Enantioselective synthesis of atropisomeric indoles via iron catalysed oxidative cross-coupling

Richard R. Surgenor[1], Xiangqian Liu[1], William Myers[2] & Martin D. Smith[1]*

[1]Chemistry Research Laboratory, University of Oxford, 12 Mansfield Road, Oxford, OX1 3TA, UK.
[2]Inorganic Chemistry Laboratory, University of Oxford, South Parks Road, Oxford, OX1 3QR, UK.

E-mail: martin.smith@chem.ox.ac.uk; homepage: http://msmith.chem.ox.ac.uk/

Abstract

Heterobiaryl compounds that exhibit axial chirality are of increasing value and interest across several fields, but direct oxidative methods for their enantioselective synthesis are elusive. Here we disclose that an iron catalyst in the presence of a chiral PyBOX ligand and an oxidant enables direct coupling between naphthols and indoles to yield atropisomeric heterobiaryl compounds with high levels of enantioselectivity. The reaction exhibits remarkable chemoselectivity and exclusively yields cross-coupled products without competing homocoupling. Mechanistic investigations enable us to postulate that an indole radical is generated in the reaction but that this is likely an off-cycle event, and that the reaction proceeds through formation of a chiral Fe-bound naphthoxy radical which is trapped by a nucleophilic indole. We envision that this simple, cheap, and sustainable catalytic manifold will facilitate access to a range of heterobiaryl compounds and enable their applications across the fields of materials science, medicinal chemistry, and catalysis.

Atropisomeric biaryls comprise a privileged class of compounds whose applications span the fields of medicinal chemistry, catalysis and materials science; as such, a panoply of elegant and efficient methods have been developed for their synthesis[1]. The most convergent route to biaryls is generally the transition metal mediated cross-coupling of two partners[2,3] (although significant advances in metal-free methods have been demonstrated recently)[4]. Whilst this strategy generally results in cross-coupled products in good yields and predictable levels of chemo- and regioselectivity, these advantages may be offset by the requirement to synthesize two specifically functionalized coupling partners (Figure 1a)[5]. In principle, oxidative coupling represents a more direct, atom economic and environmentally benign approach as it creates the desired aryl-aryl linkage from two C–H bonds[6,7]. This realization has led to a significant number of oxidative *homo*-coupling procedures that can generate C_2-symmetric BINOL-like structures in an enantioselective fashion. These include reactions mediated by transition metals including copper[8-10], iron[11] and vanadium,[12] amongst others. However, in the absence of specific functional groups, controlling the regio-, chemo- and enantioselectivity of the corresponding *hetero*-couplings remains a formidable challenge, and successful examples have been limited to the synthesis of BINOL or NOBIN type scaffolds[13-16]. In particular, Katsuki demonstrated that iron salan complexes are effective in the enantioselective heterocoupling of naphthols[17], and Pappo showed that chiral iron phosphate complexes act as effective precatalysts for the enantioselective synthesis of non C_2-symmetric BINOLs (Figure 1b)[18]. We considered whether this oxidative cross-coupling approach could be used in the development of a method for the enantioselective synthesis of axially chiral indoles, which are emerging as a valuable member of the atropisomeric biaryl family[19-21].

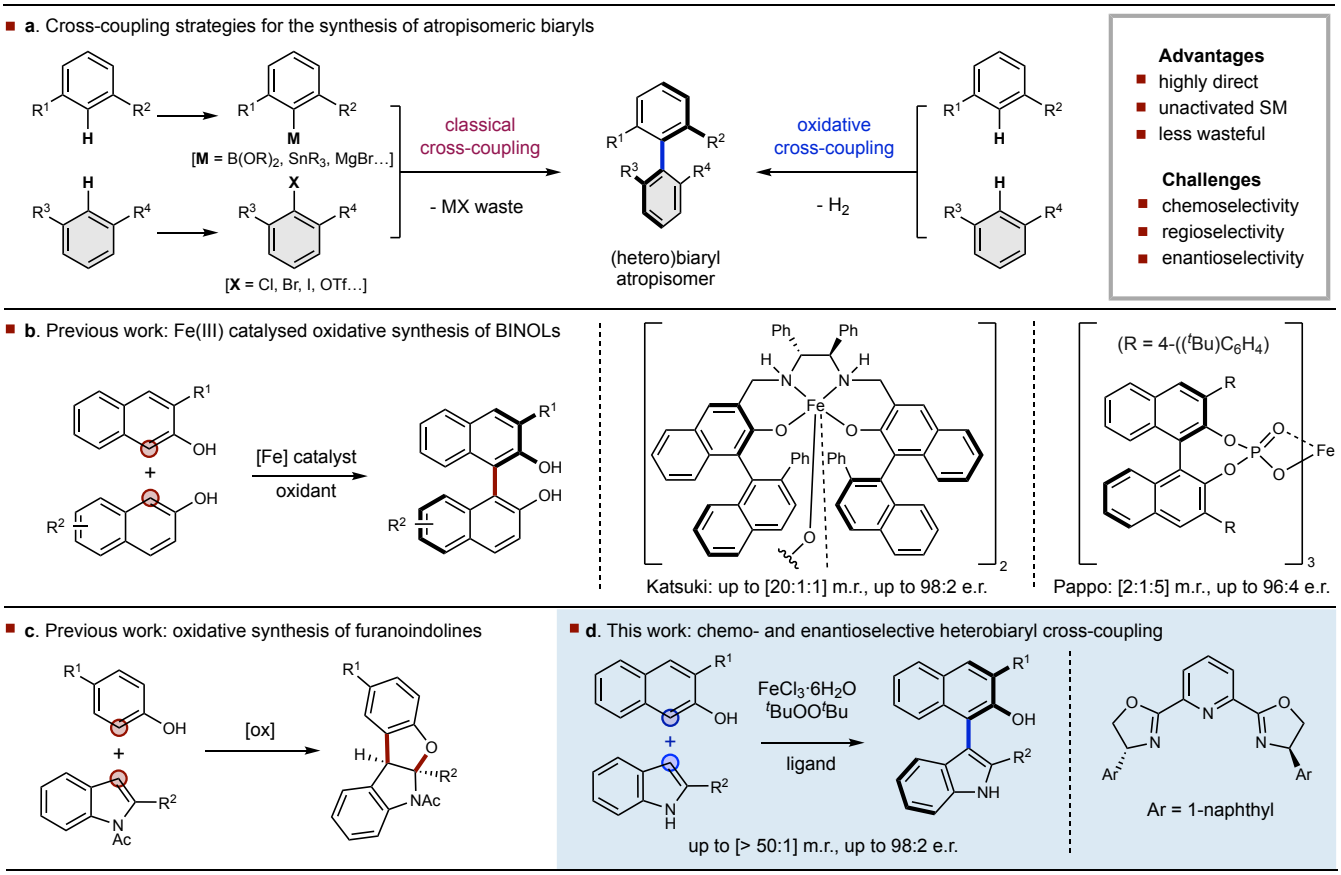
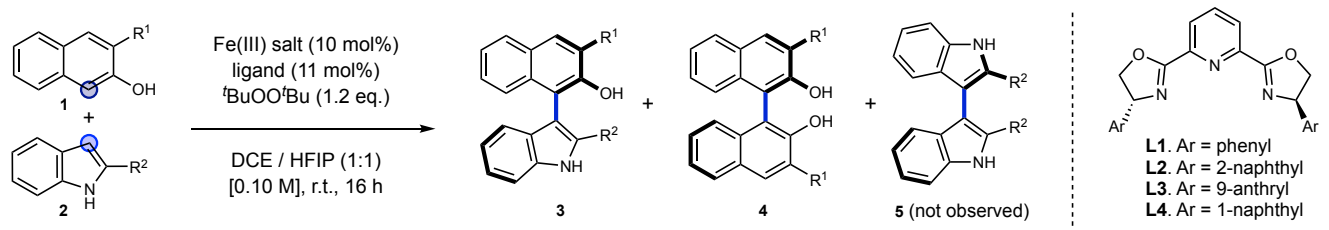


Figure 1. Oxidative cross coupling reactions. a Cross-coupling strategies to assemble biaryls include transition metal catalysed cross-coupling between specifically functionalized partners and direct oxidative cross-coupling where the desired aryl-aryl linkage is formed from two C–H bonds. **b** Previous work: iron catalysed enantioselective oxidative syntheses of C_1-symmetric BINOLs. m.r. = molar ratio of *hetero*-coupled : *homo*-coupled : *homo*-coupled products. e.r. = enantiomeric ratio. **c** Previous work: synthesis of benzofuranoindolines by oxidative coupling has been achieved by a variety of different methods ([ox] = oxidant). **d** This work: direct chemo- and enantioselective cross-coupling to form configurationally stable heterobiaryls.

Oxidative cross-couplings between indoles and phenols have been disclosed in the synthesis of benzofuranoindolines[22,23], which are key components of complex natural products including diazonamide and phalarine (Figure 1c). A range of oxidants (including hypervalent iodine reagents[24], iron(III) salts[25] and electrochemistry[26]) have been successfully employed in such cross-coupling reactions, some of which demonstrate exceptional levels of cross-coupling selectivity. We reasoned that if the steric bulk on the phenol, and particularly the indole component was increased, the overall process could favour rearomatization rather than [3+2] annulation to generate an atropisomeric heterobiaryl (Figure 1d). We began by screening a range of oxidants for the reaction between a 1:1.1 mixture of 2-naphthol and 2-methylindole. In a preliminary screen of conditions (see supplementary information S25), hypervalent iodine reagents and VOF_3[27] were poorly selective for the desired heterocoupling process, whilst $[Cu(OH)\cdot TMEDA]_2Cl_2$ in air favoured formation of the homocoupled BINOL product. We were delighted to find that catalytic iron(III) chloride in 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) with di-*tert*-butylperoxide as co-oxidant[28,29], gave exclusively the cross-coupled heterobiaryl product **3a** in 96% yield, as a single indole C-3 regioisomer (Table 1, entry 1). The remarkable selectivity of this reaction is noteworthy: we do not observe any trace of the potential homocoupled BINOL **4** or 3,3'-bisindole side **5** products. The rotational barrier of this product was determined to be $\Delta G^{\ddagger}_{353K}$ = 26.0 kcal mol^{-1}; the potential configurational lability of this material (a class 2 atropisomer)[30] motivated us to continue to investigate compounds with higher rotational barriers. We reasoned that a larger substituent at the C-2 position of the indole would significantly increase the barrier to rotation of the product. Hence, we subjected 2-*tert*-butylindole to the same reaction conditions; this afforded 39% of the desired heterocoupled product **3b** in addition to a 48% yield of the homocoupled BINOL product (Table 1, entry 2). One strategy to mitigate homocoupling is to modulate the oxidation potential and nucleophilicity of the phenol component through the installation of an electron withdrawing group[31-33]. When a naphthol bearing a C-3 methyl ester was used in the cross-coupling reaction with 2-*tert*-butylindole without a large excess of either component, exclusive formation

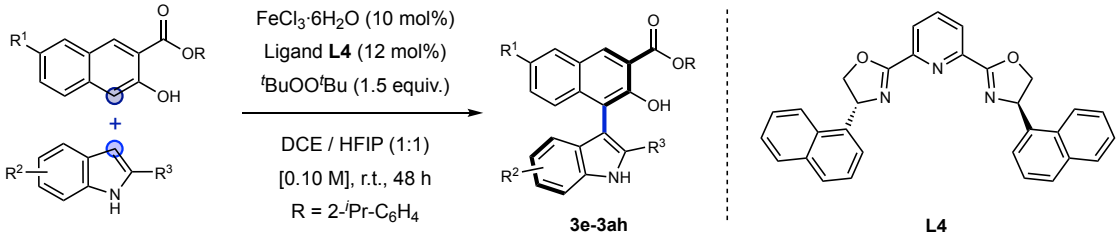
of the cross-coupled product **3c** was observed in 89% yield (Table 1, entry 3). The rotational barrier of this molecule was determined to be $\Delta G^{\ddagger}_{413K}$ = 38.3 kcal mol^{-1}; a barrier of this magnitude essentially precludes racemisation unless forcing thermal conditions are employed.

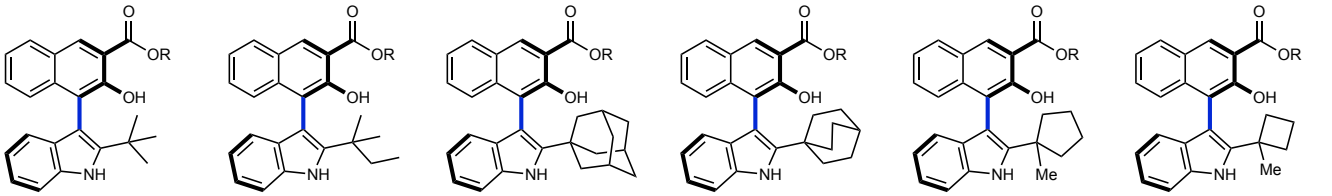


Entry	[Fe] salt	Ligand	Heterobiaryl	R^1	R^2	Yield of 3 (4)	[3:4] m.r.	e.r. of 3
1[a]	$FeCl_3$	none	**3a**	H	Me	96%	>50:1	n/a
2[a]	$FeCl_3$	none	**3b**	H	^{t}Bu	39% (48%)	5:6	n/a
3[a]	$FeCl_3$	none	**3c**	CO_2Me	^{t}Bu	89%	>50:1	n/a
4[a]	$FeCl_3$	**L1**	**3c**	CO_2Me	^{t}Bu	56%	>50:1	60:40
5[a]	$FeCl_3{\cdot}6H_2O$	**L1**	**3c**	CO_2Me	^{t}Bu	80%	>50:1	70:30
6	$FeCl_3{\cdot}6H_2O$	**L1**	**3c**	CO_2Me	^{t}Bu	60%	>50:1	75:25
7	$FeCl_3{\cdot}6H_2O$	**L1**	**3d**	CO_2Ph	^{t}Bu	67%	>50:1	84:16
8	$FeCl_3{\cdot}6H_2O$	**L2**	**3d**	CO_2Ph	^{t}Bu	63%	>50:1	88:12
9	$FeCl_3{\cdot}6H_2O$	**L3**	**3d**	CO_2Ph	^{t}Bu	58%	>50:1	75:25
10	$FeCl_3{\cdot}6H_2O$	**L4**	**3d**	CO_2Ph	^{t}Bu	71%	>50:1	89:11
11[b]	$FeCl_3{\cdot}6H_2O$	**L4**	**3d**	CO_2Ph	^{t}Bu	75%	>50:1	90:10
12[b]	$FeCl_3{\cdot}6H_2O$	**L4**	**3e**	CO_2R^*	^{t}Bu	63%	>50:1	92:8
13[b,c,d]	$FeCl_3{\cdot}6H_2O$	**L4**	**3e**	CO_2R^*	^{t}Bu	91%[e]	>50:1	94:6

Table 1: Reaction Optimization. Conditions: performed on 0.1 mmol scale, Fe salt (10 mol%), ligand (11 mol %) naphthol (1.0 eq.), indole (1.1 eq.), ^{t}BuOO^{t}Bu (1.2 eq.), DCE/HFIP, 1:1 (v/v); [naphthol] = 0.1 M, r.t., 16 h. Yields and molar ratios (m.r.) of products determined by quantitative ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard. Numbers in parentheses refer to yields of homocoupled (BINOL) product; e.r. = enantiomeric ratio, determined by chiral stationary phase HPLC; R* = 2-isopropylphenyl; [a] [naphthol] = 0.2 M. [b] 12 mol% ligand used. [c] $FeCl_3{\cdot}6H_2O$ pulverized by sonication in DCE for 30 min before adding ligand. [d] indole (1.5 eq.), ^{t}BuOO^{t}Bu (1.5 eq.), 48 h. [e] isolated yield.

With an effective catalyst system in hand for the chemoselective production of the desired heterobiaryl, we focused on selection of an appropriate chiral ligand to facilitate an atropselective reaction. We discovered that ligands of the bis-oxazoline family were viable for an enantioselective transformation, with phenyl substituted PyBOX ligand **L1** affording the heterocoupled product in the presence of anhydrous iron(III) chloride in a modest 60:40 e.r.[34] Both yield and e.r. were improved (80% yield at 75:25 e.r.) on switching to the hexahydrate salt (which is both cheaper and easier to handle; Table 1, entry 5). We recognized that the group at C-3 of the naphthol partner might also have an impact beyond enhancing chemoselectivity and found that e.r. of **3d** increased (to 84:16) with a larger (phenyl) ester group. We subsequently explored different PyBOX ligands in combination with changes at the C-3 ester, finding that the combination of 1-naphthyl substituted PyBOX ligand **L4** with a 2-isopropylphenyl ester substrate afforded the heterobiaryl product **3e** in 63% yield and 92:8 e.r. (Table 1, entry 12). Modulation of reaction time, an increase in the quantity of ligand (to 12 mol%) and indole (to 1.5 eq.) and sonication of the Fe salt prior to ligand addition all continued the aggregation of marginal gains to ultimately afford the desired heterocoupled biaryl product in 91% yield and 94:6 e.r. With an optimized set of reaction conditions, we explored the substrate scope for the reaction (Figure 2). In all cases, the mass balance is accounted for as unreacted naphthol starting material, and the 3,3'-bisindole product **5** is not observed.





3e 91%; (93%)
[>50:1]; 94:6 e.r.

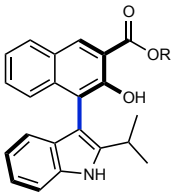
3f 83%; (92%)
[>50:1]; 95:5 e.r.

3g 71%; (88%)
[>50:1]; 91:9 e.r.

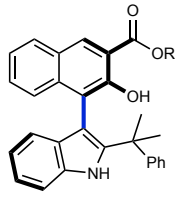
3h 80%; (86%)
[>50:1]; 86:14 e.r.

3i 75%; (95%)
[>50:1]; 94:6 e.r.

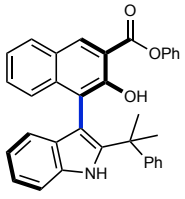
3j 90%; (94%)
[>50:1]; 96:4 e.r.



3k 93%; (98%)
[>50:1]; 60:40 e.r.



3l 80%; (91%)
[>50:1]; 96:4 e.r.



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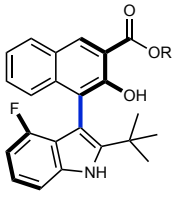

3n 80%; (94%)
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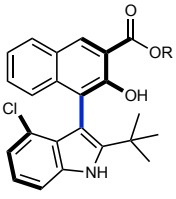

3o 82%; (90%)
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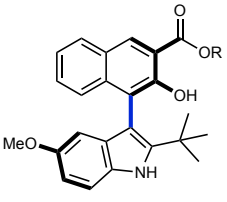
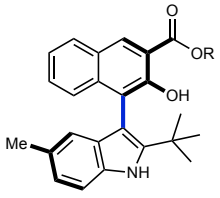


3p 97%; (99%)
[>50:1]; 93:7 e.r.



3q 78%; (89%)
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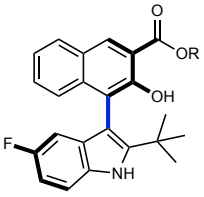

3r 60%; (90%)
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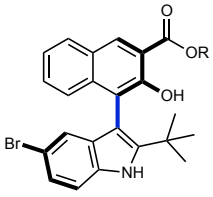

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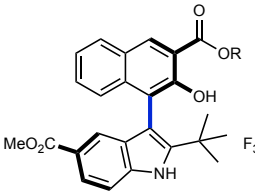
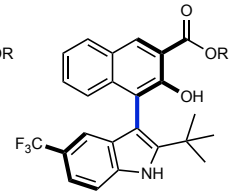


3t 40%; (92%)
[18:1]; 85:15 e.r



3u 28%; (97%)
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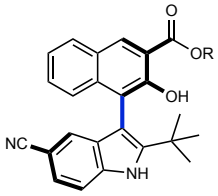

3v 13%; (97%)
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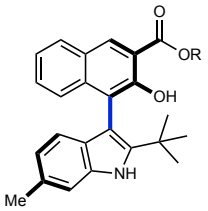

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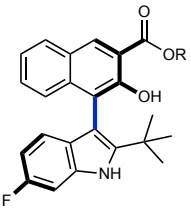
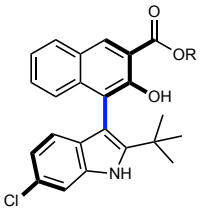


3x 63%; (100%)
[45:1]; 84:16 e.r.



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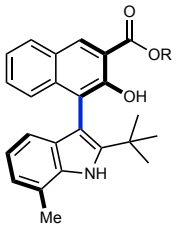

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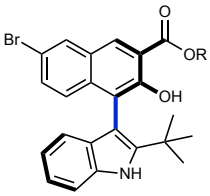

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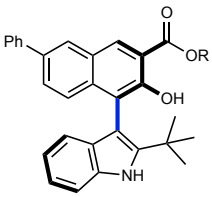

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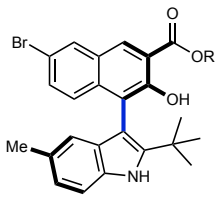

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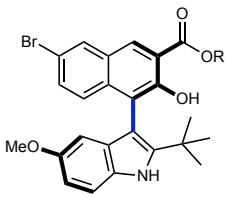

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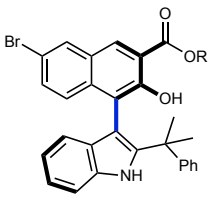
[>50:1]; 91:9 e.r.



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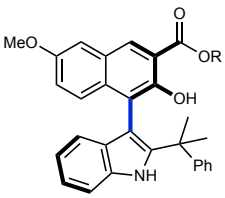

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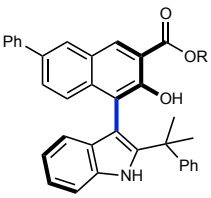
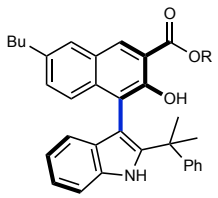


3ag 45%; (85%)
[>50:1]; 95:5 e.r.



3ah 66%; (80%)
[>50:1]; 93:7 e.r.

Figure 2. Scope of Enantioselective Indole-Naphthol Coupling. Reaction Conditions: All performed on 0.1 mmol scale: $FeCl_3 \cdot 6H_2O$ (10 mol%), ligand **L4** (12 mol%) naphthol (1.0 eq.), indole (1.5 eq.), $^tBuOO^tBu$ (1.5 eq.), DCE/HFIP, 1:1 (v/v); [naphthol] = 0.10 M, r.t., 48 h. Yields refer to isolated and purified material. Figures in parentheses indicate yields based upon remaining naphthol starting material determined by quantitative ^1H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard. Figures in square brackets represent the ratio of [heterocoupled biaryl **3** : homocoupled BINOL **4**] determined by quantitative ^1H NMR spectroscopy; e.r. = enantiomeric ratio, determined by chiral stationary phase HPLC.

The size of the indole C-2 substituent is important in determining the rotational barrier of the biaryl products and hence we explored substrates with sterically hindered groups in this position. An indole bearing a *tert*-amyl group couples effectively to afford **3f** in 83% yield and high enantioselectivity (95:5 er) with no trace of other products. Similarly, 2-adamantyl and bicyclo[2.2.2.]octane groups are also tolerated to afford **3g** (71% yield; 91:9 e.r.) and **3h** (80% yield; 86:14 e.r.) with good levels of selectivity. Other cycloalkyl groups including 2-methylcyclopentyl and 2-methylcyclobutyl are also effective in this reaction, affording biaryls **3i** (75% yield, 94:6 e.r.) and **3j** (90% yield, 96:4 e.r.) respectively. Changing to a smaller group at this position such as *iso*-propyl does not impact cross-coupling efficiency or chemoselectivity (affording **3k** in 93% yield as the sole product) but does lead to a significant reduction in enantioselectivity (to 60:40 e.r.). Enantioselectivity is restored with an indole bearing an α,α-dimethylbenzyl group (to afford **3l** in 80% yield and 96:4 e.r.). The combination of a phenyl ester on the naphthol with the α,α-dimethylbenzyl indole was also viable and more selective in this reaction, generating **3m** in 85% yield and 98:2 e.r. We subsequently explored substitution around the indole ring, and indoles bearing halogens such as fluorine or chlorine both undergo oxidation without incident to afford biaryls **3n** (80% yield, 90:10 e.r.) and **3o** (82% yield, 94:6 e.r.) respectively. We next examined C-5 substitution on the indole reactant. Electron donating groups such as methoxy are highly effective, affording biaryl **3p** in 97% yield and 93:7 e.r. 5-Alkyl groups are also well tolerated, affording biaryl **3q** in 78% yield and 93:7 e.r. We observed that electron withdrawing groups such as fluorine in this position led to lower conversions as in **3r** (60% yield, 92:8 e.r.), and considered that this may provide some insight into the mechanism of this transformation. Consequently, we decided to study a series of different electron withdrawing groups in this position to evaluate the impact on the reaction. A 5-bromo substituent led to biaryl **3s** in only 40% yield, but with a relatively high enantioselectivity (90:10 e.r.). More powerful electron withdrawing groups on the indole coupling partner led to the generation of biaryls bearing an ester **3t** (40% yield, 85:15 e.r.), a trifluoromethyl group **3u** (28% yield, 72:28 e.r.) or a cyano group **3v** (13% yield, 85:15 e.r.) in lower yields and enantioselectivities; we also saw a reduction in chemoselectivity as manifested by the competitive formation of small quantities of the C_2-symmetric BINOL product. It is clear that the electronic nature of the substituents on the indole has an impact on conversion and selectivity. C-6 substitution is tolerated albeit with slightly lower enantioselectivity: 6-methyl **3w** (79% yield, 88:12 e.r.), 6-fluoro **3x** (63% yield, 84:16 e.r.) and 6-chloro **3y** (56% yield, 89:11 e.r.) are all effectively produced. An indole bearing a C-7 methyl group is also a competent partner in this reaction, leading to the corresponding biaryl **3z** in 85% yield and 86:14 e.r. We next examined whether the introduction of different groups on the naphthol coupling partner was possible. A 6-bromo substituent coupled effectively to afford biaryl **3aa** in 66% yield and 93:7 e.r.; a more conjugating group in 6-phenyl was also successful to afford **3ab** with lower conversion (52% yield) and 90:10 e.r. We are able to accommodate groups on both coupling partners: a 6-methyl indole coupled with a 6-bromo naphthol to exclusively afford the *hetero*-coupled biaryl **3ac** (67% yield; 88:12 e.r.). This principle can be extended to the formation of different biaryls such as **3ad** (76% yield, 91:9 e.r.). Different substituents on the naphthol component can also be combined with different C-2 substituents on the indole component to afford an array of different products; these are exemplified by the formation of biaryl compounds bearing bromo **3ae** (54% yield, 95:5 e.r.), methoxy **3af** (82% yield, 92:8 e.r.), aryl **3ag** (45% yield, 95:5 e.r.) and alkyl **3ah** (66% yield, 93:7 e.r.) groups.

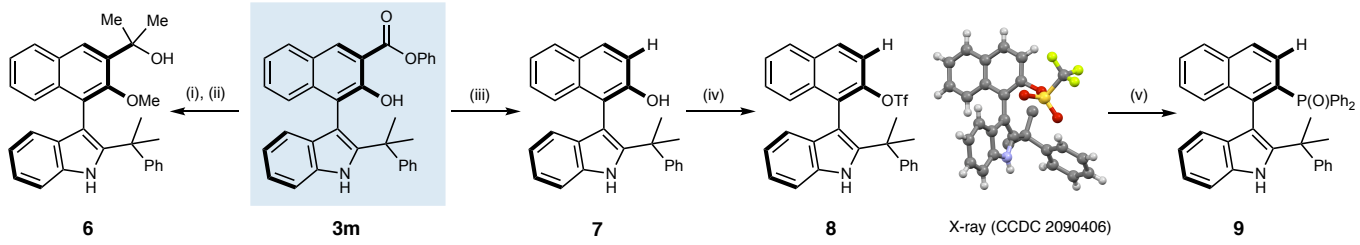


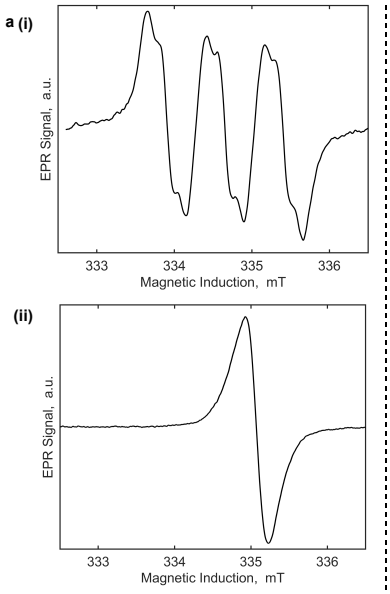
Figure 3: Chemoselective derivatizations. (i) Me_2SO_4 (1.5 eq.), K_2CO_3 (1.2 eq.), acetone, reflux, 24 h, 90% (97:3 e.r.). (ii) MeMgCl (3.0 eq.), THF, r.t. – 65 °C, 16 h, 71% (97:3 e.r.). (iii) $Pd(OAc)_2$ (10 mol.%), 1,2-bis(dicyclohexylphosphino)ethane (20 mol.%), Et_3SiH (1.5 eq.), toluene, 160 °C, 16 h, 69% (97:3 e.r.). (iv) Tf_2O (1.5 eq.), DIPEA (2.0 eq.), CH_2Cl_2, 0 °C – r.t., 48 h, 94% (97:3 e.r.). (v) $Ph_2P(O)H$, $Pd(OAc)_2$ (10 mol.%), 1,4-bis(diphenylphosphino)butane (20 mol.%), DMSO, 120 °C, 96 h, 56% (94% BRSM, 97:3 e.r.).

The atropisomeric biaryl **3m** contains a number of different functional groups, and to demonstrate their orthogonality, chemoselective derivatizations were implemented (Figure 3). The C-3 ester on the naphthol **3m** (97:3 e.r.), which is

implicated in the observed selectivity in the cross-coupling process, can be transformed into tertiary alcohol **6** which is valuable in catalysis by *O*-functionalization followed by the addition of an excess of Grignard reagent. The C-3 ester group can also be conveniently removed by a palladium(II) catalysed reductive decarboxylation in the presence of stoichiometric triethylsilane to afford **7**. Although this requires high temperatures, the magnitude of the barrier to rotation enables this to be performed without compromising enantiointegrity. The phenol in **7** can be simply transformed into triflate **8**; the absolute configuration of this compound was confirmed by X-ray crystallography. This compound can function as a divergent intermediate for a range of cross-coupling reactions, as exemplified by the formation of **9**, through a palladium(II) coupling with diphenylphosphine oxide.

The majority of mechanisms proposed for Fe catalysed oxidative cross-couplings are based upon an Fe(III)/Fe(IV) cycle, which broadly parallel the accepted mechanisms for the operation of heme-containing enzymes[35,36]. Cross-coupling selectivity in non-heme systems are usually determined by differences in oxidation potentials that control which cross-coupling partner is oxidized preferentially, in conjunction with other parameters that influence nucleophilicity and acidity[11,37]. To probe the determinants of reactivity and selectivity in our system, we measured the oxidation potentials of 2-*tert*-butyl indole (0.71 V vs Ag/AgCl) and 2-isopropylphenyl 3-hydroxy-2-naphthoate (1.42 V vs Ag/AgCl) in HFIP. These measurements clearly show that under these conditions the indole is significantly easier to oxidize than the naphthol component. To determine whether our oxidation state measurements were reflected by the presence of radical species in solution, we employed EPR spectroscopy (Figure 4a). We were able to observe a species (g = 2.0051) in low spin concentration that we identified as the indole radical (by virtue of its characteristic ^{14}N hyperfine signature) by stirring the indole in HFIP/DCE without precautions to exclude oxygen. In the presence of the Fe(III) catalyst, a different species also consistent with an indole radical[38,39] can be observed (g = 2.00265). This lacks the ^{14}N hyperfine structure observed previously, most likely due to reduced nitrogen character in the wavefunction and rapid relaxation as a consequence of being proximal to the metal centre no other radical species apart from Fe(III) were observable (see supplementary information S96-97). We were also able to capture the indole radical species by the addition of trapping agents triethylphosphite and 5,5-dimethylpyrroline-*N*-oxide. This led to the observation of adducts of the proposed indole radical (by HRMS ESI); the corresponding naphthol adducts were not observed. (see supplementary information S92-93). We also determined the oxidation potentials of the indoles used in the synthesis of **3r**-**3v** (Figure 4b) and found that the presence of electron withdrawing groups had a significant impact: the oxidation potential of the unsubstituted indole is 0.71 V, whereas this value rises to 1.22 V for the 5-cyano derivative. This is consistent with the electronic nature of the 5-substituent on the indole limiting the ease of oxidation, which would impact on the rate of formation of indole radicals. However, the spin concentration was very low throughout our ESR experiments, and we considered that our observation of the indole radical was potentially an off-cycle event occurring independently of the cross-coupling. This is consistent with the lack of formation of the homocoupled indole product under the reaction conditions in the absence of the phenol component, where the indole starting material can be isolated unchanged. In contrast, we were able to isolate the homocoupled BINOL derivative in 66% yield when naphthol **1** was treated under the reaction conditions in the absence of indole **2**. The formation of this product likely occurs via the reaction of a ligated naphthoxy radical, which is trapped by a naphthol as a π-nucleophile[40], and we considered whether this mechanism could be operative for our observed heterocoupling. This led us to consider whether the divergent reactivity of 5-substituted indoles observed previously might be explained by the relative nucleophilicity of these substrates. Mayr has determined nucleophilicity parameters for indoles, which demonstrate that electron withdrawing groups in the 5-position lead to a significant reduction in rates of attack upon a standardized electrophile[41]. This is coherent with observations from Baran who showed that reactions between indoles and ketone-derived radicals were less efficient with electron-deficient indoles[42]. To probe this further, we performed a Hammett analysis of the coupling reactions that yield **3p**-**3v**. The Hammett plot (ratio of the initial reaction rate (k_S/k_U) vs σ_p parameters) gave a linear graph with a negative slope ($\rho = -0.49$, $R^2 = 0.99$; see supplementary information S102). This is indicative of the build-up of positive charge on the indole during the rate-determining transition state and is consistent with its proposed role as a π-nucleophile. In cases where the conversion to the heterobiaryl is low (**3r**-**3v**), we were able to recover both unreacted indole and naphthol. This is consistent with slow trapping of the ligated naphthoxy radical with indole limiting the rate of reaction where the nucleophilicity is relatively low and is also reflected in the (incrementally) lower ratio of heterocoupled:homocoupled products when electron deficient indoles are used.

We propose the Fe(III) salt forms octahedral PyBOX complex **10** in the presence of the ligand **L4** (see supplementary information S90 for mass spectrometry data consistent with this complex). This can undergo ligand exchange to form a complex in which the naphthol binds in a bidentate fashion (see supplementary information S91 for mass spectrometry evidence for this species). Oxidation to Fe(IV) complex **11** occurs with di-*tert*-butylperoxide, (which also liberates a *tert*-butoxy radical); subsequent reversible single electron transfer (SET) generates an Fe(III) ligated naphthoxy radical **12**. We propose that indole radicals **13** can be generated from indoles in the presence of Fe(III) complex **10** and an external oxidant (Figure 4c) or by SET from Fe(IV) complex **11**. This radical may be complexed (reversibly) to the Fe(III) center[43,44] which would confer extra stability to this species and potentially render it persistent[45]; this, in conjunction with the extremely low concentration of this species, is consistent with our observation that the homocoupled 3,3'-bisindole is not a product of this reaction. We believe that it is likely this oxidation does not play a significant role in the cross-coupling reaction.



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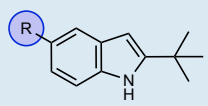

R	E_{ox} (V)	Yield (3)	Ratio [3:4]
H	0.71	91%	>50:1
F	0.92	60%	44:1
Br	0.97	40%	21:1
CO_2Me	1.00	40%	18:1
CF_3	1.03	28%	17:1
CN	1.22	13%	15:1

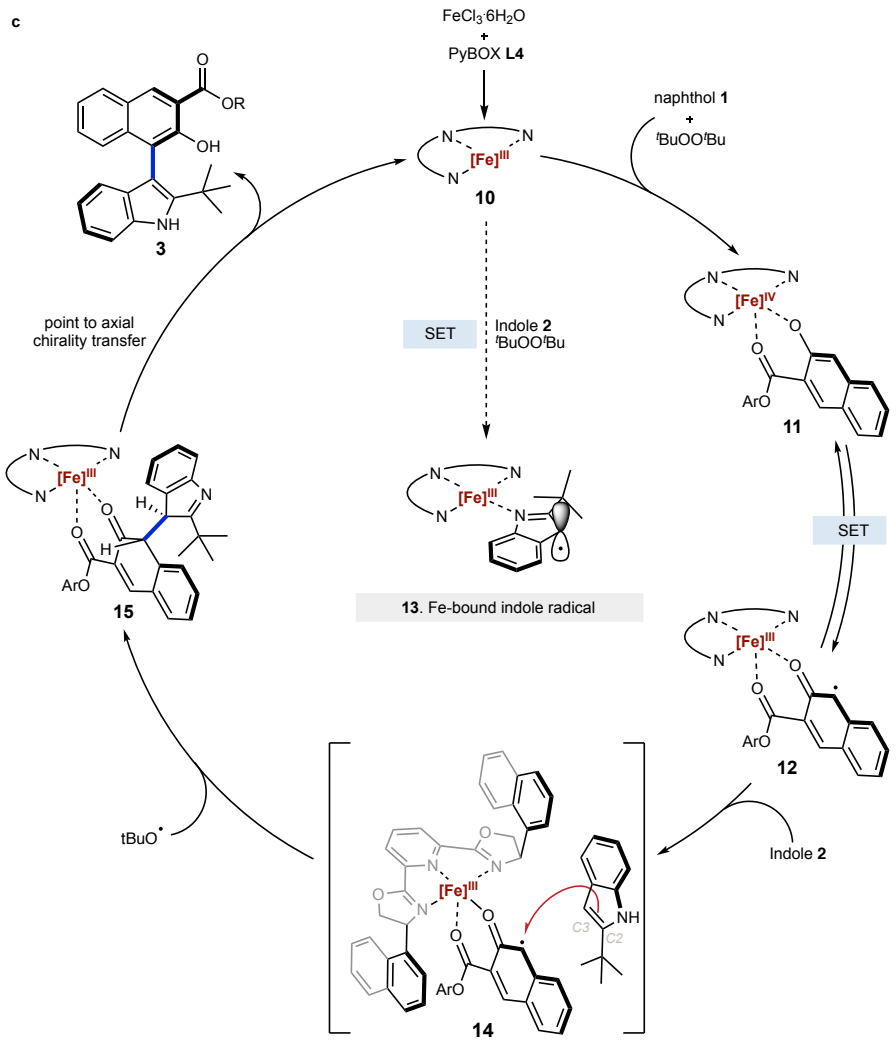

Figure 4: **Mechanistic investigations and proposed catalytic cycle**. **a** X-band CW-EPR at 295 K of (i) 2-*tert*-butylindole in HFIP/DCE. (ii) 2-*tert*-butylindole, $FeCl_3 \cdot 6H_2O$ (0.1 eq.), ligand **L4** (0.1 eq.), ^{t}BuOO^{t}Bu (1.0 eq.), HFIP/DCE. **b** Oxidation potentials of 5-substituted indoles and yields in cross-coupling reaction with 2-isopropylphenyl 3-hydroxy-2-naphthoate **1d**. Oxidation potentials measured vs Ag/AgCl. **c** Outline catalytic cycle. [Fe] = FeL_n (L = Cl^-, H_2O, solvent, ^{t}BuO$^-$, naphthol, indole). Binding geometries of naphthol and indole partners are indicative only. SET = single electron transfer.

Katsuki has previously noted the necessity of two *cis*-sites on the Fe centre being available to enable binding of two naphthols for cross-coupling to generate BINOLs[46]. In our system, binding both an indole and a bidentate naphthol on the same metal center makes the requirement for close approach of the indole to its naphthoate partner extremely challenging from a geometric perspective. As such, we tentatively propose that the addition of the indole could occur via an outer sphere mechanism in which the key facially selective addition to the Fe(III) naphthoxy radical species is directed by the C_2-symmetric ligand as in **14**. The resultant radical could subsequently undergo hydrogen atom

abstraction[47] or oxidation to afford **15**[48,49], followed by ligand exchange to enable release of the enantioenriched heterobiaryl system **3** and an Fe(III) complex able to continue the catalytic cycle. Although we have proposed an outer sphere coupling between a chiral Fe-bound naphthoxy radical and an indole, this does not preclude the possibility of an alternative cycle involving an indole radical being operative in the catalytic reaction, and further mechanistic studies are underway.

Conclusion

We have described a process for the enantioselective synthesis of atropisomeric heterobiaryl derivatives via a direct oxidative cross-coupling that constructs the key biaryl linkage from two C–H bonds. This reaction utilizes a cheap and abundant Fe catalyst in the presence of a readily available chiral PyBOX ligand to enable a remarkably chemoselective cross-coupling between indoles and phenols. We envision that this process will enable the application of these and similar heterobiaryl compounds across the fields of materials science, catalysis and medicine.

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Authorship

R.R.S., X.L. and M.D.S. conceived and designed the study; R.R.S. and X.L. performed the synthetic experiments and analyzed data for all compounds; W.M. performed the ESR study. R.R.S, X.L., W.M. and M.D.S. co-wrote the paper.

Data Availability

Crystallographic data for compound **8** has been deposited with the Cambridge Crystallographic Data Centre under deposition number CCDC 2090406. These data can be obtained free of charge from www.ccdc.cam.ac.uk/data_request/cif. Any relevant data not present in the manuscript or supplementary information are available from the authors.

Additional Information

Supplementary information, X-ray data (CIF) for compound **8** and chemical compound information are available in the online version of the paper. Reprints and permissions information is available online at www.nature.com/reprints. Correspondence and requests for materials should be addressed to M.D.S.

Competing Financial Interests

The authors declare no competing financial interests.

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