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# Ortho-selective C–H arylation of phenols with *N*-carboxyindoles under Brønsted acid- or Cu(I)-catalysis†

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Control over chemo- and regioselectivity is a critical issue in the heterobiaryl synthesis via C–H oxidative coupling. To address this challenge, a strategy to invert the normal polarity of indoles in the heterobiaryl coupling was developed. With *N*-carboxyindoles as umpoled indoles, an exclusively *ortho*-selective coupling with phenols has been realized, employing a Brønsted acid- or Cu(I)-catalyst (as low as 0.01 mol%). A range of phenols and *N*-carboxyindoles coupled with exceptional efficiency and selectivity at ambient temperature and the substrates bearing redox-active aryl halides (–Br and –I) smoothly coupled in an orthogonal manner. Notably, preliminary examples of atropselective heterobiaryl coupling have been demonstrated, based on a chiral disulfonimide or a Cu(I)/chiral bisphosphine catalytic system. The reaction was proposed to occur through S<sub>N</sub>2' substitution or a Cu(I)–Cu(III) cycle, with Brønsted acid or Cu(I) catalysts, respectively.

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## Introduction

Bi(hetero)aryl motifs are widely found in bioactive natural products and are commonly utilized as chiral auxiliaries and ligands.<sup>1</sup> These compounds have been synthesized by transition metal-catalyzed coupling between aryl halides (RX) and aryl metal species (RM) which requires pre-functionalization of the parent (hetero)arenes. Transition metal-catalyzed dehydrogenative C–H/C–H coupling may provide an appealing option.<sup>2</sup> In addition, several non-metal protocols,<sup>3</sup> such as hypervalent iodine chemistry,<sup>4</sup> electrochemical oxidations,<sup>5</sup> and photoredox catalysis,<sup>6</sup> have also emerged. In many cases, however, control of chemo (homo- vs. heterocoupling)- or regio-selectivity remains challenging. For instance, oxidative functionalization of phenols may lead to homo-coupling and/or quinone formation.<sup>7</sup> Control of site-selectivity of phenols (*o*-, *m*-, *p*-, and *O*-)<sup>8</sup> and indoles<sup>9</sup> also presents a prominent challenge in the absence of directing groups for which extra steps are required for the installation and removal.<sup>10</sup>

We anticipated that inverting the polarity of nucleophilic indoles may enable precise control of chemoselectivity for the

oxidative C–H heterobiaryl coupling.<sup>11</sup> In the past, C3-umpoled indoles were accessed through electrophilic activation,<sup>12a,b</sup> oxidation,<sup>12c,d</sup> or hydroarylation of *N*-acylindole derivatives.<sup>12e–g</sup> More recently, the groups of Kita, Yorimitsu, Procter, and Maulide have developed metal-free C–H heteroarylation based on the activation of sulfoxides.<sup>13,14</sup> In this context, Yorimitsu and coworkers reported an *ortho*-selective coupling of phenols with the activated (hetero)aryl sulfoxides that was proposed to proceed through an interrupted Pummerer attack to form the sulfoxonium **I** and charge-accelerated [3,3]-sigmatropic rearrangement to afford the biaryl compound.<sup>15a</sup> Procter and coworkers developed heteroarylation of phenols with activated benzothiophene-*S*-oxides,<sup>15b–d</sup> which occurred selectively at the *ortho*-<sup>15c</sup> or *para*-position<sup>15d</sup> of phenols (Scheme 1A).

In continuation of our interest in aliphatic Umpolung chemistry based on N–O bond redox,<sup>16</sup> we turned our attention to the aromatic Umpolung by way of *N*-hydroxyindoles which was pioneered by Somei and coworkers.<sup>17</sup> Somei and others disclosed C3-arylation of indoles via [3,3]-sigmatropic rearrangement of *N*-carboxyindoles<sup>18</sup> that were accessed by nucleophilic aromatic substitution (S<sub>N</sub>Ar)<sup>18a,b</sup> or by the *O*-arylation of *N*-hydroxyindoles with biaryliodonium salt.<sup>18c</sup> S<sub>N</sub>2' substitution *N*-hydroxyindoles with indoles and pyrroles was also demonstrated (Scheme 1B).<sup>18d,e</sup> Nonetheless, these biaryl coupling had extremely limited scope and occurred with only modest yields and selectivity. More recently, Buchwald and coworkers demonstrated Cu-catalyzed asymmetric alkylation of *N*-carboxyindoles.<sup>19</sup> Despite these advances, the development of a general and selective oxidative C–H arylation protocol based on the *N*-hydroxyindole derivatives as umpoled coupling

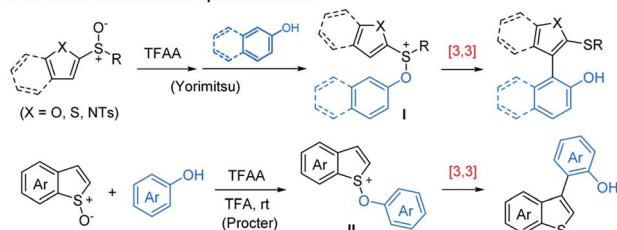
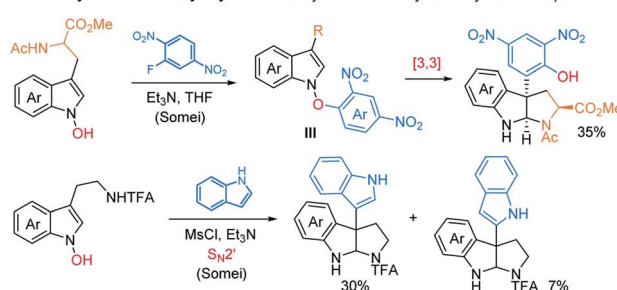
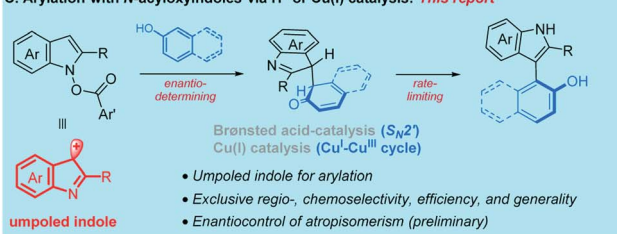
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## A. Sulfoxide-mediated interrupted Pummerer

B. Prior Arylation with *N*-aryloxyindoles: low yield & selectivity and very limited scopeC. Arylation with *N*-acyloxyindoles via  $H^+$  or  $Cu(I)$  catalysis: **This report**

Scheme 1 Inversion of polarity in the heterobiaryl coupling.

partners remains elusive. We disclose herein two catalytic systems for the union of unpoled indoles **1** with phenols **2**, *viz.*  $HNTf_2$  or  $[Cu(OTf)]_2 \cdot C_6H_6$ , that operate at ambient temperature with exceptional efficiency, generality, and chemo- and regioselectivity (Scheme 1D). Details of this discovery, preliminary enantioselective control of atropisomerism, and the mechanistic study are described.

## Results and discussion

The requisite *N*-hydroxyindole derivatives were synthesized according to the literature.<sup>20</sup> Particularly, for the C2-substituted *N*-hydroxyindoles used in this study, a sequence comprising Sonogashira coupling of *o*-halonitrobenzenes, partial reduction into hydroxylamines, and Larock-type cyclization, were found general.<sup>20d</sup> With an *N*-carboxyindole **1a** and 3,5-dimethoxyphenol **2a** as prototypical substrates, we set out to explore the possibility of a non-metal catalyzed C–H/C–H coupling, employing various Brønsted acids (entries 1–6, Table 1).<sup>21,22</sup> Weak acids underwent a sluggish conversion to **3aa** (entries 1 and 2). The product **3aa** had two inequivalent methoxy groups in the <sup>1</sup>H and <sup>13</sup>C NMR spectra and was assigned as an *ortho*-isomer to the OH, which was later confirmed by the single-crystal X-ray diffraction analysis of a related **3ba**.<sup>22</sup> Superacids, such as TfOH, HBF<sub>4</sub>, or  $HNTf_2$  significantly accelerated the formation of **3aa**, reducing the reaction time to several hours (entries 3–5). Unlike TfOH and HBF<sub>4</sub> which were not completely

Table 1 Coupling of **1a** and **2a**: Brønsted and Lewis acid catalysts<sup>a</sup>

Entry	Catalyst	Time	<b>3aa</b> <sup>b</sup> (%)
1	(PhO) <sub>2</sub> P(O)OH	4 days	26 <sup>c</sup>
2	CF <sub>3</sub> CO <sub>2</sub> H	3.5 days	43 <sup>c</sup>
3	TfOH	12 h	84
4	HBF <sub>4</sub> ·OEt <sub>2</sub>	8 h	86
5	$HNTf_2$	16 h	83
6	$HNTf_2$ <sup>d</sup>	8 h	85
7	$HNTf_2$ (1 mol%) <sup>d,e</sup>	22 h	85
8	AuCl(PPh <sub>3</sub> ), AgOTf	2 days	10
9	Fe(OTf) <sub>3</sub>	1 day	96
10	Zn(OTf) <sub>2</sub>	2.5 days	96
11	Cu(OTf) <sub>2</sub>	0.5 h	53 <sup>f</sup>
12	Cu(OTf) <sub>2</sub> (1 mol%)	3 h	69 <sup>g</sup>
13	CuBr	5 h	96
14	Cu(MeCN) <sub>4</sub> ·BF <sub>4</sub>	10 min	74
15	$[Cu(OTf)]_2 \cdot C_6H_6$	5 min	76 <sup>f</sup>
16 <sup>h</sup>	$[Cu(OTf)]_2 \cdot C_6H_6$ (0.1 mol%) <sup>e</sup>	0.5 h	93
17 <sup>h</sup>	$[Cu(OTf)]_2 \cdot C_6H_6$ (0.01 mol%) <sup>e</sup>	1 h	>99
18 <sup>h,i</sup>	$[Cu(OTf)]_2 \cdot C_6H_6$ (0.1 mol%) <sup>e</sup>	8 h	89

<sup>a</sup> **1a** (0.1 mmol), **2a** (0.2 mmol) and catalyst (10 mol%) in CHCl<sub>3</sub> (0.1 M).

<sup>b</sup> Determined by <sup>1</sup>H NMR with CH<sub>2</sub>Br<sub>2</sub> as an internal standard.

<sup>c</sup> Starting **1a** remained. <sup>d</sup> 0.2 M in CHCl<sub>3</sub>. <sup>e</sup> The catalyst was added as a stock solution in CHCl<sub>3</sub> (entry 7) and in EtOAc (entries 16–18).

<sup>f</sup> Messy mixture due to decomposition of **1a**. <sup>g</sup> 2-Ph-indole **4a** (10%) was observed as byproduct. <sup>h</sup> CHCl<sub>3</sub> (0.05 M). <sup>i</sup> **2a** (1.2 equiv.).

soluble,  $HNTf_2$  formed a homogeneous solution in chloroform and gave more reproducible results. The reaction was further accelerated at a higher concentration (entry 6). Reduction of the catalyst loading to 1 mol% still maintained significant activity, furnishing **3aa** in 85% yield in a day (entry 7).

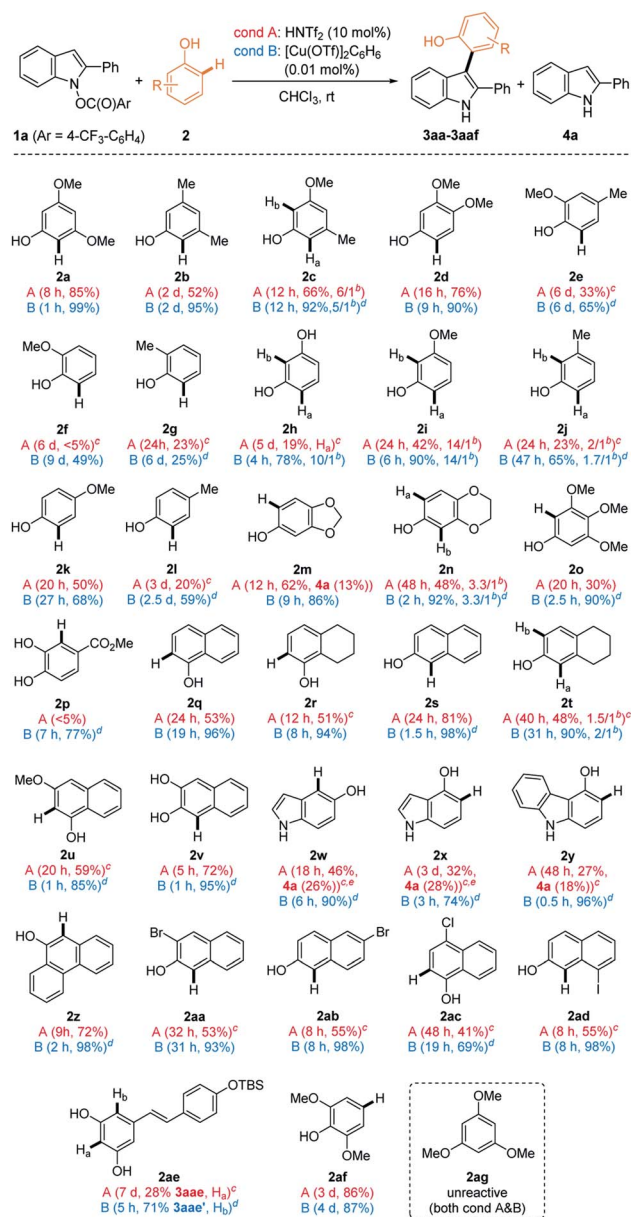
Although  $HNTf_2$  provided an efficient metal-free catalytic system, we went on to examine Lewis acids for more efficient cross-coupling (entries 8–18, Table 1; see Table S1† for full details of optimization).<sup>22</sup> Lewis acids, such as Fe(OTf)<sub>3</sub> and Zn(OTf)<sub>2</sub> gave excellent yields of **3aa**, although it took several days (entries 7–9). A dramatic acceleration could be observed with Cu(OTf)<sub>2</sub>, but the reaction was accompanied by the extensive decomposition of starting materials and **3aa** was obtained in only 53% yield (entry 11). Reducing the amount of Cu(OTf)<sub>2</sub> gave marginally improved yield (entry 12). On the other hand, Cu(I) catalysts were significantly more efficient (entries 13–15). For instance, the reaction with  $[Cu(OTf)]_2 \cdot C_6H_6$  was complete only in 5 min at room temperature, delivering **3aa** in 76% yield (entry 15). To our initial surprise, lowering the catalyst loading and diluting the reaction mixture led to a higher yield (entries 16 and 17; Table S4†). Presumably, this is due to poor solubility of  $[Cu(OTf)]_2 \cdot C_6H_6$  in CHCl<sub>3</sub> and only a tiny amount of soluble catalyst mediated the reaction, while excess Cu-catalyst led to unselective decomposition of **1a**. This observation led us to lower the catalyst loading to 0.01 mol% of



$[\text{Cu}(\text{OTf})_2] \cdot \text{C}_6\text{H}_6$ , to obtain **3aa** in quantitative yield (entry 17). When the amount of nucleophile **2a** was reduced to 1.2 equivalent, 89% of **3aa** was still obtained, attesting to the remarkable chemoselectivity of this protocol (entry 18).

With two different cross-coupling conditions established (conditions A: 10 mol% of  $\text{HNTf}_2$  and conditions B: 0.01 mol% of  $[\text{Cu}(\text{OTf})_2] \cdot \text{C}_6\text{H}_6$ ), we explored the general applicability of the phenol nucleophiles in the heterobiaryl coupling with unpoled indole **1a** (Table 2). Initially, monocyclic phenols (**2a–2p**) were

Table 2 Scope of phenol nucleophiles<sup>a</sup>



<sup>a</sup> Reaction conditions: **1a** (0.1 mmol) and **2** (2 equiv.) in  $\text{CHCl}_3$ ; conditions A (10 mol% of  $\text{HNTf}_2$ , in  $\text{CHCl}_3$  (0.2 M)) and conditions B (0.01 mol% of  $[\text{Cu}(\text{OTf})_2] \cdot \text{C}_6\text{H}_6$  in  $\text{CHCl}_3$  (0.05 M)); isolated yield after chromatography. <sup>b</sup> Regioisomeric ratio ( $H_a : H_b$ ). <sup>c</sup> 20 mol% of  $\text{HNTf}_2$ . <sup>d</sup> 0.1 mol% of  $[\text{Cu}(\text{OTf})_2] \cdot \text{C}_6\text{H}_6$ . <sup>e</sup> At 60 °C.

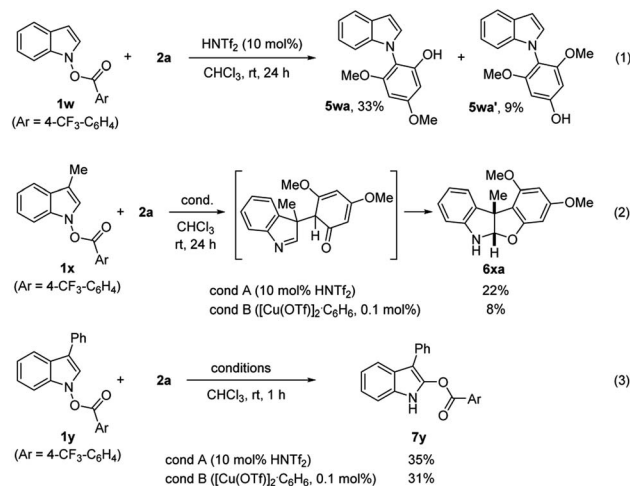
employed in the reaction. Not surprisingly, electron-rich phenols underwent more facile coupling (e.g. **2a** vs. **2b**; **2i** vs. **2j**; **2k** vs. **2l**). Phenols having *ortho*-substituents (**2e–2g**) underwent markedly slower reaction, suggesting developing steric congestion in their transition states. Interestingly, an electron-donating group at the *m*-position of phenols, accelerated the coupling reaction, compared to the *p*-position (e.g. **2i** vs. **2k**; **2j** vs. **2l**). This is presumably because the *m*-substituent is placed *para*- to the reacting center, increasing the electron-density in the proposed [3,3]-sigmatropic rearrangement (e.g. in **IV** to **3**, Scheme 1C). Likewise, the arylation of **2c** preferentially occurred at  $H_a$  having -OMe (rather than Me) at the *p*-position. Notably, in case regioisomeric mixture was obtained (**2c**, **2h–j**, **2n**, and **2t**),<sup>23</sup> similar ratios were noted in both catalytic systems, which led us to posit that they partly share the same catalytic manifold. In general, Cu(I)-catalyst had the more general scope and can be reliably employed for substrates that are challenging with  $\text{HNTf}_2$  catalyst (e.g. **2f** and **2p**). Fused phenols (**2q–2ad**) were then examined and they also underwent smooth coupling with **1a** with exclusive selectivity for the *ortho*-position. For example, 1-naphthol **2q**,  $H_4$ -1-naphthol **2r**, and 2-naphthol **2s** underwent uneventful coupling to form **3aq–3as**, as their single respective regioisomers. Unexpectedly,  $H_4$ -2-naphthol **2t** slightly favored substitution at the less activated C1 over C3 (cf. **2d**), which is presumably due to a subtle conformational influence. Easily oxidized catechol derivatives (**2p** and **2v**), and phenols embedded within indoles (**2w** and **2x**), carbazole (**2y**), and phenanthrol (**2z**) smoothly reacted. Functional groups such as esters (**2p**), bromo- (**2aa**, **2ab**), chloro- (**2ac**), and iodoarenes (**2ad**) furnished respective products uneventfully. Compatibility of these aryl halides suggested that the current protocol could be used in an orthogonal fashion to other transition metal-catalyzed coupling. The current *ortho*-selective indoloylation provided a unique opportunity for the modification of phenolic natural products. For example, TBS-protected resveratrol **2ae**<sup>24</sup> coupled with **1a** only at  $H_a$  using  $\text{HNTf}_2$  (condition A), although the yield of **3aee** was modest (28%). Alternatively, with Cu(I) catalyst (condition B), exclusive indoloylation at  $H_b$  was obtained to give its regioisomer **3aeb'** in 71% yield.<sup>23</sup> Although a proper rationale for this divergence could not be found at the moment, the ability to switch regioselectivity in a catalyst-dependent manner must be highly useful. With some phenols (**2m** and **2w–2y**), a reduced indole **4a** from **1a** was observed in varying amounts. However, even in these cases, side reactions such as oxidative dimerization into 2,2'-biphenol or 3,3'-bisindole derivatives could not be observed, which suggested highly chemoselective coupling of **1a**. To demonstrate the practicality of the current method, synthesis of **3aa** and **3ak** was conducted in a gram scale (3 mmol of **1a**), giving comparable yields (**3aa**: 75% (condition A) and 97% (condition B); **3ak**: 48% (condition A) and 68% (condition B)). Lastly, 2,6-disubstituted **2af** with both *ortho*-positions blocked underwent *p*-arylation instead, but very slowly. It should be pointed out that the current coupling requires unprotected phenol and did not work with anisole derivative such as **2ag**, even under forcing conditions (60 °C, both conditions A & B). Likewise, other electron-rich (hetero) arenes, such as indoles, pyrrole, and benzofurans, failed to



provide the corresponding coupled product, under both conditions A and B (for a list of unsuccessful nucleophiles, see Chart S1†).

We then inspected substituted indoles for generality, using **2a** as a phenolic partner (Table 3). The presence of various aryl groups at C2 having different electron-density were well tolerated as in the formation of **3ba–3fa**. Various groups at C2, such as 2-naphthyl (**3ga**), 1-naphthyl (**3ha**), and alkyl groups (**3ia–3la**) were also allowed. Next, substitution at the C4–C7 of indoles was investigated. Those with 6- $\text{CF}_3$  (**1m**), 6-Me (**1n**), 5-F/6-F/7-F (**1o**, **1p**, and **1q**), 4-Br (**1r**), and 6- $\text{CO}_2\text{Me}$  (**1s**) all reacted smoothly. Despite steric hindrance, indoles having a 4-Me-substituent (**1t–1v**) delivered the corresponding products **3ta–3va** uneventfully.

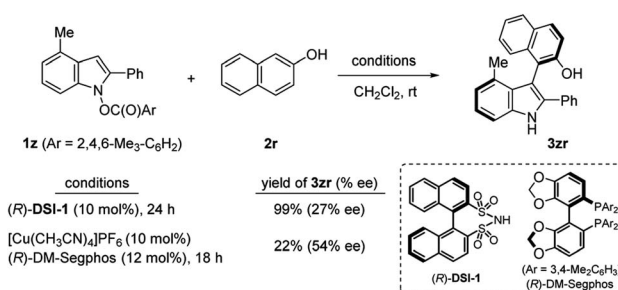
Notwithstanding the generality demonstrated in Table 3, the feasibility of the coupling with phenols requires the presence of C2-substitution. For example, C2/C3-unsubstituted indole derivative **1w** failed to give the desired product under both conditions. Instead, with  $\text{HNTf}_2$  catalyst, a mixture of *N*-substitution products **5wa** and **5wa'** were obtained in modest yield (eqn (1), Scheme 2). Presumably, in the absence of flanking C2-substituents, a C-attack of phenols that is sterically more demanding than an O-attack may be preferred. Substrate **1x** having C3-Me moiety underwent C3-selective coupling followed by cyclization, providing a benzofuroindoline **6xa** in low yield (eqn (2)). In contrast, **1y** with a C3-Ph group failed to couple with **2a** but instead underwent unprecedented 1,5-carboxy rearrangement to afford **7y** in modest yield (eqn (3)).



Scheme 2 Reactions of differently substituted *N*-carboxyindoles.

Then we turned our attention to atrop-selective indolylolation of phenols. Synthesis of axially chiral indolyl biaryl compounds has been previously realized by chiral Brønsted acid,<sup>25</sup> and transition metal catalysts.<sup>26</sup> However, given the unprecedented reversed polarity of indoles, it is highly intriguing whether the current heterobiarylation protocol can be rendered enantioselective. Toward this end, **1z** having 4-Me and *N*-mesitylene carboxylate as a leaving group was prepared (Scheme 3). Two catalytic systems appeared as viable solutions: a disulfonimide (*R*)-**DSI-1** (10 mol%) delivered the coupled product **3zr** in almost quantitative yield, albeit with a low 27% ee. To our delight, Cu(i)/DM-Segphos combination delivered **3zr** in 54% ee. The modest yield in the latter case was due to the extensive decomposition of **1z** into the reduced indole **4z** (68%) and 1,1'-bi(2-naphthol) (29%). These preliminary results offer an outstanding prospect of successful enantio-control in the future.

Having established the generality in the indolylolation of phenols as well as the feasibility of the asymmetric synthesis, we then conducted a kinetic analysis of the Cu(i)-catalyzed system that gave consistently high yield (>95%) with little side-products. The reaction was determined to be the first order in both **1a** and **2a**, and a half order in dimeric  $[\text{Cu}(\text{OTf})_2]_2 \cdot \text{C}_6\text{H}_6$ . The latter result suggested that the dominant form of the Cu-species is an inactive off-cycle dimer that is in equilibrium with an active monomeric Cu(i) complex.<sup>27</sup>



Scheme 3 Preliminary atropselective indolylolation of 2-naphthol.

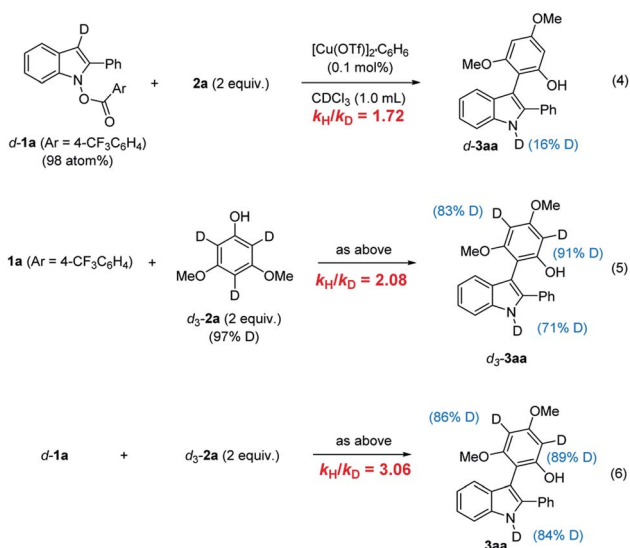
Table 3 Scope of *N*-carboxyindole electrophiles<sup>a</sup>

	<p><b>1</b> (Ar = 4-<math>\text{CF}_3</math>-<math>\text{C}_6\text{H}_4</math>)</p> <p><b>2a</b> (Ar'-H)</p> <p><b>3ba–3ua</b></p> <p><b>4</b></p>
<p><b>3ba</b>, R = Me A (5 h, 88%), B (2 h, 93%)</p> <p><b>3ca</b>, R = OMe A (6 d, 39%), B (48 h, 81%)</p> <p><b>3da</b>, R = <math>\text{CF}_3</math> A (8 h, 76%), B (2 h, 99%)</p> <p><b>3ea</b>, R = Cl A (6 h, 76%), B (1 h, 98%)</p> <p><b>3fa</b>, R = CN A (0%, 20% of <b>4f</b>), B (48 h, 70%)</p>	<p><b>3ga</b>, R = 2-Naph A (48 h, 82%), B (1 h, 95%)</p> <p><b>3ha</b>, R = 1-Naph A (5 d, 15%, 43% of <b>4h</b>),<sup>b</sup> B (9 h, 89%)</p> <p><b>3ia</b>, R = <i>n</i>-Pr A (8 h, 75%), B (7 h, 72%)</p> <p><b>3ja</b>, R = <i>o</i>-Pr A (24 h, 37%),<sup>b</sup> B (24 h, 36%)</p> <p><b>3ka</b>, R = <i>o</i>-Hex A (3.5 d, 41%),<sup>b</sup> B (10 h, 58%)</p> <p><b>3la</b>, R = <i>t</i>-Bu A (36 h, 33%),<sup>b</sup> B (10 h, 85%)</p>
<p><b>3ta</b>, Ar' = Ph A (12 h, 69%), B (12 h, 89%)</p> <p><b>3ua</b>, Ar' = 4-MeO-<math>\text{C}_6\text{H}_4</math> A (26 h, 51%), B (14 h, 74%)</p> <p><b>3va</b>, Ar' = 4-<math>\text{CF}_3</math>-<math>\text{C}_6\text{H}_4</math> A (3 h, 87%), B (2 h, 99%)</p>	<p><b>3ma</b>, R = 6-<math>\text{CF}_3</math> A (8 h, 78%), B (21 h, 91%)</p> <p><b>3na</b>, R = 6-Me A (12 h, 73%), B (3 h, 96%)</p> <p><b>3oa</b>, R = 5-F A (24 h, 88%), B (1 h, 94%)</p> <p><b>3pa</b>, R = 6-F A (3 h, 79%), B (5 h, 96%)</p> <p><b>3qa</b>, R = 7-F A (48 h, 19%, 32% of <b>4p</b>), B (6 h, 72%)</p> <p><b>3ra</b>, R = 4-Br A (24 h, 69%, 8% of <b>4n</b>),<sup>b,c</sup> B (14 h, 49%, 32% of <b>4n</b>)<sup>c</sup></p> <p><b>3sa</b>, R = 6-<math>\text{CO}_2\text{Me}</math> A (3 d, 53%),<sup>b</sup> B (6 h, 93%)</p>

<sup>a</sup> Reaction conditions: **1a** (0.1 mmol) and **2** (2 equiv.) in  $\text{CHCl}_3$ ; see text for conditions A and B. Isolated yield after chromatography. <sup>b</sup> 20 mol% of  $\text{HNTf}_2$ . <sup>c</sup> At 60 °C.

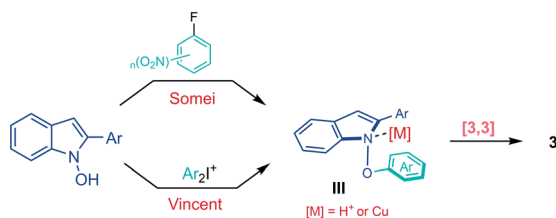
The most enlightening piece of evidence was obtained from the deuterium labeling study (Scheme 4). For the measurement of the kinetic isotope effect, we prepared *d*-**1a** and *d*<sub>3</sub>-**2a**,<sup>22</sup> and the  $k_{\text{H}}/k_{\text{D}}$  was determined from the rate constants  $k_{\text{obs}}$  (s<sup>-1</sup>) measured in separate reactions.<sup>28</sup> The reaction of *d*-**1a** with **2a** showed a significant primary kinetic isotope effect ( $k_{\text{H}}/k_{\text{D}} = 1.72$ ) and in the reaction of **1a** and *d*<sub>3</sub>-**2a**,  $k_{\text{H}}/k_{\text{D}}$  (2.08) were observed (eqn (4) and (5)). When both *d*-**1a** and *d*<sub>3</sub>-**2a** are deuterated (eqn (6)), a combined isotope effect was manifested. These kinetic isotope effects suggested that re-aromatization step (**IV** to **3**) in which both the C3–H bond of the indole *d*-**1a** and the *ortho*-C–H bond of the phenol *d*<sub>3</sub>-**2a** are cleaved may, at least in part, limit the turnover. Interestingly, significant incorporation of deuterium at the N1 of **3aa** was observed when deuterated phenol *d*<sub>3</sub>-**2a** was employed. For instance, employing *d*-**1a** as the only deuterium source resulted in a minimal introduction of *d*-atom (eqn (4)), but the use of *d*<sub>3</sub>-**2a** resulted in a larger degree of *d*-incorporation at N1 (eqn (5)). This indicated the N1–H hydrogen mostly came from the *ortho*-hydrogen of the phenol **2a**.

Based on the above data, the mechanism of the heterobiaryl coupling of umpoled indoles was put forward as in Scheme 5. From the precedents of [3,3]-sigmatropic rearrangement of *N*-phenoxyindoles **III** to the product **3** (Scheme 5A), we initially considered similar routes for both Brønsted acid- and Cu(i)-catalysis. However, the required S<sub>N</sub>2 attack forming a weak N–O bond (50–60 kcal mol<sup>-1</sup>) was difficult to imagine.<sup>29</sup> To this end, we attempted to prepare *N*-phenoxy-2-Ph-indole **9** from the reaction of *N*-hydroxy-2-Ph-indole **8** with a benzyne precursor (eqn (7)). We could not observe **9** during the reaction, and the corresponding [3,3]-sigmatropic rearrangement product **10** was directly obtained in 48% yield in 2 h. This result suggested that the [3,3]-rearrangement of the intermediate **9** is not catalyzed by H<sup>+</sup> or Cu(i). Furthermore, in contrast to our current protocols which required electron-rich phenols for efficient conversion, unsubstituted phenol underwent smooth [3,3]-rearrangement at rt. These led us to consider an alternative mechanism.

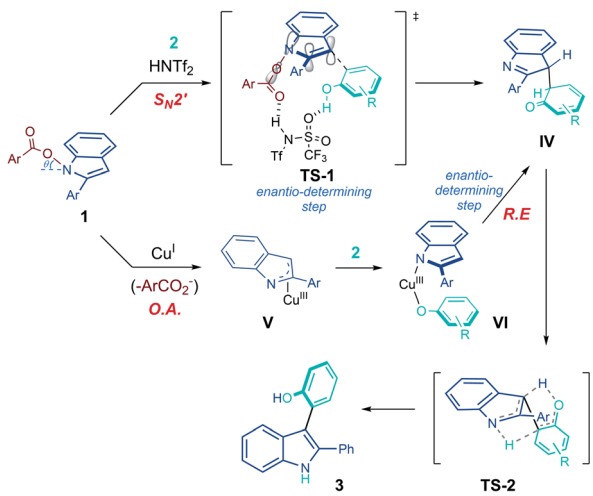


Scheme 4 Kinetic isotope effect.

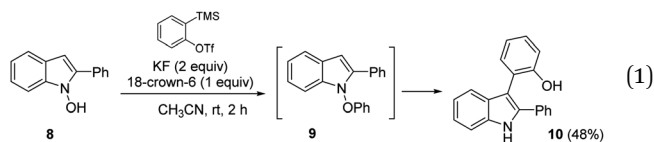
## A. [3,3]-sigmatropic (Somei/Vincent)



## B. Our proposed mechanism



Scheme 5 A proposed mechanism.



During the study on the asymmetric heterobiarylation (Scheme 3), we inspected the effect of *N*-carboxylate leaving groups on the %ee of the product **3zr**, employing a set of *N*-carboxylates of varying steric and electronic demand (4-CF<sub>3</sub>C<sub>6</sub>H<sub>4</sub>CO<sub>2</sub><sup>-</sup>, 4-MeO-C<sub>6</sub>H<sub>4</sub>CO<sub>2</sub><sup>-</sup>, and 2-Naph-CO<sub>2</sub><sup>-</sup>; Tables S5 and S6 in ESI†). Interestingly, with Brønsted acid (*R*)-**DSI-1**, the %ee of **3zr** varied widely from 13% ee to 19% ee, depending on the carboxylates. In contrast, the %ee of **3zr** with Cu(i)/DM-Segphos system remained almost similar (67–69% ee) irrespective of the leaving carboxylates. This suggest that the carboxylates play a role in the enantio-determining step of Brønsted acid-catalysis but not in the Cu(i)-catalysis. A concerted S<sub>N</sub>2' mechanism<sup>18d,e</sup> where the sulfonimides bind both to the *N*-carboxylate and the phenols (**TS-1**) may account for such an outcome (Scheme 5B).<sup>30</sup> In contrast, with Cu(i)/L\* system, the enantio-determining step may come after the liberation of the carboxylate and the %ee of **3** may be insensitivity to the carboxylates of **1**. Oxidative addition of Cu(i) into N–O bond in **1** to form aza-allyl Cu(III) **V**,<sup>19</sup> followed by ligand exchange with phenols, and reductive elimination from **VI** to **IV** may account for the observation. In the reaction of **1** with a stoichiometric amount of Cu-complex (**1**:Cu = 1:1) in the absence of phenols, immediate (<1 h)

decomposition of **1** was noted, further suggesting an oxidative addition of Cu(I) into **1**.

As Somei suggested,<sup>18e</sup> the carboxylate O-atom deviates from the indole plane ( $\theta$ ) as a result of repulsion between N- and O-lone pairs, which becomes more pronounced with a bulky C2-substituent on the indole **1** as in our case. The resulting sp<sup>3</sup> like N1-atom may assist the proposed S<sub>N</sub>2' substitution by aligning the  $\sigma^*(\text{N}-\text{O})$  parallel to the  $\pi^*(\text{C}=\text{C})$  for facile nucleophilic attack at C3 or may facilitate the oxidative addition by allowing coordination of Cu(d) with both  $\sigma^*(\text{N}-\text{O})$  and  $\pi^*(\text{C}=\text{C})$  orbital.<sup>31</sup>

In the atrop-selective processes (Scheme 3), the incipient centered chirality in **IV** may be transferred to the axial chirality in **3** via a **TS-2**. The observation of small but discernible primary kinetic isotope effect with both *d*-**1a** and *d*<sub>3</sub>-**2a** could be rationalized by the simultaneous intramolecular proton transfers in the transition state such as **TS-2**.

## Conclusions

In summary, we have developed an efficient *ortho*-indolylation of phenols, based on Brønsted acid- or Cu(I)-catalyzed reaction of *N*-carboxyindole derivatives. We demonstrated that such polarity-inverted indoles participate in the C–H arylation with phenols, which is unprecedented to the best of our knowledge. We proposed that the reaction proceeded through an S<sub>N</sub>2' substitution for Brønsted acid catalysis or through oxidative addition for Cu(I)-catalysis. The sp<sup>3</sup> hybridized nitrogen of the *N*-carboxyindoles was proposed to facilitate both processes. We also demonstrated a preliminary atropselective biaryl synthesis. Efforts to improve the enantioselectivity and to understand the mechanistic underpinning more precisely are currently underway and will be reported in due course.

## Author contributions

C.-M. P. discovered the transformation and performed the initial study with Cu(OTf)<sub>2</sub> catalyst. N. H. N. and S. M. O. performed all the experimental work. S. S. conceived Brønsted acid- and Cu(I) catalysis, directed the project, wrote the paper, and designed mechanistic study. All authors discussed the results and commented on the manuscript.

## Conflicts of interest

The authors declare no conflict of interest.

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