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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_N2' substitution or a Cu(I)–Cu(III) cycle, with Brønsted acid or Cu(I) catalysts, respectively.

Introduction

Bi(hetero)aryl motifs are widely found in bioactive natural products and are commonly utilized as chiral auxiliaries and ligands.[1] 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.[2] In addition, several non-metal protocols,[3] such as hypervalent iodine chemistry,[4] electrochemical oxidations,[5] and photoredox catalysis,[6] 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.[7] Control of site-selectivity of phenols (*o*-, *m*-, *p*-, and *O*-)[8] and indoles[9] also presents a prominent challenge in the absence of directing groups for which extra steps are required for the installation and removal.[10]

We anticipated that inverting the polarity of nucleophilic indoles may enable precise control of chemoselectivity for the oxidative C–H heterobiaryl coupling.[11] In the past, C3-umpoled indoles were accessed through electrophilic activation,[12a,b] oxidation,[12c,d] or hydroarylation of *N*-acylindole derivatives.[12e–g] More recently, the groups of Kita, Yorimitsu, Procter, and Maulide have developed metal-free C–H heteroarylation based on the activation of sulfoxides.[13,14] 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.[15a] Procter and coworkers developed heteroarylation of phenols with activated benzothiophene-*S*-oxides,[15b–d] which occurred selectively at the *ortho*-[15c] or *para*-position[15d] of phenols (Scheme 1A).

In continuation of our interest in aliphatic Umpolung chemistry based on N–O bond redox,[16] we turned our attention to the aromatic Umpolung by way of *N*-hydroxyindoles which was pioneered by Somei and coworkers.[17] Somei and others disclosed C3-arylation of indoles *via* [3,3]-sigmatropic rearrangement of *N*-carboxyindoles[18] that were accessed by nucleophilic aromatic substitution (S_NAr)[18a,b] or by the *O*-arylation of *N*-hydroxyindoles with biaryliodonium salt.[18c] S_N2' substitution *N*-hydroxyindoles with indoles and pyrroles was also demonstrated (Scheme 1B).[18d,e] 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.[19] 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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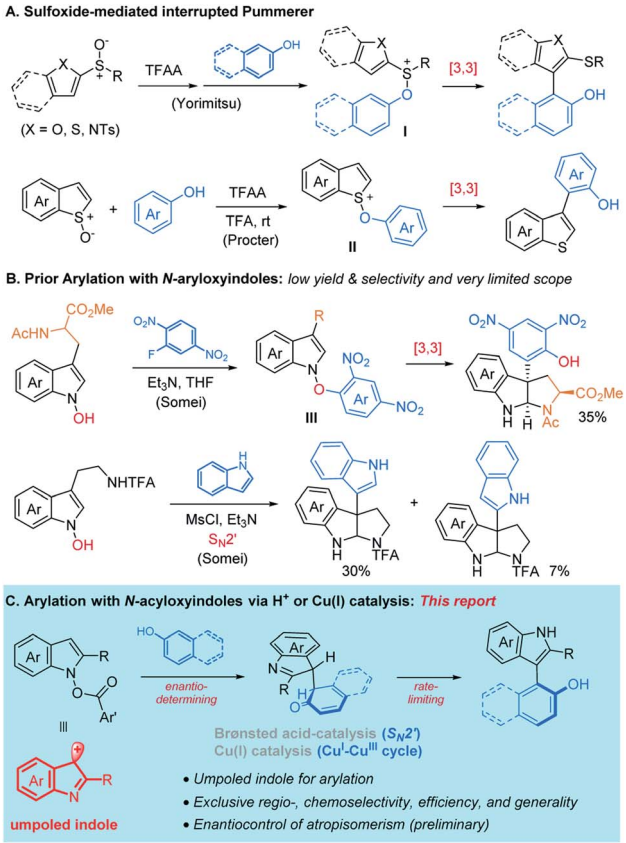


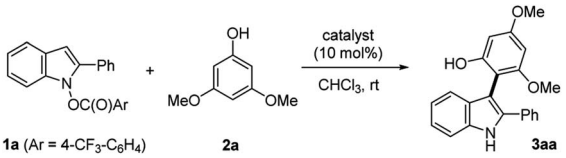
Scheme 1 Inversion of polarity in the heterobiaryl coupling.

partners remains elusive. We disclose herein two catalytic systems for the union of umpoled 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.[20] 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.[20d] 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).[21,22] Weak acids underwent a sluggish conversion to **3aa** (entries 1 and 2). The product **3aa** had two inequivalent methoxy groups in the ^1H and ^{13}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**.[22] Superacids, such as TfOH, HBF_4, or $HNTf_2$ significantly accelerated the formation of **3aa**, reducing the reaction time to several hours (entries 3–5). Unlike TfOH and HBF_4 which were not completely

Table 1 Coupling of **1a** and **2a**: Brønsted and Lewis acid catalysts[a]



Entry	Catalyst	Time	**3aa**[b] (%)
1	$(PhO)_2P(O)OH$	4 days	26[c]
2	CF_3CO_2H	3.5 days	43[c]
3	TfOH	12 h	84
4	$HBF_4 \cdot OEt_2$	8 h	86
5	$HNTf_2$	16 h	83
6	$HNTf_2$[d]	8 h	85
7	$HNTf_2$ (1 mol%)[d,e]	22 h	85
8	$AuCl(PPh_3)$, AgOTf	2 days	10
9	$Fe(OTf)_3$	1 day	96
10	$Zn(OTf)_2$	2.5 days	96
11	$Cu(OTf)_2$	0.5 h	53[f]
12	$Cu(OTf)_2$ (1 mol%)	3 h	69[g]
13	CuBr	5 h	96
14	$Cu(MeCN)_4 \cdot BF_4$	10 min	74
15	$[Cu(OTf)]_2 \cdot C_6H_6$	5 min	76[f]
16[h]	$[Cu(OTf)]_2 \cdot C_6H_6$ (0.1 mol%)[e]	0.5 h	93
17[h]	$[Cu(OTf)]_2 \cdot C_6H_6$ (0.01 mol%)[e]	1 h	>99
18[h,i]	$[Cu(OTf)]_2 \cdot C_6H_6$ (0.1 mol%)[e]	8 h	89

[a] **1a** (0.1 mmol), **2a** (0.2 mmol) and catalyst (10 mol%) in $CHCl_3$ (0.1 M). [b] Determined by ^1H NMR with CH_2Br_2 as an internal standard. [c] Starting **1a** remained. [d] 0.2 M in $CHCl_3$. [e] The catalyst was added as a stock solution in $CHCl_3$ (entry 7) and in EtOAc (entries 16–18). [f] Messy mixture due to decomposition of **1a**. [g] 2-Ph-indole **4a** (10%) was observed as byproduct. [h] $CHCl_3$ (0.05 M). [i] **2a** (1.2 equiv.).

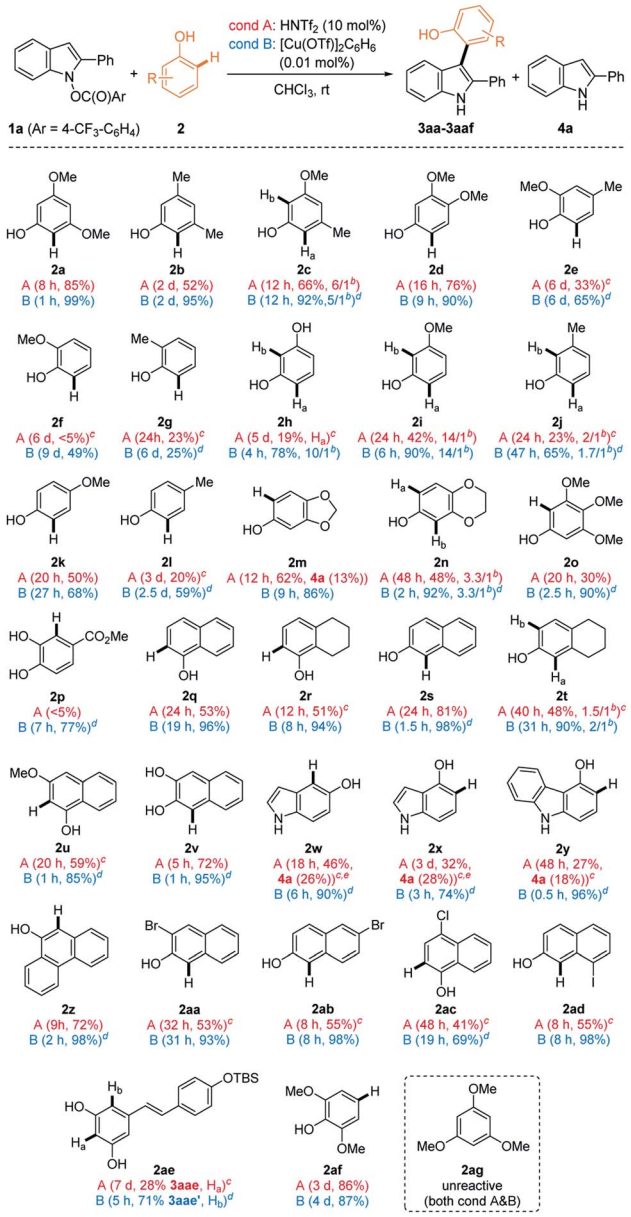
soluble, $HNTf_2$ formed a homogeneous solution in chloroform and gave more reproducible results. The reaction was further accelerated at a higher concentration (entry 6). Reduction of the catalyst loading to 1 mol% still maintained significant activity, furnishing **3aa** in 85% yield in a day (entry 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).[22] Lewis acids, such as $Fe(OTf)_3$ and $Zn(OTf)_2$ gave excellent yields of **3aa**, although it took several days (entries 7–9). A dramatic acceleration could be observed with $Cu(OTf)_2$, 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 $Cu(OTf)_2$ 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 $CHCl_3$ 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

$[Cu(OTf)]_2 \cdot C_6H_6$, 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 $HNTf_2$ and conditions B: 0.01 mol% of $[Cu(OTf)]_2 \cdot C_6H_6$), we explored the general applicability of the phenol nucleophiles in the heterobiaryl coupling with umpoled indole **1a** (Table 2). Initially, monocyclic phenols (**2a–2p**) were employed in the reaction. Not surprisingly, electron-richer 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**),[23] 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 $HNTf_2$ 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 indolylation provided a unique opportunity for the modification of phenolic natural products. For example, TBS-protected resveratrol **2ae**[24] coupled with **1a** only at H_a using $HNTf_2$ (condition A), although the yield of **3aae** was modest (28%). Alternatively, with Cu(I) catalyst (condition B), exclusive indolylation at H_b was obtained to give its regioisomer **3aae′** in 71% yield.[23] 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

Table 2 Scope of phenol nucleophiles[a]



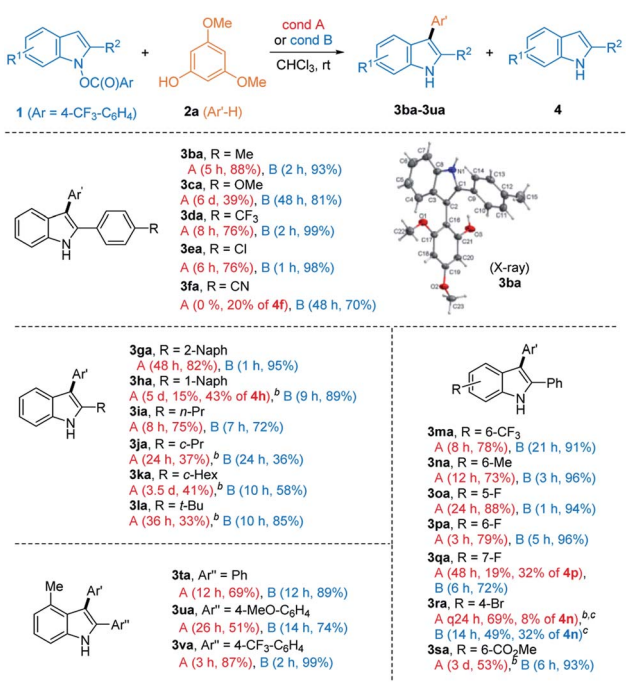
[a] Reaction conditions: **1a** (0.1 mmol) and **2** (2 equiv.) in $CHCl_3$; conditions A (10 mol% of $HNTf_2$, in $CHCl_3$ (0.2 M)) and conditions B (0.01 mol% of $[Cu(OTf)]_2 \cdot C_6H_6$ in $CHCl_3$ (0.05 M)); isolated yield after chromatography. [b] Regioisomeric ratio (H_a : H_b). [c] 20 mol% of $HNTf_2$. [d] 0.1 mol% of $[Cu(OTf)]_2 \cdot C_6H_6$. [e] At 60 °C.

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

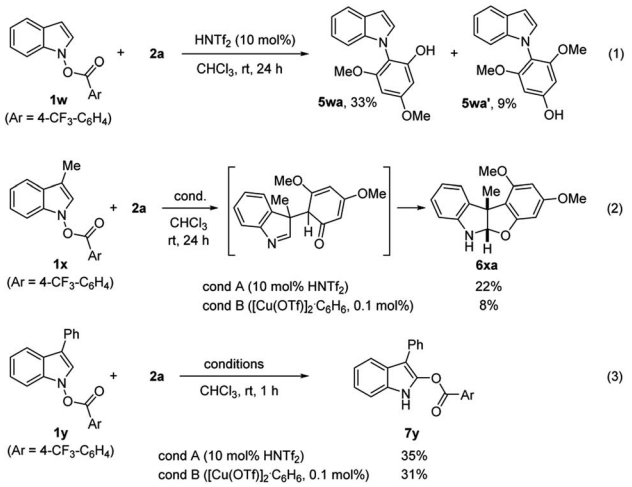
We then inspected substituted indoles for generality, using **2a** as a phenolic partner (Table 3). The presence of various aryl groups at C2 having different electron-density were well tolerated as in the formation of **3ba–3fa**. Various groups at C2, such as 2-naphthyl (**3ga**), 1-naphthyl (**3ha**), and alkyl groups (**3ia–3la**) were also allowed. Next, substitution at the C4–C7 of indoles was investigated. Those with 6-CF_3 (**1m**), 6-Me (**1n**), 5-F/6-F/7-F (**1o**, **1p**, and **1q**), 4-Br (**1r**), and 6-CO_2Me (**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 $HNTf_2$ 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)).

Table 3 Scope of *N*-carboxyindole electrophiles[a]



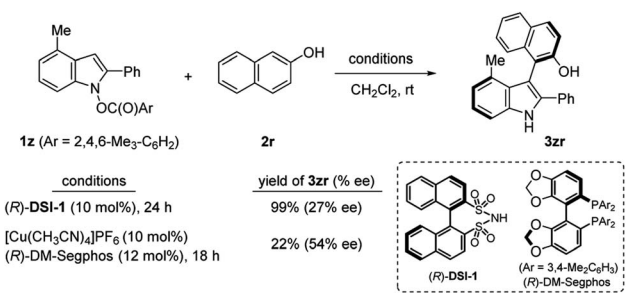
[a] Reaction conditions: **1a** (0.1 mmol) and **2** (2 equiv.) in $CHCl_3$; see text for conditions A and B. Isolated yield after chromatography. [b] 20 mol% of $HNTf_2$. [c] At 60 °C.



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

Then we turned our attention to atrop-selective indolylation of phenols. Synthesis of axially chiral indolyl biaryl compounds has been previously realized by chiral Brønsted acid,[25] and transition metal catalysts.[26] 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.

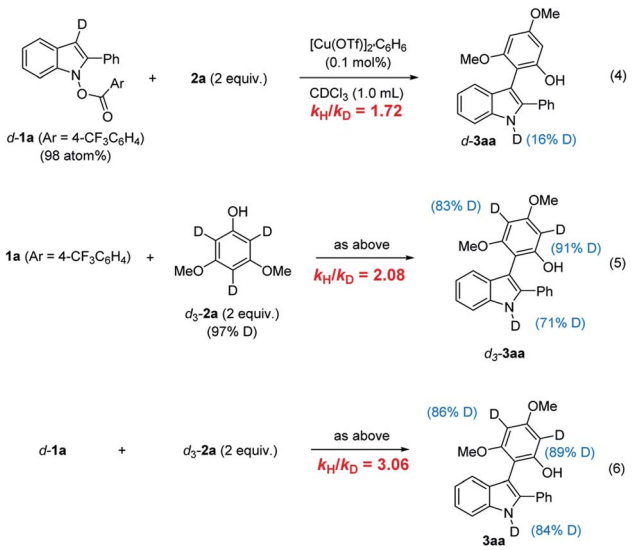
Having established the generality in the indolylation of phenols as well as the feasibility of the asymmetric synthesis, we then conducted a kinetic analysis of the Cu(I)-catalyzed system that gave consistently high yield (>95%) with little side-products. The reaction was determined to be the first order in both **1a** and **2a**, and a half order in dimeric $[Cu(OTf)]_2 \cdot C_6H_6$. 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.[27]



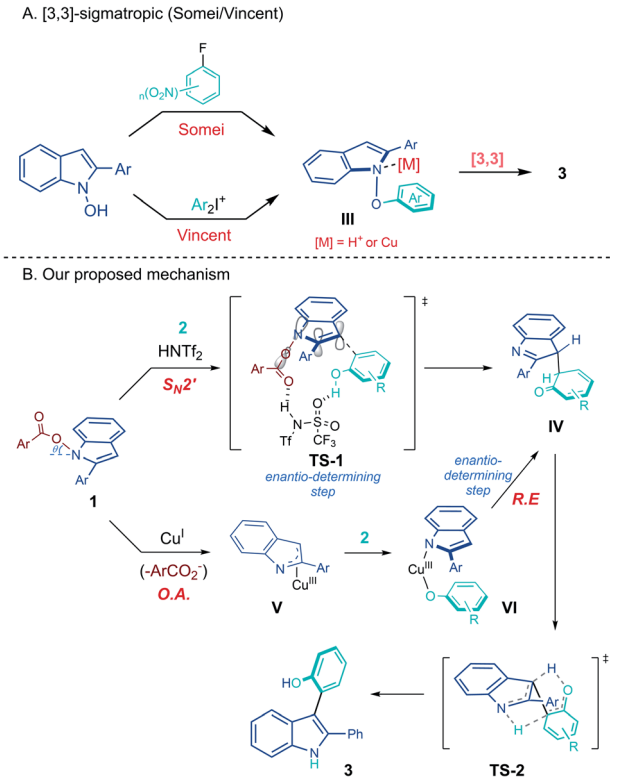
Scheme 3 Preliminary atropselective indolylation of 2-naphthol.

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_3-**2a**,[22] and the k_H/k_D was determined from the rate constants k_{obs} (s^{-1}) measured in separate reactions.[28] The reaction of *d*-**1a** with **2a** showed a significant primary kinetic isotope effect ($k_H/k_D = 1.72$) and in the reaction of **1a** and d_3-**2a**, k_H/k_D (2.08) were observed (eqn (4) and (5)). When both *d*-**1a** and d_3-**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_3-**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_3-**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_3-**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**.

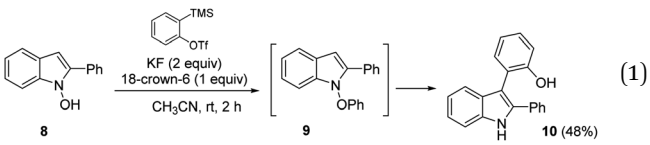
Based on the above data, the mechanism of the heterobiaryl coupling of umpoled indoles was put forward as in Scheme 5. From the precedents of [3,3]-sigmatropic rearrangement of *N*-phenoxyindoles **III** to the product **3** (Scheme 5A), we initially considered similar routes for both Brønsted acid- and Cu(I)-catalysis. However, the required S_N2 attack forming a weak N–O bond (50–60 kcal mol^{-1}) was difficult to imagine.[29] 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^+ 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.



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-$CF_3C_6H_4CO_2$–, 4-MeO–$C_6H_4CO_2$–, and 2-Naph–CO_2–; 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_N2' mechanism[18d,e] where the sulfonimides bind both to the *N*-carboxylate and the phenols (**TS-1**) may account for such an outcome (Scheme 5B).[30] 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 from aza-allyl Cu(III) **V**,[19] 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,[18e] the carboxylate O-atom deviates from the indole plane (θ) 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^3 like N1-atom may assist the proposed S_N2' substitution by aligning the σ^*(N–O) parallel to the π^*(C=C) for facile nucleophilic attack at C3 or may facilitate the oxidative addition by allowing coordination of Cu(*d*) with both σ^*(N–O) and π^*(C=C) orbital.[31]

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_3-**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_N2' substitution for Brønsted acid catalysis or through oxidative addition for Cu(I)-catalysis. The sp3 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 $Cu(OTf)_2$ 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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Notes and references

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