Communication

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Metal-Free Approach to Biaryls from Phenols and Aryl Sulfoxides by Temporarily Sulfur-Tethered Regioselective C–H/C–H Coupling

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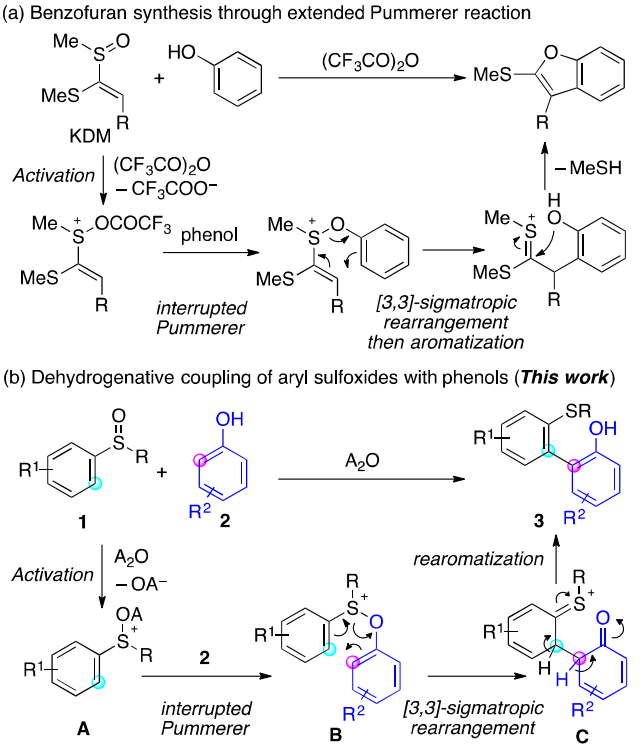
Supporting Information Placeholder

ABSTRACT: We have developed metal-free regiocontrolled dehydrogenative C–H/C–H cross-coupling of aryl sulfoxides with phenols by means of trifluoroacetic anhydride. Since the reaction would proceed through an interrupted Pummerer reaction followed by sulfonium-tethered [3,3]-sigmatropic rearrangement, the C–H/C–H coupling takes place exclusively between the *ortho* positions of both substrates. Various functional groups including carbonyl, halo, siloxy, and even boryl moieties are compatible. The biaryl products naturally possess hydroxy and sulfanyl groups, which allows the products to be useful synthetic intermediates, as evidenced by the syntheses of π-expanded heteroarenes such as unprecedented 7,12-dioxa[8]helicene.

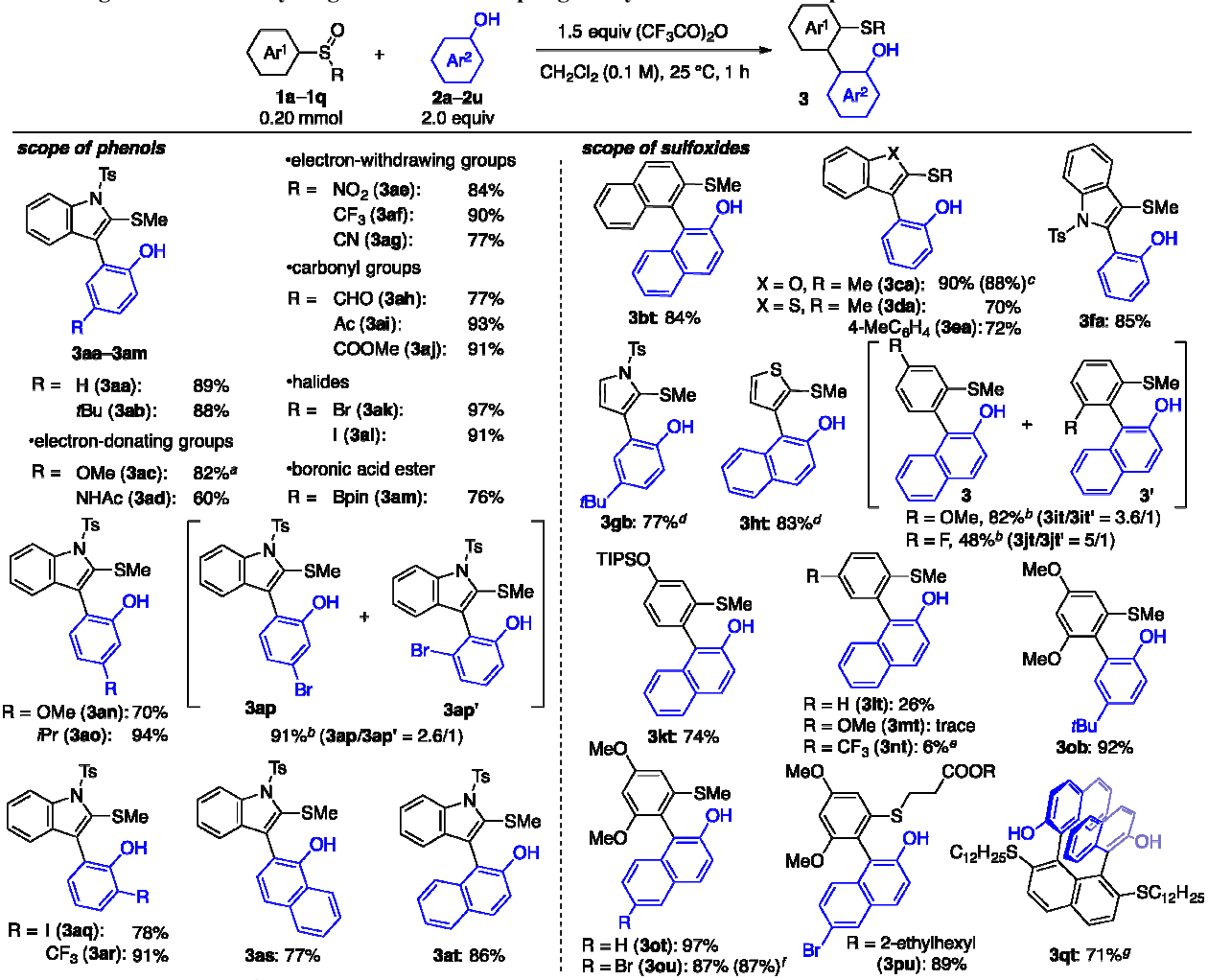
Biaryl motifs represent a privileged substructure in bioactive compounds and organic functional materials. Therefore, a number of synthetic approaches to biaryl skeletons have been exploited. Over the past 40 years, transition metal-catalyzed cross-coupling reactions of aryl halides with aryl organometallic reagents have occupied a central place in biaryl synthesis.[1] For the last decade, direct aromatic C–H arylation has been emerging as a game-changing means to connect two aromatic rings.[2] The most straightforward and ideal method would be dehydrogenative C–H/C–H coupling reaction starting from two individual arenes. Since the pioneering discovery by Fagnou in 2007,[3] dehydrogenative C–H/C–H cross-coupling reactions have been actively investigated by utilizing transition metal catalysts such as copper-catalyzed asymmetric BINOL synthesis.[4,5] However, catalyst loadings to achieve efficient C–H/C–H coupling were usually high and most of transition metal complexes are expensive. In addition, heavy metal contaminations of products can be a fatal problem in research on bioactive agents[6] as well as organic electronic devices.[7] Consequently, it has been desired to establish new methodologies to realize efficient metal-free dehydrogenative C–H/C–H cross-coupling.[4d,8] To this end, radical-mediated processes promoted by hypervalent iodine reagents[9] or anodic oxidation[10] have been developed. However, these strategies incur poor regioselectivity, mediocre functional group compatibility, and/or employment of large excess amounts of radical-accepting arenes. Although several regioselective reactions have been reported including base-mediated arylation of heteroaromatic *N*-oxides,[11] Bartoli-type reaction of 2-halonitroarenes with arylmagnesium reagents,[12] chiral Brønsted acid-catalyzed atropselective synthesis of 2,2'-diamino-1,1'-binaphthalenes through benzidine rearrangement,[13] and Brønsted acid-mediated reaction of hydroxy arenes with 2,5- or 2,6-substituted 1,4-benzoquinone analogues,[14] a restricted range of arenes could engage in these transformations.

Scheme 1. C–H/C–H coupling based on extended Pummerer reaction



Recently, extended Pummerer reactions of unsaturated sulfoxides have been attracting increasing attention[15] since they offer characteristic transformations utilizing the unique reactivity of sulfur. Some extended Pummerer reactions result in fascinating C(sp^2)–H functionalization at the β position of the sulfinyl group.[16] Indeed, we reported the synthesis of benzofurans by connecting phenols with peculiar vinyl sulfoxides, ketene dithioacetal monoxides (KDM), at each of their β C(sp^2)–H bonds (Scheme 1a).[17] A plausible mechanism includes 1) the activation of the sulfoxide with trifluoroacetic anhydride, 2) capture of the resulting sulfonium with phenol, 3) sulfonium-accelerated [3,3]-sigmatropic rearrangement[18] with concomitant loss of the aromaticity of phenol, and 4) overall aromatization. During the course of the reaction, the cationic sulfonium moiety acts as a directing group to realize regioselective C–C bond formation.

Table 1. Regiocontrolled dehydrogenative cross-coupling of aryl sulfoxides 1 with phenols 2



[a]Performed at –40 °C for 2 h. [b]Combined yield of regioisomers. Isomeric ratios are in parentheses. [c]Performed on 19 mmol scale. [d]Performed at 40 °C. [e]Yield was determined by ^{1}H NMR analysis. [f]Performed on 5.0 mmol scale. [g]Reaction conditions: **1q** (0.20 mmol), 2-naphthol (**2t**, 3.5 equiv), $(CF_3CO)_2O$ (3.0 equiv), CH_2Cl_2 (0.1 M), 25 °C, 1 h.

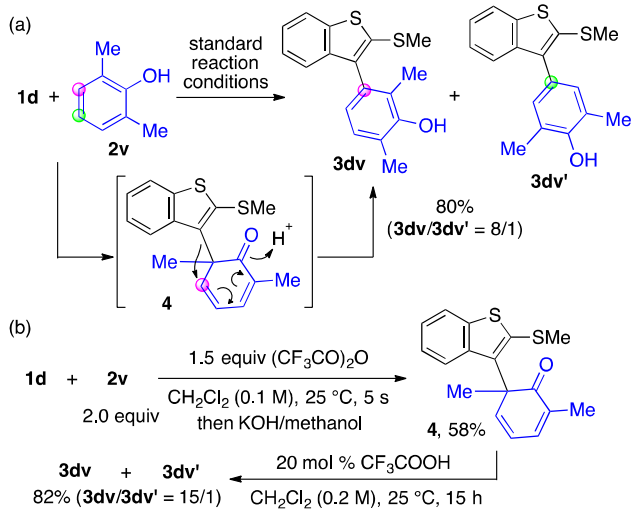
We envisioned that this extended Pummerer strategy with phenols as substrates would be applicable to the synthesis of biaryls. Our working hypothesis is depicted in Scheme 1b. Activation of the aryl sulfoxide **1** followed by nucleophilic substitution at the cationic sulfur center with phenol **2** would form intermediate **B**. Given that [3,3]-sigmatropic rearrangement would occur with the loss of the aromaticity of both aryl sulfonium and phenol, regiocontrolled C–C bond formation should result by a temporarily sulfonium-tethered intramolecular process. Finally, rearomatization of **C** furnishes biaryl product **3**. Biaryl **3** has synthetically useful hydroxy and sulfanyl moieties, further transformation being highly expected.[19]

Treatment of 2-(methylsulfinyl)-1-tosylindole (**1a**) and phenol (**2a**) with trifluoroacetic anhydride in CH_2Cl_2 at 25 °C afforded an 89% yield of 3-(2-hydroxyphenyl)-2-methylsulfanyl-1-tosylindole (**3aa**) as the sole product (Table 1). As expected, the C–C bond formation took place exclusively between the *ortho* (or *β*) positions of **1a** and **2a**. Phenols having an electron-donating or -withdrawing group at the 4-position reacted with **1a** to provide the corresponding biaryls **3ac**–**aj** in good yields. Carbonyl, halogen, and pinacolatoboryl moieties were well tolerated under the reaction conditions to yield **3ah**–**am**. Arylation of 3-methoxyphenol (**2n**) or 3-isopropylphenol (**2o**) with **1a** occurred exclusively at the less hindered 6-position yielding **3an** or **3ao** as the single product, while that of 3-bromophenol (**2p**) gave a mixture of regioisomers **3ap** and **3ap'** with moderate selectivity favoring sterically less demanding **3ap**. This reaction also accommodates 2-substituted phenols to afford the corresponding sterically congested 2,6-disubstituted phenols **3aq** and **3ar** efficiently. Naphthols **2s** and **2t** were also converted to the corresponding arylated products **3as** and **3at**, respectively. Notably, 2-naphthol (**2t**) reacted at the C1 position exclusively due to the stronger double-bond character of the C1–C2 bond of the naphthalene core than that of the C2–C3 bond. These *ortho*-selectivities clearly indicate the reactions proceeded via the sulfonium-tethered process shown in Scheme 1b.

This biaryl synthesis was also applicable to a wide range of aryl sulfoxides. Indeed, 2-methylsulfinyl-substituted naphthalene **1b**, benzofuran **1c**, and benzothiophene **1d** afforded the desired products in good to excellent yields. Instead of the methylsulfinyl moiety, an aromatic *p*-tolylsulfinyl moiety served as an effective directing group. In the reaction of unsymmetrical diaryl sulfoxide **1e**, the potentially reactive *p*-tolyl group remained intact, and regioselective arylation occurred at the benzothiophene unit of the weaker aromaticity to yield **3ea**. C–C bond formation

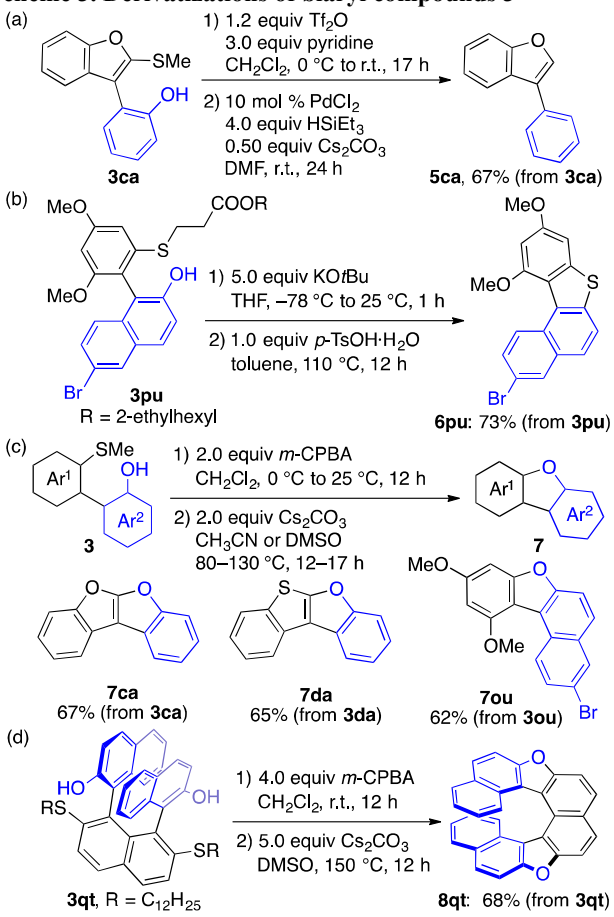
proceeded at the 2-position when 3-(methylsulfinyl)indole **1f** was employed. Monocyclic pyrrolyl and thienyl sulfoxides **1g** and **1h** also reacted at their 3-positions with perfect regioselectivity. Not only heteroaromatic sulfoxides but also phenyl sulfoxides **1i–l**, **1o**, and **1p** participated in the arylation.[20] The triisopropylsilyl ether in **1k** survived under the reaction conditions as well as improved the regioselectivity of the arylation due to the steric hindrance (**3it** and **3jt** vs. **3kt**). Preferably, the phenyl groups of the sulfoxides should be electron-rich as parent methyl phenyl sulfoxide (**1l**) afforded the product **3lt** in 26% yield. We assume that the electron-donating group(s) at the 3- (and 5-) position(s) would stabilize the corresponding cationic intermediate **C** in Scheme 1b to facilitate the [3,3]-sigmatropic rearrangement of **B** to **C**. Indeed, 4-methoxyphenyl methyl sulfoxide (**1m**), which stabilizes not **C** but **B**, afforded a trace amount of product **3mt** due to the elevated activation energy barrier for the pathway from **B** to **C**. Unfortunately, 4-trifluoromethylphenyl methyl sulfoxide (**1n**) afforded the product **3nt** in very low yield. The coupling reaction of 2,7-di(dodecylsulfinyl)naphthalene (**1q**) with 2-naphthol (**2t**) occurred at the *peri* positions to afford 1,8-dinaphthylated naphthalene **3qt** regioselectively in 71% yield. The formation of sterically congested 1,2,7,8-substituted **3qt** highlights the efficiency, robustness, and potentiality of the present methodology (*vide infra*, specifically in Scheme 3d). The reactions could be conducted on larger scales, as demonstrated in the synthesis of **3ca** and **3ou**, which clearly show the robustness of our system.

Scheme 2. Mechanistic investigations



To further verify our mechanistic proposal in Scheme 1b, the reaction of 2,6-dimethylphenol (**2v**) was performed. If this reaction proceeded through a Friedel-Crafts pathway, 4-arylated-2,6-dimethylphenol **3dv'** should be the conceivable major product. However, C–C bond formation proceeded at the 3-position of **2v** preferentially to furnish **3dv** as the major product, along with **3dv'** as the minor isomer (Scheme 2a). On the basis of this result, we are tempted to propose a mechanism for the *meta*-selective coupling. According to the scenario shown in Scheme 1b, cyclohexadienone intermediate **4** would be generated via an interrupted Pummerer reaction/[3,3]-sigmatropic rearrangement pathway. With the aid of trifluoroacetic acid generated *in situ*, **4** would then undergo protonation-induced 1,2-shift[21] of the benzothiophene unit. Notably, intermediate **4** was indeed isolated in 58% yield when the coupling reaction was quenched by methanolic KOH immediately in 5 s (Scheme 2b). Naturally, treatment of **4** with catalytic trifluoroacetic acid gave **3dv**.[22]

Scheme 3. Derivatizations of biaryl compounds 3



After the conversion of the phenolic hydroxy group into a triflate, global reduction by means of a hydrosilane/palladium catalyst system[23] gave **5ca** (Scheme 3a), traceless biaryl coupling[24] hence being achieved. Instead of the reductive removal of the tethering units, we could take advantage of these functional groups for derivatizations of **3** into π-expanded heteroarenes. After removal of the propionate moiety on **3pu** under basic conditions,[25] *p*-toluenesulfonic acid-mediated intramolecular condensation[26] furnished benzonaphthothiophene **6pu** in 73% yield over two steps (Scheme 3b). The sulfanyl moiety of **3** could be easily oxidized to a sulfonyl moiety by *m*-CPBA. As the methylsulfonyl moiety is a good leaving group, intramolecular S_NAr reactions resulted in the formations of highly fused dibenzofuran analogues **7ca**, **7da**, and **7ou** in good yields (Scheme 3c). This S_NAr-based cyclization was also applicable to the synthesis of a polycyclic and non-planar screw-shaped helicene analogue (Scheme 3d).[27] After oxidation of **3qt**, intramolecular S_NAr cyclization culminated in a rapid access to unprecedented 7,12-dioxa[8]helicene **8qt** in 68% overall yield.

In summary, we have developed metal-free, highly regioselective dehydrogenative C–H/C–H cross-coupling of aryl sulfoxides with phenols by means of trifluoroacetic anhydride. The regiocontrolled C(sp^2)–C(sp^2) bond formation has been realized by the mechanism involving a sequence of interrupted Pummerer reaction and [3,3]-sigmatropic rearrangement directed by a temporary and removable tether between the sulfinyl group and the phenolic hydroxy group. Understandably,

the products are useful synthetic intermediates, as clearly demonstrated by the synthesis of π-expanded heteroaromatic molecules including 7,12-dioxa[8]helicene. Further expansion of the scope of substrates and creation of more interesting aromatic cores as well as asymmetric biaryl synthesis through this strategy are now in progress.[28]

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, X-ray crystallographic analysis, photophysical property, and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(20) When *para*-unsubstituted **1o** reacted with 1-naphthol (**2s**), not only the desired product **3os** but the biaryl **3os'** derived from [5,5]-sigmatropic rearrangement was obtained in a ratio of 1.7:1. See Supporting Information for more details.

(21) A similar 1,2-shift was observed in the reaction of 2,6-dimethyl(diacetoxyiodo)benzene. See: Ochiai, M.; Ito, T.; Takaoka, Y.; Masaki, Y. *J. Am. Chem. Soc.* **1991**, *113*, 1319.

(22) Although the mechanism for the formation of **3dv'** from **4** is still unclear, simple thermal [1,3]-aryl shift can be excluded because no rearrangement of **4** took place even at 130 °C in the absence of trifluoroacetic acid.

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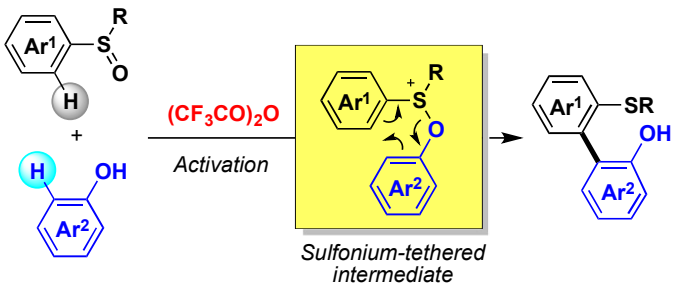
(28) As a preliminary experiment, the coupling reaction of enantiomerically pure **1b** (>99% ee) with 2-naphthol (**2t**) was performed. However, the corresponding binaphthyl **3bt** was obtained with 9% *ee* even at –40 °C. See Supporting Information for more details.


Ar1
R
S
O
H
+
H
OH
Ar2
(CF3CO)2O
Activation
Ar1
R
S
O
Ar2
Sulfonium-tethered intermediate
Ar1
SR
OH
Ar2