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Iron-catalyzed oxidative homo-coupling of indoles via C–H cleavage

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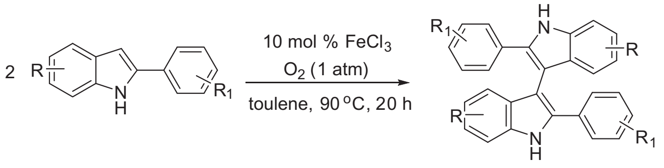
ABSTRACT

A new method for the homo-coupling of indoles has been developed by the use of $FeCl_3$ as catalyst and molecular oxygen as the only oxidant. The protocol provides a practical and straightforward approach toward 3,3′-biindolyls.

3, 3’-Biindolyls are useful structural units that are frequently found in pharmaceuticals and functional materials.[1] Accordingly, synthesis and functionalization of 3,3′-biindolyls have attracted much attention over decades.[2] The general method for the preparation of 3,3′-biindolyls involves the nucleophilic attack of indoles to istain in the presence of dimethylamine to give 3-(3-indoly)3-hydroxyoxindole. The subsequent reduction by stoichiometric $NaBH_4$ and $BF_3{\cdot}Et_2O$ affords the desired products in moderate yields.[3] Recently, transition metal-catalyzed cross-coupling reaction has emerged as the powerful synthetic tools,[4] and these protocols have successfully been employed in the synthesis of biindolyls.[5] For example, Chai reported the palladium catalyzed Suzuki–Miyaura cross-coupling of the indolyl halides with indolyl boronic compounds to give 3,3′-biindolyls efficiently.[6] However, the prefunctionalization of indoles to their halides or boronic derivatives is required for these transformations. From both scientific and environmental points of view, the development of methodology for direct activation of C–H bond is of great significance, and metal catalyzed C–H bond functionalization has attracted much attention currently.[7] Recently, Shi et al. reported the oxidative dimerization of indole derivatives to give 3,3′-linked products via Pd catalyzed direct C–H transformations in presence of stoichiometric $AgNO_3$ as oxidant and $MgSO_4$ as additive.[8] Our group also developed a new access to 2,3′-linked biindolyl scaffolds recently using catalytic $Pd(TFA)_2$ with 1.5 equiv $Cu(OAc)_2{\cdot}H_2O$ as oxidant.[9] Though these reactions represent the most attractive transformation for biindolyl formation, the use of expensive palladium and stoichiometric heavy-metal oxidants limits their wider application.

Iron has been increasingly explored in organic transformations because of its low price, nontoxicity, and environmentally benign characters.[10] Although the iron-catalyzed formation of C–C[11] and C-heteroatom[12] bonds has been developed in recent years, the direct formation of C–C bonds through iron-catalyzed C–H bond activation is still rare.[13] Herein, we report a mild and selective method for dimerization of N-free indoles by iron catalysis employing oxygen as the oxidant to afford 3,3′-biindolyls in good to moderate yields (Scheme 1). The method using oxygen instead of heavy-metals as oxidant offers a more economical and environment benign process.

On the outset of our study,[9,14] 2-phenylindole **1a** was chosen as the model substrate to probe the reaction conditions by use of 10 mol % $FeCl_3$ catalyst in toluene at 90 °C for 20 h under nitrogen atmosphere (Table 1). The desired 3,3′-homo-coupling product **2a** was isolated in 7% yield when *tert*-butyl hydroperoxide (TBHP) was used as stoichiometric oxidant (Table 1, entry 1). Although the yield was quite low, it was promising since the result indicated the possibility of oxidative homo-coupling of indoles at C3 position via iron-catalyzed C–H presence activation. The developed result was obtained when di-*tert*-butyl peroxide (*t*BuOO*t*Bu) was utilized as oxidant (Table 1, entry 2). No desired product was detected by



Scheme 1. Iron(III) catalysed oxidative homo-coupling of 2-arylindoles.

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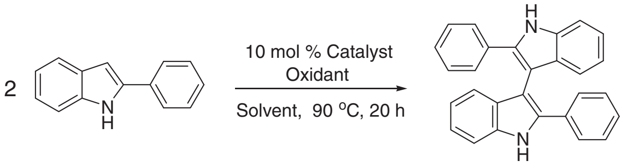
Table 1
Oxidative homo-coupling of 2-phenylindole under various conditions[a]



1 a 2 a

Entry	Catalyst	Oxidative	Solvent	Yield[b] (%)
1	$FeCl_3$	TBHP	Toluene	7[c]
2	$FeCl_3$	*t*BuOO*t*Bu	Toluene	15[d]
3	$FeCl_3$	DDQ	Toluene	n.r[d]
4	$FeCl_3$	Oxone	Toluene	45[d]
5	$FeCl_3$	Air	Toluene	37
6	$FeCl_3$	O_2	Toluene	61
7	$CuCl_2$	O_2	Toluene	n.r
8	$PdCl_2$	O_2	Toluene	n.r
9	$Pd(OAc)_2$	O_2	Toluene	n.r
10	$NiCl_2$	O_2	Toluene	n.r
11	$FeCl_3{\cdot}6H_2O$	O_2	Toluene	43
12	$FeCl_2$	O_2	Toluene	12
13	$Fe(acac)_3$	O_2	Toluene	9
14	Fe_2O_3	O_2	Toluene	n.r
15	—	O_2	Toluene	n.r
16	$FeCl_3$	O_2	DCE	29
17	$FeCl_3$	O_2	CH_3CN	n.r
18	$FeCl_3$	O_2	DMF	n.r
19	$FeCl_3$	O_2	EtOAc	<10
20	$FeCl_3$	O_2	THF	n.r
21	$FeCl_3$	O_2	Toluene	42[e]

[a] Reaction conditions: 2-phenylindole (1 mmol), catalyst (0.1 mmol), solvent (4 mL), at 90 °C for 20 h, under oxygen atmosphere.

[b] Isolated yields based on 2-phenylindole.

[c] TBHP (1.5 equiv, 1.5 mmol) 0.30 mL, 5–6 M in decane, under nitrogen atmosphere.

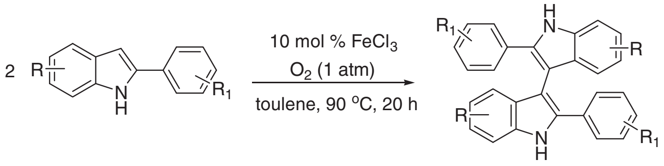
[d] Oxidant (1.5 equiv, 1.5 mmol) under nitrogen atmosphere.

[e] 1.5 equiv *p*-hydroquinone was added.

the addition of 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) (Table 1, entry 3). When potassium peroxomonosulfate (oxone) was used as oxidant, the yield of **2a** was remarkably increased to 45% (Table 1, entry 4). To our delight, the desired homo-coupling product was delivered in 37% yield in air instead of the hazardous and toxic peroxides (Table 1, entry 5). The optimal result was further revealed by the use of oxygen and a 61% isolated yield was obtained (Table 1, entry 6). Treatment of 2-phenylindole with other transition metals including copper, palladium, and nickel failed to give the product (Table 1, entries 7–10). The desired 3,3′-biindolyl product was also obtained when $FeCl_3{\cdot}6H_2O$ was applied as catalyst, but in lower yield (43%) (Table 1, entry 11). Other iron reagents such as $FeCl_2$, $Fe(acac)_3$, and Fe_2O_3 were found to be ineffective (Table 1, entries12–14). No reaction was observed in the absence of metal catalyst (Table 1, entry 15). A study of the reaction in various solvents identified toluene as the suitable alternative to DCE, acetonitrile, DMF, EtOAc, and THF (Table 1, entries 16–20).

The generality of this transformation was examined under the optimized reaction conditions, and the results are summarized in Table 2. A broad range of 2-arylindole bearing both electron-donating and electron-withdrawing substituents on the 2-aryl ring of indole could be successfully used in the homo-coupling reaction to synthesize the desired 3,3′-biindolyls in good to moderate yields (Table 2, entries 1–19). Notably, the carbon–halogen bonds in 2-aryl ring could tolerate the reaction conditions, which made it particularly attractive for the further assembly through the cross-coupling reactions (Table 2, entries 8–14). The location of substituents on 2-aryl rings played an important role in this reaction. *Ortho*-substituted of 2-aryl ring of indoles gave the coupling products in lower yields compared with *para*- or *meta*-substituted (Table 2, entries 4 and 11). This might be due to the increased steric hindrance during the coupling process. The reaction also proceeded well when changing the substituents on the indole ring (Table 2, entries 16–19). However, the reaction was sluggish when indole and 2-methylindole were as the substrate.

Table 2
Substrate scope of iron(III)-catalyzed oxidative homo-coupling of substituted 2-arylindoles[a]



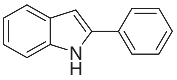
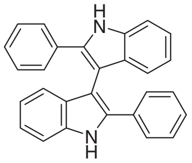
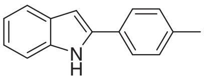
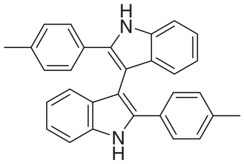
Entry	Substrate	Product	Yield[b] (%)
1			61
2			56

Table 2 (*continued*)

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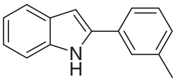
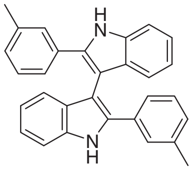
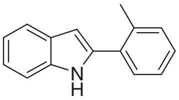
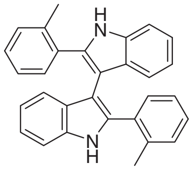
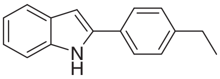
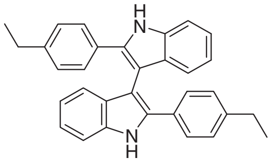
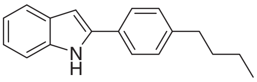
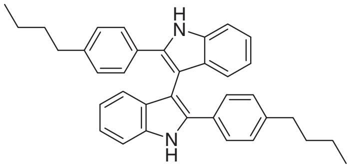
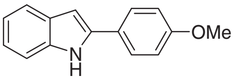
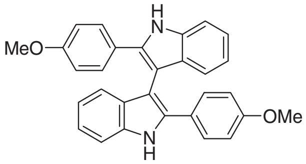
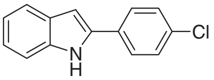
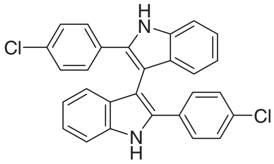
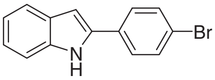
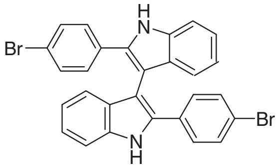
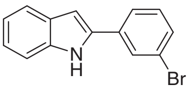
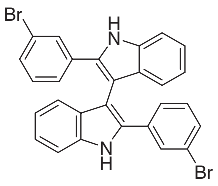
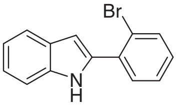
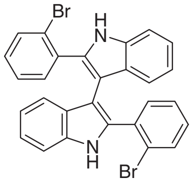
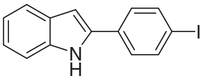
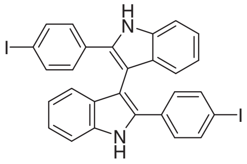
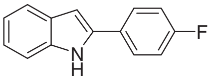
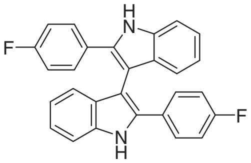
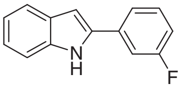
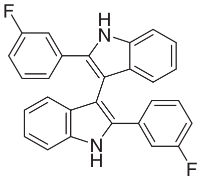
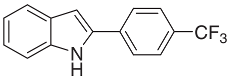
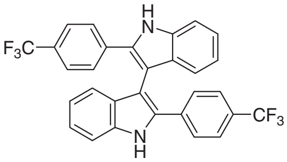
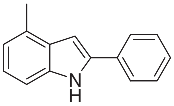
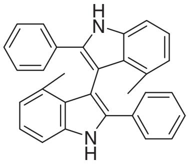
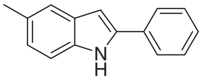
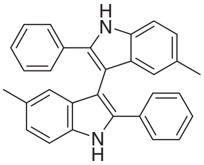
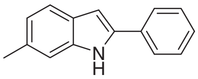
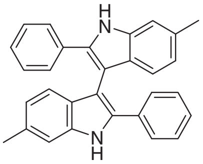
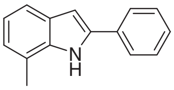
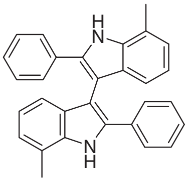
3			73
4			43
5			51
6			48
7			55
8			71
9			62
10			71
11			49
12			68

(*continued on next page*)

Table 2 (*continued*)

Entry	Substrate	Product	Yield[b] (%)
13			50[c]
14			73
15			56[c]
16			60
17			56
18			68
19			75

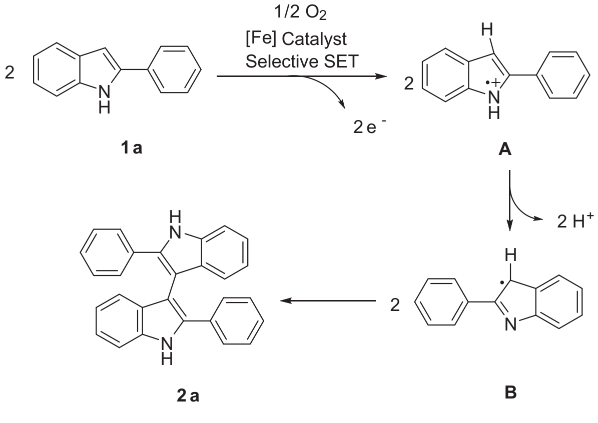
[a] Conditions: 2-arylindoles (0.6 mmol), $FeCl_3$ (0.06 mmol), toluene (4 mL), 90 °C, 20 h in 1 atm oxygen atmosphere unless otherwise noted.

[b] Isolated yields.

[c] The reaction condition was at 120 °C for 24 h.

The detailed mechanism of this homo-coupling reaction is not clear at the current stage. Based on the findings of previous studies,[15] a tentative mechanism for the transformation as shown in Scheme 2. The reaction is initiated by the iron assisted single-electron-transfer (SET) oxidation of the 2-phenylindole **1a** to form the nitrogen cation radical **A**. The following hydrogen abstraction of radical **A** generates the intermediate **B**, which is combined with another **B** to give the corresponding 3,3′-biindolyls **2a**.[16] We performed the reaction in the presence of 1.5 equiv free-radical scavenge of *p*-hydroquinone and found that the yield was drastically decreased (Table 1, entry 21). This result supports the proposed radical pathway.

In conclusion, we have demonstrated a new method for the direct formation of 3,3′-biindolyls by an iron-catalyzed dimerization



Scheme 2. Proposed mechanism.

of 2-arylindole using molecular oxygen as the only oxidant. The reaction proceeded well for a range of electron-rich as well as electron-poor 2-arylindoles and is tolerant of functional group such as chlorine, bromine, and iodine. The reaction provides a facile and efficient route to the preparation of 3,3′-biindolyls.

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Supplementary data

Supplementary data (general synthetic method, ^{1}H NMR, ^{13}C NMR and HRMS-EI data of the products) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.10.088.

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16. *The typical procedure for the preparation of 3,3′-biindolyls*: To a solution of 2-phenyl-1*H*-indole (0.6 mmol, 116 mg) in toulene (4.0 mL) was added FeCl$_3$ (10 mg, 0.06 mmol, 10 mol %). The resulting mixture was then heated under oxygen atmosphere at 90 °C for 20 h. When the reaction was completed, as determined by TLC analysis, the reaction mixture was cooled to room temperature and filtered through a pad of cellite. The solvent was removed under reduced pressure and the residue was purified on a silica gel column using ethyl acetate/petroleum ether (1:10) as an eluent to afford the indicated compound **2a** as white solid.^{1}H NMR (400 MHz, DMSO-d_6, TMS) δ 11.64 (s, 2H), 7.61 (d, J = 7.6 Hz, 4H), 7.54 (d, J = 8.4 Hz, 2H), 7.21 (t, J = 7.6 Hz, 4H), 7.15–7.10 (m, 4H), 7.02 (d, J = 8.0 Hz, 2H), 6.87 (t, J = 7.6 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 137.0, 135.1, 133.4, 129.9, 128.8, 127.3, 126.8, 122.3, 119.8, 119.6, 111.8, 106.8.