

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

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## Abstract

Heterobiaryl compounds that exhibit axial chirality are of increasing value and interest across several fields, but direct oxidative methods for their enantioselective synthesis remain 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<sup>1</sup>. The most convergent route to biaryls is generally the transition metal mediated cross-coupling of two partners<sup>2,3</sup> (although significant advances in metal-free methods have been demonstrated recently)<sup>4</sup>. 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)<sup>5</sup>. 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<sup>6,7</sup>. This realization has led to a significant number of oxidative homo-coupling procedures that can generate *C*<sub>2</sub>-symmetric BINOL-like structures in an enantioselective fashion. These include reactions mediated by transition metals including copper<sup>8-10</sup>, iron<sup>11</sup> and vanadium,<sup>12</sup> 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<sup>13-16</sup>. In particular, Katsuki demonstrated that iron salan complexes are effective in the enantioselective heterocoupling of naphthols<sup>17</sup>, and Pappo showed that chiral iron phosphate and disulfonate complexes act as effective precatalysts for the enantioselective synthesis of non *C*<sub>2</sub>-symmetric BINOLs and NOBINs (Figure 1b)<sup>18,19</sup>. We considered whether this oxidative cross-coupling approach could be used in the development of a method for the enantioselective synthesis of axially chiral 3-aryl indoles, which are emerging as a valuable member of the atropisomeric biaryl family<sup>20</sup>. The synthesis of atropisomeric aryl indoles has been a particular focus for enantioselective catalysis since the definitive reports of 3-aryl indoles from Li and Shi<sup>21</sup>, Gu<sup>22</sup> and Tan<sup>23</sup>.

Oxidative cross-couplings between indoles and phenols have been disclosed in the synthesis of benzofuranoidolines<sup>25,26</sup>, which are key components of complex natural products including diazonamide and phalarine (Figure 1c). A range of oxidants (including hypervalent iodine reagents<sup>27</sup>, iron(III) salts<sup>28</sup> and electrochemistry<sup>29</sup>) 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).

## Results

We began by screening a range of oxidants for the reaction between a 1:1.1 mixture of 2-naphthol **1a** and 2-methylindole. In a preliminary screen of conditions (see supplementary information S25), hypervalent iodine reagents and VOF<sub>3</sub><sup>30</sup> were poorly selective for the desired heterocoupling process, whilst [Cu(OH)·TMEDA]<sub>2</sub>Cl<sub>2</sub> 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<sup>31,32</sup>, 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<sup>-1</sup>; the potential configurational lability of this material (a class 2 atropisomer)<sup>33</sup> 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<sup>34-36</sup>. When a naphthol bearing a C-3 methyl ester **1b** 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<sup>-1</sup>; a barrier of this magnitude essentially precludes racemisation unless forcing thermal conditions are employed.

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.<sup>37</sup> Both yield and e.r. were improved (80% yield at 70:30 e.r.) on switching to the hexahydrate salt (which is both cheaper and easier to handle; Table 1, entry 6). This is most likely due to the greater solubility of complexes derived from the hexahydrate salt vs anhydrous Fe salts. 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 **3e** 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 13). Modulation of reaction time, an increase in the quantity of ligand (to 12 mol%) and indole (to 1.5 equiv.) 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. These conditions were not effective with 3-cyano substituted naphthol (**1e**), leading to <5% conversion, but the cross-coupling of 3-bromo 2-naphthol **1f** to afford **3g** proceeded with perfect chemoselectivity and good enantioselectivity (92% yield, 85:15 e.r.). With an optimized set of reaction conditions, we explored the substrate scope for the reaction (Table 2), focusing on naphthol **1d**. In all cases, the mass balance is accounted for as unreacted naphthol starting material, and the 3,3'-bisindole product **5** is not observed.

The size of the indole C-2 substituent is crucial 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 **3h** 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 **3i** (71% yield; 91:9 e.r.) and **3j** (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 **3k** (75% yield, 94:6 e.r.) and **3l** (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 **3m** 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  $\alpha,\alpha$ -dimethylbenzyl group (to afford **3n** in 80% yield and 96:4 e.r.). The combination of a phenyl ester on the naphthol with the  $\alpha,\alpha$ -dimethylbenzyl indole was also viable and more selective in this reaction, generating **3o** 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 **3p** (80% yield, 90:10 e.r.) and **3q** (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 **3r** in 97% yield and 93:7 e.r. 5-Alkyl groups are also well tolerated, affording biaryl **3s** 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 **3t** (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 **3u** 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 **3v** (40% yield, 85:15 e.r.), a trifluoromethyl group **3w** (28% yield, 72:28 e.r.) or a cyano group **3x** (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<sub>2</sub>-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 **3y** (79% yield, 88:12 e.r.), 6-fluoro **3z** (63% yield, 84:16 e.r.) and 6-chloro **3aa** (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 **3ab** 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 **3ac** in 66% yield and 93:7 e.r.; a more conjugating group in 6-phenyl was also successful to afford **3ad** 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 **3ae** (67% yield; 88:12 e.r.). This principle can be extended to the formation of different biaryls such as **3af** (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 **3ag** (54% yield, 95:5 e.r.), methoxy **3ah** (82% yield, 92:8 e.r.), aryl **3ai** (45% yield, 95:5 e.r.) and alkyl **3aj** (66% yield, 93:7 e.r.) groups.

The atropisomeric biaryl **3o** contains a number of different functional groups, and to demonstrate their orthogonality, chemoselective derivatizations were implemented (Figure 2). The C-3 ester on the naphthol **3o** (97:3 e.r.), which is implicated in the observed selectivity in the cross-coupling process, can be transformed into tertiary alcohol **6** 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. 3-Aryl indole phosphine oxides such as this have been directly reduced to phosphines, which have been employed in catalysts for organocatalytic enantioselective reactions<sup>38,39</sup>.

## Discussion

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<sup>40,41</sup>. 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<sup>11,42</sup>. 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 has a lower oxidation potential 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. By stirring the indole in HFIP/DCE without the exclusion of oxygen, 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 <sup>14</sup>N hyperfine signature, Figure 3a). In the presence of the Fe(III) catalyst, a different species also consistent with an indole radical<sup>43,44</sup> can be observed (*g* = 2.00265, Figure 3b). This lacks the <sup>14</sup>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 S99-105). We were also able to capture the adducts of the proposed indole radical species (by HRMS ESI) by the addition of trapping agents

triethylphosphite and 5,5-dimethylpyrroline-*N*-oxide in low yields (see supplementary information S97-98). We determined the oxidation potentials of the indoles used in the synthesis of **3t-3x** (Figure 3c) and found that the presence of electron withdrawing groups at the C-5 position 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, as the spin concentration was very low throughout our ESR heterocoupling experiments, we considered whether the observation of the indolyl radical was potentially an off-cycle event occurring independently of the cross-coupling. To probe the significance of this species further, we constructed indole **2w** that contains an internal alkene radical trap at the C2-position. We reasoned that if the indolyl radical was playing a major role in the C–C bond forming event, this species would be intercepted through an intramolecular radical cyclization rather than undergoing competitive intermolecular cross-coupling in the presence of **1c**. When a mixture of naphthol **1c** and indole **2w** were treated with catalytic iron(III) chloride in HFIP/DCE with di-*tert*-butylperoxide as the co-oxidant, this led to the formation of the cross-coupled product **3ak** in 69% yield, alongside a small quantity of oxidative cyclisation product of the indole **2x** (< 5%) and some recovered naphthol (10%, Figure 3e). However, when indole **2w** alone was subject to identical conditions (Figure 3f), oxidative cyclization product **2x** was isolated in 34% yield (alongside 21% recovered starting material; see supplementary information S91-93 for a discussion of mechanism). These observations suggest that despite the lower oxidation potential of the indoles, oxidation of the heterocyclic component does not play a productive role within the catalytic cycle. The EPR observation of a very low concentration of an Fe-bound indole radical in the cross-coupling reaction thus likely reflects slow indole oxidation, that does not lead to isolable products unless it may be trapped by an appropriate (intramolecular) acceptor. This is also consistent with the lack of formation of the homo-coupled indole product under the reaction conditions in the absence of the naphthol component, where indole starting material can be recovered. In contrast, we were able to isolate the homocoupled BINOL derivative in 68% yield when naphthol **1d** was treated under the reaction conditions in the absence of an indole. The formation of this product likely occurs via the reaction of a ligated naphthoxy radical, which is trapped by a naphthol as a  $\pi$ -nucleophile<sup>45</sup>, and we hence considered whether this mechanism could be operative for our observed heterocoupling. MALDI-TOF analysis of the reaction between mixture naphthol **1c** and indole **2b** ( $R^2 = t\text{-Bu}$ ) under standard conditions allowed us to identify a species consistent with a Fe-bound naphthoxide complex (see supplementary information S96 for mass spectrometry evidence for this species). We considered 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<sup>46</sup>. This is coherent with observations from Baran who showed that reactions between indoles and ketone-derived radicals were less efficient with electron-deficient indoles<sup>47</sup>. To probe this further, we performed a Hammett analysis of the coupling reactions that yield **3t-3x**. The Hammett plot (ratio of the initial reaction rate ( $k_S/k_U$ ) vs  $\sigma_p$  parameters) gave a linear graph with a negative slope ( $\rho = -0.49$ ,  $R^2 = 0.99$ ; see supplementary information S107). 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  $\pi$ -nucleophile. In cases where the conversion to the heterobiaryl is low (**3u-3x**), 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 **L4** that can undergo ligand exchange to form a complex in which the naphthol binds in a bidentate fashion (see supplementary information S90 and S96 for mass spectrometry data consistent with these complexes). 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**.<sup>48</sup> We propose that indole radicals **13** can be generated from indoles in the presence of Fe(III) complex **10** and an external oxidant (Figure 3d) or by SET from Fe(IV) complex **11**. This radical may be complexed (reversibly) to the Fe(III) center<sup>49,50</sup> which would confer extra stability to this species and potentially render it persistent<sup>51</sup>; 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 species does not play a significant role in the cross-coupling reaction.

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<sup>52</sup>. In our system, binding both an indole and a bidentate naphthol on the same metal center makes the requirement for their close approach extremely challenging from a geometric perspective. As such, we tentatively propose that addition of the  $\pi$ -nucleophilic 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<sub>2</sub>-symmetric ligand as in **14**. The resultant radical could subsequently undergo hydrogen atom abstraction<sup>53</sup> or oxidation to afford **15**<sup>54,55</sup>, followed by ligand exchange to enable release of the enantioenriched heterobiaryl system **3** and an Fe(III) complex able to continue the catalytic cycle.

## 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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## Author Contributions

R.R.S., X.L., M.J.H.K. and M.D.S. conceived and designed the study; R.R.S., X.L. and M.J.H.K. 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.

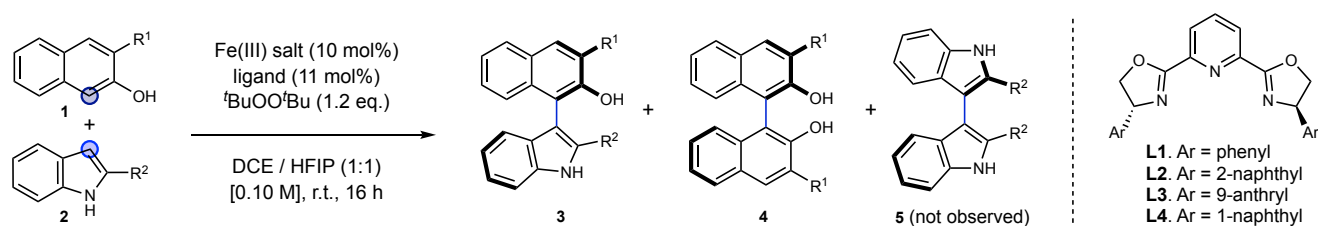
## Additional Information

Correspondence and requests for materials should be addressed to M.D.S.

## Competing Interests

The authors declare no competing interests.

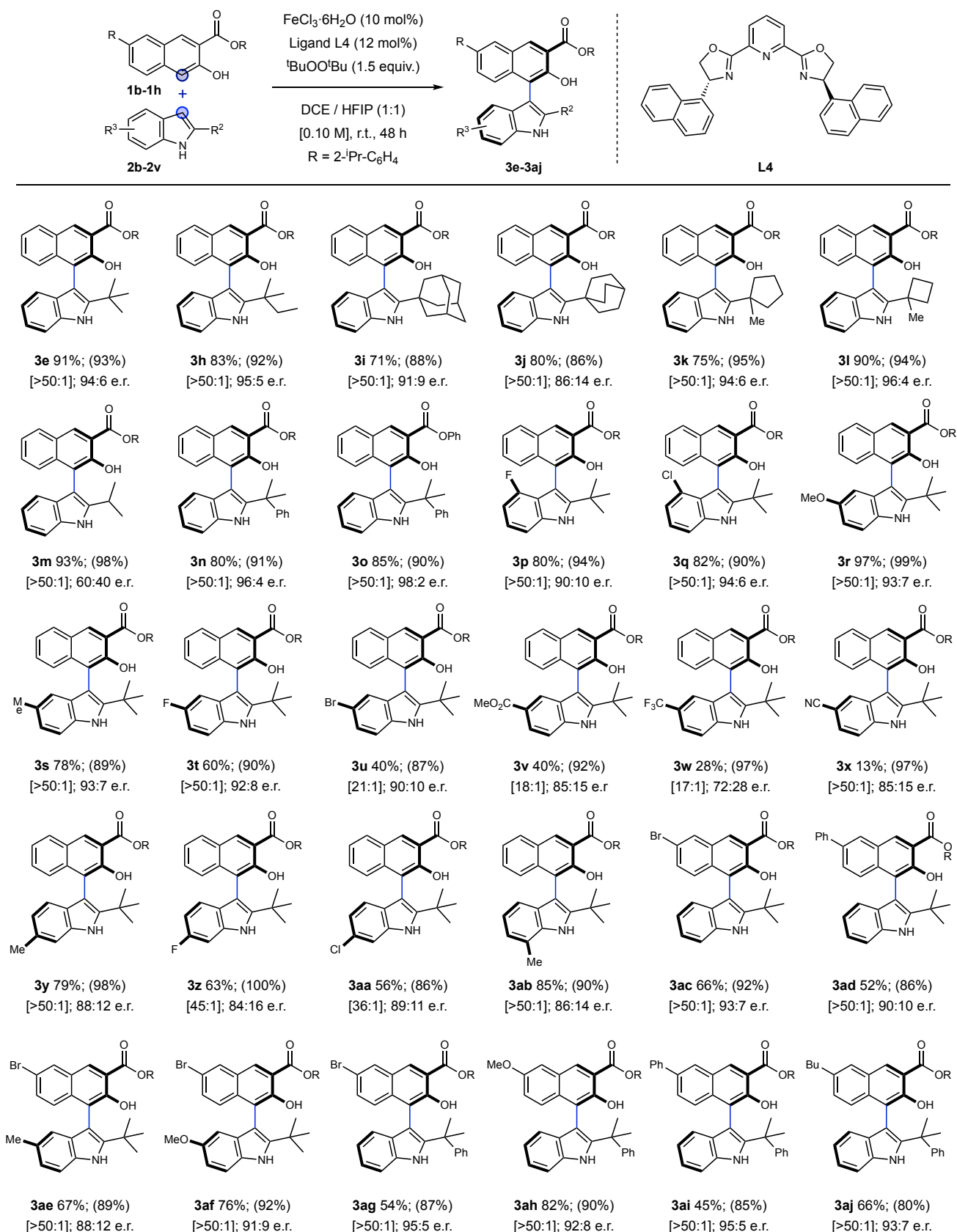
**Table 1 Reaction optimization**



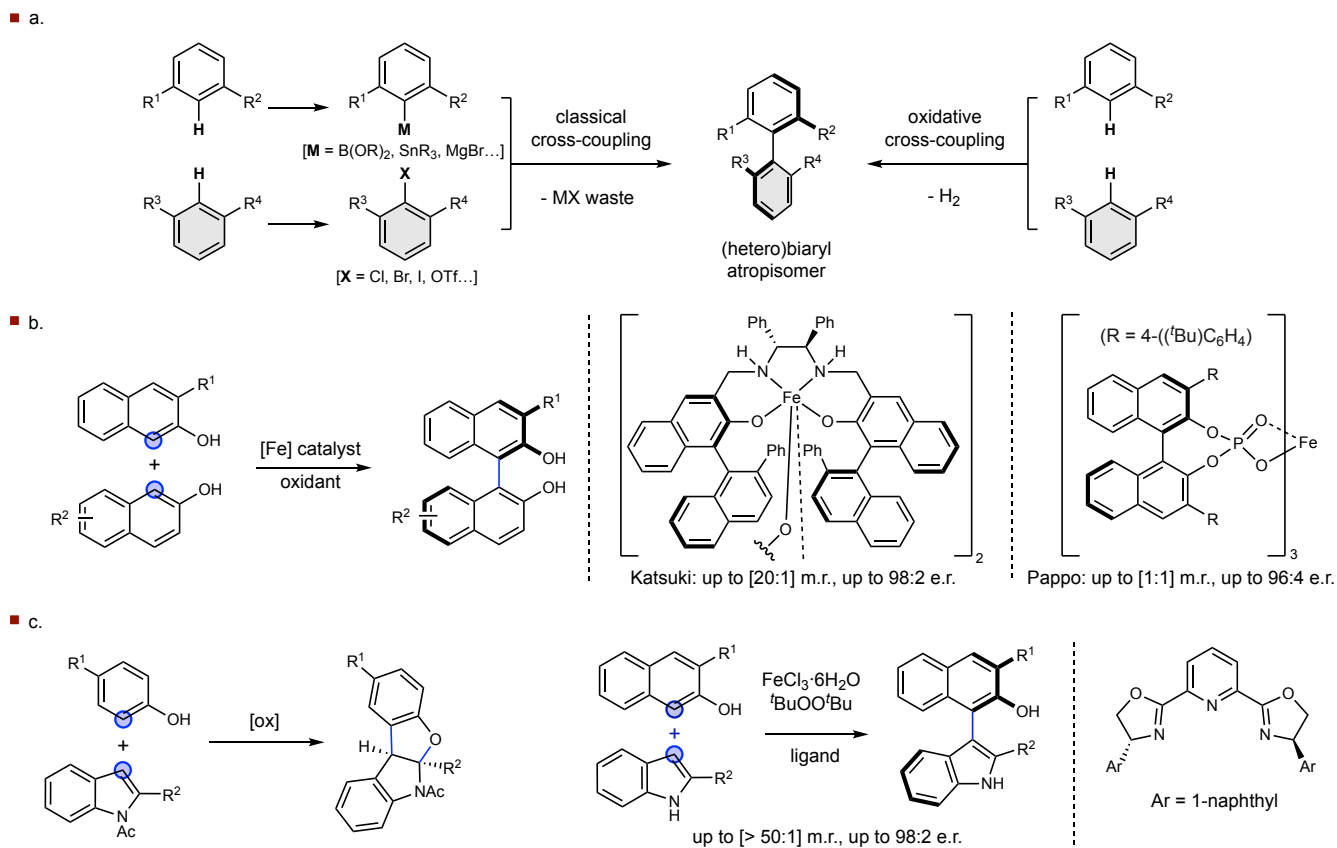
Entry	[Fe] salt	Ligand	Heterobiaryl	R <sup>1</sup> (naphthol)	R <sup>2</sup>	Yield of <b>3</b> ( <b>4</b> )	[ <b>3</b> : <b>4</b> ] m.r.	e.r. of <b>3</b>
1 <sup>a</sup>	FeCl <sub>3</sub>	none	<b>3a</b>	H ( <b>1a</b> )	Me	96%	>50:1	n/a
2 <sup>a</sup>	FeCl <sub>3</sub>	none	<b>3b</b>	H( <b>1a</b> )	<sup>t</sup> Bu	39% (48%)	5:6	n/a
3 <sup>a</sup>	FeCl <sub>3</sub>	none	<b>3c</b>	CO <sub>2</sub> Me ( <b>1b</b> )	<sup>t</sup> Bu	89%	>50:1	n/a
4 <sup>a</sup>	FeCl <sub>3</sub>	<b>L1</b>	<b>3c</b>	CO <sub>2</sub> Me ( <b>1b</b> )	<sup>t</sup> Bu	56%	>50:1	60:40
5 <sup>a</sup>	FeCl <sub>3</sub> ·6H <sub>2</sub> O	<b>L1</b>	<b>3c</b>	CO <sub>2</sub> Me ( <b>1b</b> )	<sup>t</sup> Bu	80%	>50:1	70:30
6	FeCl <sub>3</sub> ·6H <sub>2</sub> O	<b>L1</b>	<b>3c</b>	CO <sub>2</sub> Me ( <b>1b</b> )	<sup>t</sup> Bu	60%	>50:1	75:25
7	FeCl <sub>3</sub> ·6H <sub>2</sub> O	<b>L1</b>	<b>3d</b>	CO <sub>2</sub> Ph ( <b>1c</b> )	<sup>t</sup> Bu	67%	>50:1	84:16
8	FeCl <sub>3</sub> ·6H <sub>2</sub> O	<b>L2</b>	<b>3d</b>	CO <sub>2</sub> Ph ( <b>1c</b> )	<sup>t</sup> Bu	63%	>50:1	88:12
9	FeCl <sub>3</sub> ·6H <sub>2</sub> O	<b>L3</b>	<b>3d</b>	CO <sub>2</sub> Ph ( <b>1c</b> )	<sup>t</sup> Bu	58%	>50:1	75:25
10	FeCl <sub>3</sub> ·6H <sub>2</sub> O	<b>L4</b>	<b>3d</b>	CO <sub>2</sub> Ph ( <b>1c</b> )	<sup>t</sup> Bu	71%	>50:1	89:11
11 <sup>b</sup>	FeCl <sub>3</sub> ·6H <sub>2</sub> O	<b>L4</b>	<b>3d</b>	CO <sub>2</sub> Ph ( <b>1c</b> )	<sup>t</sup> Bu	75%	>50:1	90:10
12 <sup>b</sup>	FeCl <sub>3</sub> ·6H <sub>2</sub> O	<b>L4</b>	<b>3e</b>	CO <sub>2</sub> R* ( <b>1d</b> )	<sup>t</sup> Bu	63%	>50:1	92:8
13 <sup>b,c,d</sup>	FeCl <sub>3</sub> ·6H <sub>2</sub> O	<b>L4</b>	<b>3e</b>	CO <sub>2</sub> R* ( <b>1d</b> )	<sup>t</sup> Bu	91% <sup>e</sup>	>50:1	94:6
14 <sup>b,c,d</sup>	FeCl <sub>3</sub> ·6H <sub>2</sub> O	<b>L4</b>	<b>3f</b>	CN ( <b>1e</b> )	<sup>t</sup> Bu	<5% <sup>e</sup>	>50:1	65:35
15 <sup>b,c,d</sup>	FeCl <sub>3</sub> ·6H <sub>2</sub> O	<b>L4</b>	<b>3g</b>	Br ( <b>1f</b> )	<sup>t</sup> Bu	92% <sup>e</sup>	>50:1	85:15

Conditions: performed on 0.1 mmol scale, Fe salt (10 mol%), ligand (11 mol %) naphthol (1.0 equiv.), indole (1.1 equiv.), <sup>t</sup>BuOO<sup>t</sup>Bu (1.2 equiv.), 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 <sup>1</sup>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; <sup>a</sup> [naphthol] = 0.2 M. <sup>b</sup> 12 mol% ligand used. <sup>c</sup> FeCl<sub>3</sub>·6H<sub>2</sub>O pulverized by sonication in DCE for 30 min before adding ligand. <sup>d</sup> indole (1.5 equiv.), <sup>t</sup>BuOO<sup>t</sup>Bu (1.5 equiv.), 48 h. <sup>e</sup> isolated yield.

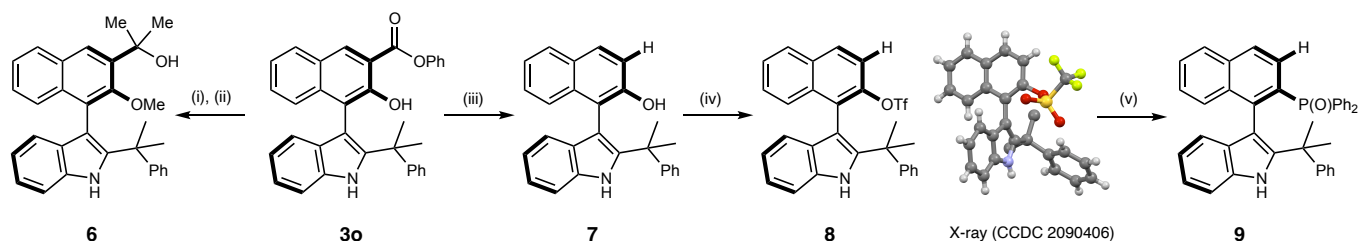
Table 2 Scope of enantioselective indole-naphthol coupling.



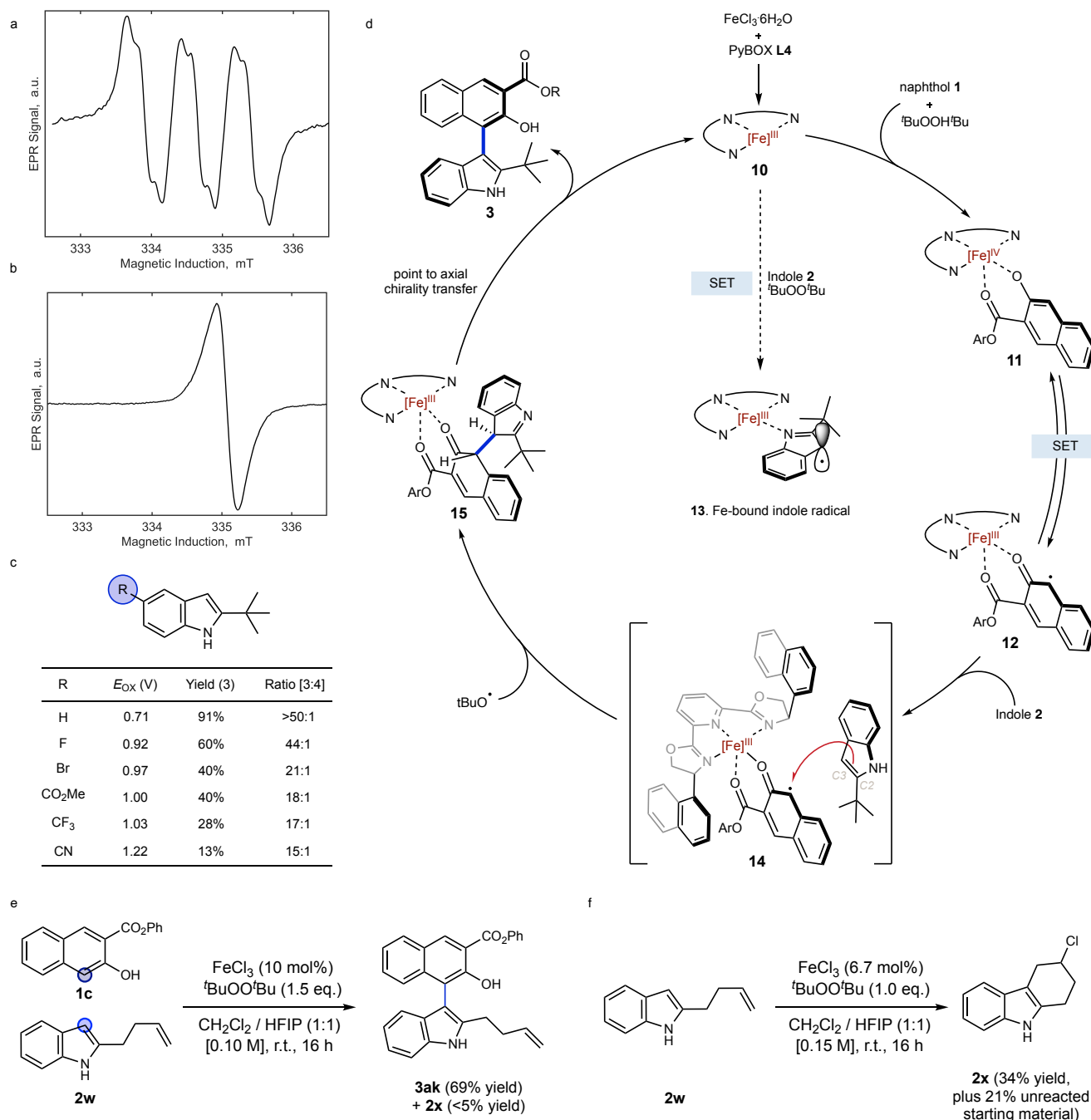
Reaction Conditions: All performed on 0.1 mmol scale:  $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$  (10 mol%), ligand **L4** (12 mol%) naphthol (1.0 equiv.), indole (1.5 equiv.),  $t\text{BuOO}^t\text{Bu}$  (1.5 equiv.), DCE/HFIP, 1:1 (v/v); [naphthol] = 0.10 M, r.t., 48 h. Yields refer to isolated and purified material. Figures in parentheses indicate yields based upon remaining naphthol starting material determined by quantitative  $^1\text{H}$  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  $^1\text{H}$  NMR spectroscopy; e.r. = enantiomeric ratio, determined by chiral stationary phase HPLC.



**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 from Katsuki et al. (*J. Am. Chem. Soc.* **132**, 13633–13635 (2010)) and Pappo et al. (*J. Am. Chem. Soc.* **138**, 16553–16560 (2016)). m.r. = molar ratio of *hetero*-coupled : homo-coupled : homo-coupled products. e.r. = enantiomeric ratio. **c** Previous work: synthesis of benzofuranindolines by oxidative coupling has been achieved by a variety of different methods ([ox] = oxidant; see Kouklovsky et al. (*Angew. Chem. Int. Ed.* **53**, 11881–11885 (2014))). **d** This work: direct chemo- and enantioselective cross-coupling to form configurationally stable heterobiaryls.



**Figure 2: Chemoselective derivatizations of enantioenriched biaryl 30.** The electrophilic C2 ester can be transformed to tertiary alcohol **6** via Grignard addition, and can also be reductively decarboxylated to afford **7**. The C–O bond in **7** can be transformed into a C–P bond in **9** via cross coupling of triflate **8**. Conditions: (i)  $\text{Me}_2\text{SO}_4$  (1.5 equiv.),  $\text{K}_2\text{CO}_3$  (1.2 equiv.), acetone, reflux, 24 h, 90% (97:3 e.r.). (ii)  $\text{MeMgCl}$  (3.0 equiv.), THF, r.t. – 65 °C, 16 h, 71% (97:3 e.r.). (iii)  $\text{Pd}(\text{OAc})_2$  (10 mol.%), 1,2-bis(dicyclohexylphosphino)ethane (20 mol.%),  $\text{Et}_3\text{SiH}$  (1.5 equiv.), toluene, 160 °C, 16 h, 69% (97:3 e.r.). (iv)  $\text{TiF}_2\text{O}$  (1.5 equiv.), DIPEA (2.0 equiv.),  $\text{CH}_2\text{Cl}_2$ , 0 °C – r.t., 48 h, 94% (97:3 e.r.). (v)  $\text{Ph}_2\text{P}(\text{O})\text{H}$ ,  $\text{Pd}(\text{OAc})_2$  (10 mol.%), 1,4-bis(diphenylphosphino)butane (20 mol.%), DMSO, 120 °C, 96 h, 56% (94% BRSM, 97:3 e.r.).



**Figure 3: Mechanistic investigations and proposed catalytic cycle.** **a** X-band CW-EPR at 295 K of 2-*tert*-butylindole in HFIP/DCE shows the presence of an indolyl radical at low concentrations. **b** X-band CW-EPR at 295 K of 2-*tert*-butylindole, FeCl<sub>3</sub>·6H<sub>2</sub>O (0.1 equiv.), ligand **L4** (0.1 equiv.), *t*BuOO*t*Bu (1.0 equiv.), HFIP/DCE indicates the presence of an Fe-bound indolyl radical. **c** Oxidation potentials of 5-substituted indoles and yields in cross-coupling reaction with 2-isopropylphenyl 3-hydroxy-2-naphthoate **1d** indicate that less electron rich  $\pi$ -nucleophiles give lower yields and lower selectivity. Oxidation potentials measured vs Ag/AgCl. **d** Outline catalytic cycle. We believe that the generation of indole radical **13** is an off-cycle event and that the catalytic cycle involves the formation of Fe(IV) complex **11** that undergoes single electron transfer (SET) to give a naphthyl radical **12** that is trapped by indole as a  $\pi$ -nucleophile (**14**). Hydrogen atom abstraction to give **15** and point to axial chirality transfer afford **3** and regenerate catalytic iron complex **10**. [Fe] = FeL<sub>*n*</sub> (L = Cl<sup>-</sup>, H<sub>2</sub>O, solvent, *t*BuO<sup>-</sup>, naphthol, indole). Binding geometries of naphthol and indole partners are indicative only. **e** Cross-coupling reaction between 2-naphthol and 2-butenyl indole as a probe for the presence of an indolyl radical. Under these conditions, intermolecular cross-coupling outcompetes intramolecular oxidative cyclization. Conditions: FeCl<sub>3</sub>·6H<sub>2</sub>O (10 mol%), naphthol (1.0 equiv.), indole (1.5 equiv.), *t*BuOO*t*Bu (1.5 equiv.), CH<sub>2</sub>Cl<sub>2</sub>/HFIP, 1:1 (v/v); [naphthol] = 0.10 M; [indole] = 0.15 M. **f** Oxidative cyclization of 2-butenyl indole in the absence of 2-naphthol leads to an intramolecular oxidative cyclization; equivalents (equiv.) reported relative to indole. Conditions: FeCl<sub>3</sub>·6H<sub>2</sub>O (6.7 mol%), indole (1.0 equiv.), *t*BuOO*t*Bu (1.0 equiv.), CH<sub>2</sub>Cl<sub>2</sub>/HFIP, 1:1 (v/v); [indole] = 0.15 M.

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## Methods

Typical procedure for oxidative cross coupling, exemplified for the formation of biaryl **3e**.

### (i) *In-situ* formation of chiral Fe complex

A ½ dram PTFE screw-top vial was charged with FeCl<sub>3</sub>·6H<sub>2</sub>O (2.7 mg, 0.010 mmol, 0.10 equiv.) and dichloroethane (500 µL). The mixture was then sonicated in a water bath for 30 min at room temperature to pulverise the solid into a fine yellow suspension. [NOTE: It is crucial reduce the particle size of the FeCl<sub>3</sub>·6H<sub>2</sub>O prior to the addition of the ligand, otherwise lower enantioselectivities will be observed]. Following sonication, a magnetic stir bar and PyBOX **L4** (5.6 mg, 0.012 mmol, 0.12 equiv.) were added. The mixture was then stirred for 2 h at room temperature to form an orange-coloured homogeneous solution. Hexafluoroisopropanol (500 µL) was then introduced and stirring continued for an additional 30 min to give a brown coloured solution.

### (ii) Reaction, work-up, analysis and purification

At room temperature, 2-isopropylphenyl 3-hydroxy-2-naphthoate **1d** (0.100 mmol, 1.00 equiv.) and 2-*tert*-butylindole **2b** (0.150 mmol, 1.50 equiv.) were simultaneously added to the solution of the pre-formed complex, forming a dark coloured solution. Di-*tert*-butyl peroxide (27.4 µL, 0.150 mmol, 1.50 equiv.) was then added using a micropipette. The reaction mixture was then sealed and stirred under an atmosphere of air at room temperature for 48 h. After this time, the solvent was removed *in vacuo* and the crude product filtered through a short plug of silica [eluting liberally with CH<sub>2</sub>Cl<sub>2</sub>]. The filtrate was then concentrated to dryness and the chemoselectivities (>50:1) and conversions (91% conversion, 2% remaining naphthol) were obtained by quantitative <sup>1</sup>H NMR analysis of the crude product, using 1,3,5-trimethoxybenzene as an internal standard. The products were purified by flash column

416 chromatography [silica gel, 50% CH<sub>2</sub>Cl<sub>2</sub> in pentane] to afford biaryl **3e** (91% isolated yield). The enantiomeric ratio  
417 was obtained by HPLC (chiral stationary phase) of the purified products (Daicel ChiralPak IC column (5% *i*-PrOH  
418 in hexane, 1.0 mL min<sup>-1</sup>, T = 25 °C, 307 nm);  $\tau_R$  (minor) = 7.5 min,  $\tau_R$  (major) = 10.9 min; 94:6 e.r.).

#### 419 **Data Availability**

420 All data (experimental procedures and characterization data) supporting the findings of this study are available within  
421 the article and its supplementary information. Crystallographic data for compound **8** has been deposited with the  
422 Cambridge Crystallographic Data Centre under deposition number CCDC 2090406. These data can be obtained free  
423 of charge from <https://www.ccdc.cam.ac.uk/structures/>.