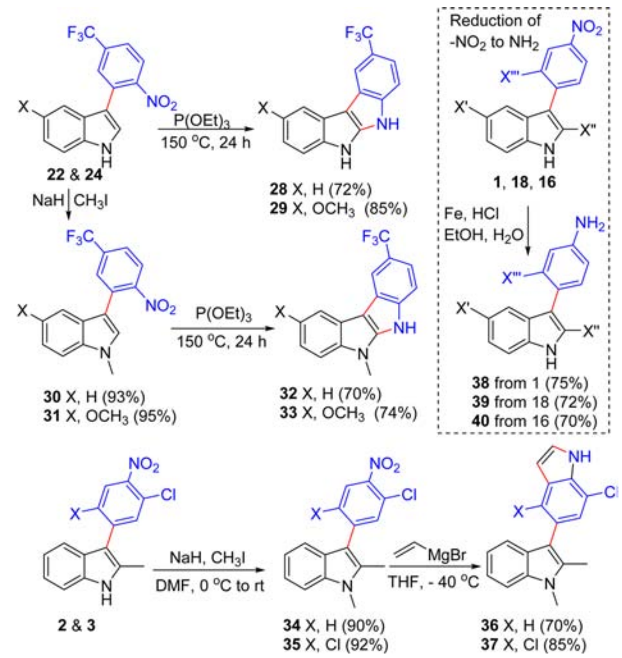
Scheme 3. Synthesis of *β*-(2-Nitrophenyl)-1*H*-indoles



Next, various substituted *β*-(2-nitrophenyl)-indoles **23**−**27** were readily synthesized by the *ortho*-C−H coupling of substituted indoles with 4-trifluoromethyl-nitrobenzene.[13]

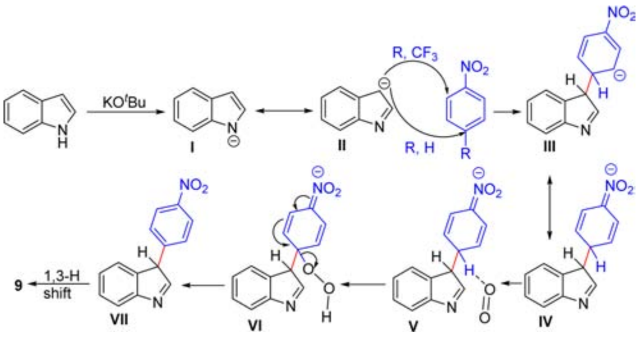
Further transformation of *β*-(2/4-nitro-aryl)-indoles was explored for the synthesis of indoloindoles, biindoles, and *β*-(2/4-amino-aryl)-indoles (Scheme 4). Construction of unsymmetrically *N*-substituted (*N*-R′ and *N*-R″) indoloindoles has been achieved earlier by Pal et al. from C-*α* amination of indoles using 2-iodo-*N*-arylsulfonylamines followed by ring closing, Pd-catalyzed coupling of the *β*-C−H bond with the C−I bond of amines.[2b] Moreover, synthesis of indolo[3,2*b*]indoles with both free N−H has not been documented.[14] Here synthesis of indoloindoles **28**−**29** has been accomplished by heating *β*-(2-nitrophenyl)-indoles **22** and **24** in $P(OEt)_3$ at 150 °C. Unsymmetrically N-substituted indoloindoles **32** and **33** were obtained from *N*-methyl-*β*-(2-nitrophenyl)-indoles **30** and **31**, respectively, by following the similar method. Next, we turn our attention to the synthesis of 3,5′-biindoles from *β*-(4-nitroaryl)-indoles. Addition of vinylmagnesium bromide to *N*-methyl-indoles **34** and **35** gave respective 3,5′-biindoles **36** and **37** in 70% and 85% yields. In the end, the nitro group in **1**, **18**, and **16** was converted into an amine using Fe-powder in EtOH/water and the resulted electron-rich aryl-indoles (**38**−**40**) were obtained in 70−75% yields.

Scheme 4. Further functionalization of *β*-nitroaryl indoles



A plausible mechanism is presented in Scheme 5 based on the reactivity as well as regio- and chemoselective outcome in the oxidative coupling of indoles with nitroarenes. It seems that the presence of the N−H group in indole is crucial for oxidative coupling with the nitrobenzene. The N−H group reacts with KO*t*Bu leading to indol-1-ide **I**, which converts into indol-3-ide **II** via resonance. Nucleophilic attack of **II** to the *para* position of nitrobenzene (if *para*-substituted, then *ortho* position) would lead to intermediate **III**, which might undergo resonance to form **IV**. Interaction of atmospheric oxygen with the hydrogen (shown in **V**, Scheme 5)[10i] could transfer hydrogen to oxygen leading to a hydroperoxide radical and carbon centered radical of intermediate **V**, which upon combination may yield intermediate **VI**.[10i] This intermediate may give 3-(4-nitrophenyl)-3*H*-indole **VII** which converts into the desired *β*-aryl-indole **9** by tautomerization. Since the reaction provided a moderate yield (40%) of product under an argon atmosphere, DMSO could also serve as an oxidant.

Scheme 5. Mechanism for Coupling of Indole with Nitroarene



In summary, we have shown that *β*-arylation in unprotected indoles could be achieved chemo- and regioselectively by employing KO*t*Bu at room temperature in air without using the TM catalyst and aryl halide coupling partner. Because of the mild conditions, this methodology tolerates sensitive functionalities such as iodo, bromo, chloro, and nitro on indole and chloro and nitro on nitroarene coupling partners. *β*-(2-Nitroaryl)-indoles were also accessed by using 4-substituted nitrobenzenes. Postmodification of the nitro group in *β*-(2/4-nitroaryl)-indoles has also been demonstrated for the synthesis of indoloindoles, and biindoles. Currently, oxidative coupling of another class of aromatic amines is in progress in our laboratory.

ASSOCIATED CONTENT

Supporting Information

Experimental details, NMR spectra, and X-ray crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(11) CCDC Nos. 1021166 (**22**)−1021167 (**2**); see Supporting Information (SI), pp S116−S131.

(12) Presumably, indol-3-ide **II** dominates over indol-1-ide **I** at a high temperature (see SI, p S7).

(13) Synthesized β-(2/4-nitroaryl)-indoles show various colors ranging from yellow, orange, to brick red (see SI, Figures S30−S31).

(14) (a) Synthesis of advanced functionalized indoles (see also ref 2b): Prasad, B.; Adepu, R.; Sandra, S.; Rambabu, D.; Krishna, G. R.; Reddy, C. M.; Deora, G. S.; Misra, P.; Pal, M. *Chem. Commun.* **2012**, *48*, 10434. (b) Prasad, B.; Sreenivas, B. Y.; Krishna, G. R.; Kapavarapu, R.; Pal, M. *Chem. Commun.* **2013**, *49*, 6716. (c) Prasad, B.; Sreenivas, B. Y.; Sushma, A.; Yellanki, S.; Medisetti, R.; Kulkarni, P.; Pal, M. *Org. Biomol Chem.* **2014**, *12*, 2864.