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Nitrosonium ion catalysis: aerobic, metal-free cross-dehydrogenative carbon–heteroatom bond formation†

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Catalytic cross-dehydrogenative coupling of heteroarenes with thiophenols and phenothiazines has been developed under mild and environmentally benign reaction conditions. For the first time, NO_x^+ was applied for catalytic C–S and C–N bond formation. A comprehensive scope for the C–H/S–H and C–H/N–H cross-dehydrogenative coupling was demonstrated with >60 examples. The sustainable cross-coupling conditions utilize ambient oxygen as the terminal oxidant, while water is the sole by-product.

The formation of carbon–heteroatom bonds is fundamental for the synthesis of natural products, pharmaceuticals and materials science.[1] To overcome the requirement for pre-functionalized starting materials, cross-dehydrogenative coupling (CDC) has emerged as a highly efficient strategy.[2] Transition-metal-catalyzed C–S and C–N bond formation has been widely reported.[3] Cost, toxicity and oxygen sensitivity of catalysts limit the general applicability.[4] Consequently, metal-free synthesis has gained increasing interest.[5] Different metal-free approaches for the C–H/S–H CDC have been reported.[6] Additionally, the unique dehydrogenative amination with phenothiazines has received significant attention.[7] High temperatures, excess of oxidants and harmful solvents are common limitations.

Nitronium and nitrosonium salts are inexpensive, stable and non-toxic single-electron oxidants.[8] Radner's group reported the synthesis of biaryls using $NOBF_4$ as catalyst (Fig. 1a).[9] Ambient oxygen was identified as the terminal oxidant and water as the by-product.[10] Later, Wang's group reported the catalytic intramolecular C–C bond formation (Fig. 1b).[11] Under acidic reaction conditions, NO^+ is generated *in situ* from $NaNO_2$. The oxidative coupling of phenols is well studied.[12] Recently, our group reported the NO^+ catalyzed coupling for the construction of C–C bonds.[13] Despite the impact of NO^+ as catalyst for oxidative C–C bond formation, the application in carbon–heteroatom bond formation *via* C–H bond functionalization is unprecedented. Herein, we demonstrate the first NO_x^+ catalyzed C–H/S–H and C–H/N–H CDC under mild and environmentally benign reaction conditions (Fig. 1d).

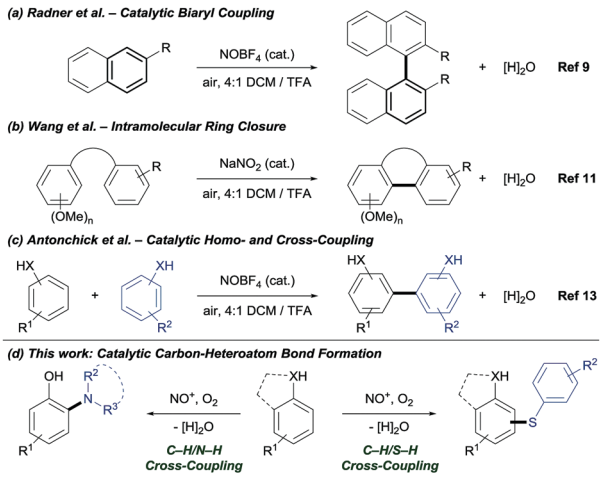

Fig. 1 Prior work on the oxidative carbon–carbon bond formation *via* C–H bond functionalization and newly developed transformation catalyzed by NO_x^+.

Nitrosonium salts are capable to convert thiols to disulfides.[14] Oxidation of thiols proceeds *via* transient *S*-nitrosation and recombination of *S*-centred radicals. Due to the low bond dissociation energy (BDE) of phenols and thiophenols, the possibility for a radical–radical recombination reaction of phenoxy and sulfur radicals was hypothesized.[15] A multi parameter optimization for the cross-coupling of *p*-cresol (**1a**) and 4-chlorothiophenol (**2a**) was performed (Table S1, ESI†). To our delight, **3a** was isolated in excellent yield, by using NO_2BF_4 as the catalyst. Hexafluoroisopropanol (HFIP) was identified as the best solvent, due to its acidic character and the unique ability to stabilize radical intermediates.[16]

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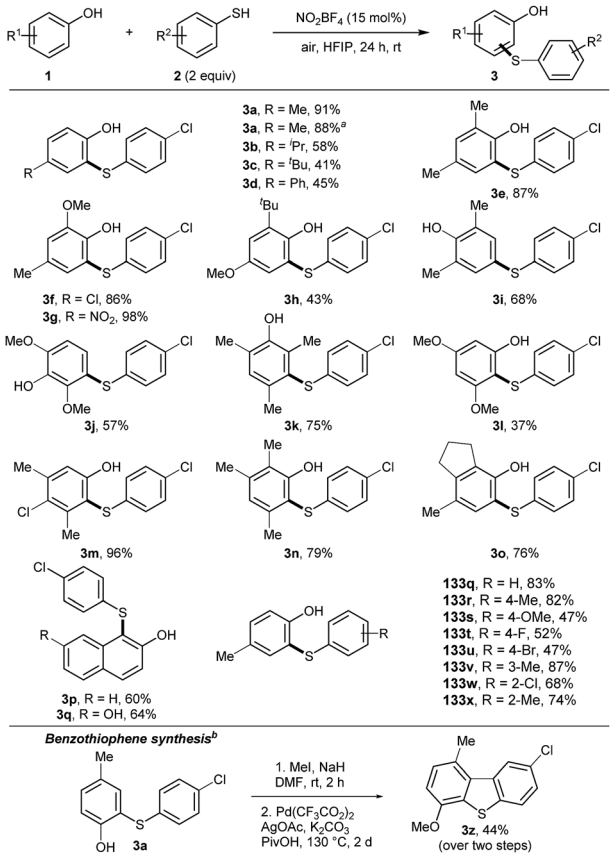
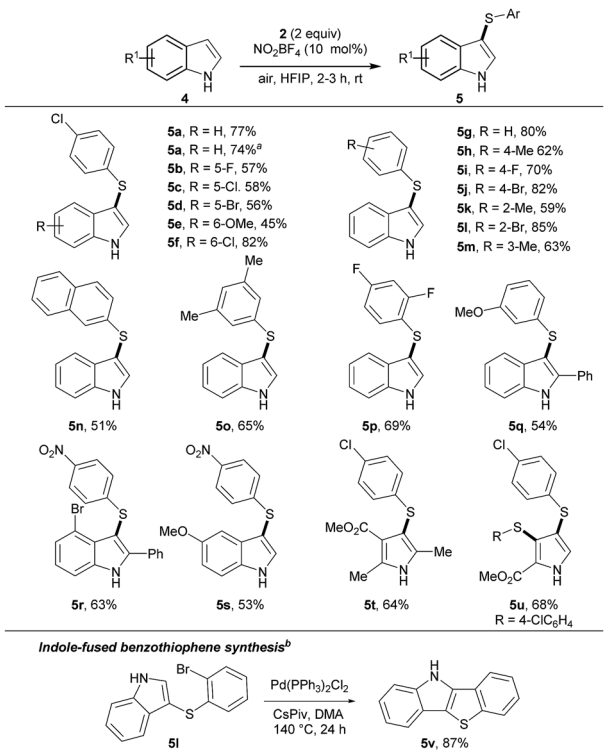


Scheme 1 Scope with respect to phenols (**1**) and thiophenols (**2**). Reaction conditions: **1** (0.1 mmol, 1 equiv.), **2** (2 equiv.), HFIP (0.05 M), at room temperature under air atmosphere. Yields are given for isolated products after column chromatography. [a]Reaction carried out with 1 mmol of phenol **1a**. [b]1. **3a** (0.3 mmol, 1 equiv.), MeI (1.5 equiv.), NaH (1.2 equiv.) in DMF (0.1 M) at room temperature; 2. $(CF_3CO_2)_2Pd$ (20 mol%), AgOAc (5 equiv.), K_2CO_3 (1.5 equiv.) in PivOH (0.3 M) at 130 °C for 2 d.

Initially, the scope for the cross-coupling of phenols and thiophenols was studied (Scheme 1). The reaction was scaled to 1 mmol, which did not alter the outcome of the reaction. Functional groups at the *para*-position of phenols were well tolerated (**3b–3d**). 2,4-Substituted phenols yielded products **3e–3h** in good to excellent yields, covering electron-rich and sterically demanding functional groups. Product **3g** was isolated in quantitative yield and product **3l** was synthesized with high *para*-selectivity. Electron-rich product **3j** revealed selectivity for the *meta*-position of phenol. The same outcome was observed for product **3k** by blocking the *ortho*- and *para*-positions. Dearomatization and subsequent 1,4-addition appeared to be an alternative pathway. **3l** was isolated in moderate yield, using a 3,5-subsituted phenol. Polysubstituted phenols allowed the isolation of products **3m–o** in 76–98% yields. Naphthol derivatives were compatible, affording products **3p**, **3q**. Next, substituted thiophenols were tested. Different functional groups on the *para*-position were well tolerated (**3s–v**). Alkyl or chloro substituents at the *ortho*- and *meta*-position afforded products **3w–3y** in good yields. Double thioarylation was not observed under the developed conditions. Alkyl and benzyl thiols did not yield the desired products either. To stress the utility of the obtained products, **3a** was transformed into benzothiophene **3z** by applying a dual C–H bond activation strategy.[17]

Next, the thioarylation of indoles was studied (Scheme 2). Unprotected indoles gave better results than *N*-protected analogues. This result makes the reaction conditions more attractive for other applications. The cross-coupling of indole **4a** and thiophenol **2a** yielded **5a** in 77% yield. Scaling the reaction to 1 mmol gave **5a** unaffectedly. Functional groups with different electronic properties at the indole skeleton were well tolerated (**5b–f**). Further, thiophenols were decorated with functional groups at the *para* (**5h–j**), *ortho* (**5k–l**) and *meta* (**5m**) position. Product **5n** was isolated in 51% yield bearing a napthyl moiety. Polysubstituted products **5o–5s** were synthesized in good yields, covering combinations of electron-rich and electron-deficient functional groups. Next, substituted pyrroles were tested. Product **5t** was isolated in 64% yield. 2-Substituted pyrrol yielded the double functionalized product **5v** in good yield. To further stress the applicability, **5l** was transformed into the indol-fused benzothiophenes **5v**.[18]

Next, the time course of the cross-coupling reactions was analysed by GC-MS-FID (Fig. 2). Interestingly, thiophenol **2a** was fully converted to disulfide **6a**, prior to the coupling step with phenol **1a** (Fig. 2A). In contrast, indole **4a** and thiophenol **2a** underwent synchronous cross-coupling without initial



Scheme 2 Scope with respect to indoles (**4**) and thiophenols (**2**). Reaction conditions: **4** (0.1 mmol, 1 equiv.), **2** (2 equiv.), HFIP (0.05 M), at room temperature under air atmosphere. Yields are given for isolated products after column chromatography. [a] Reaction carried out with 1 mmol of indol **4a**. [b] **5l** (0.08 mmol, 1 equiv.), $Pd(PPh_3)_2Cl_2$ (5 mol%), CsPiv (2 equiv.) in *N*,*N*-dimethylacetamide (0.1 M).

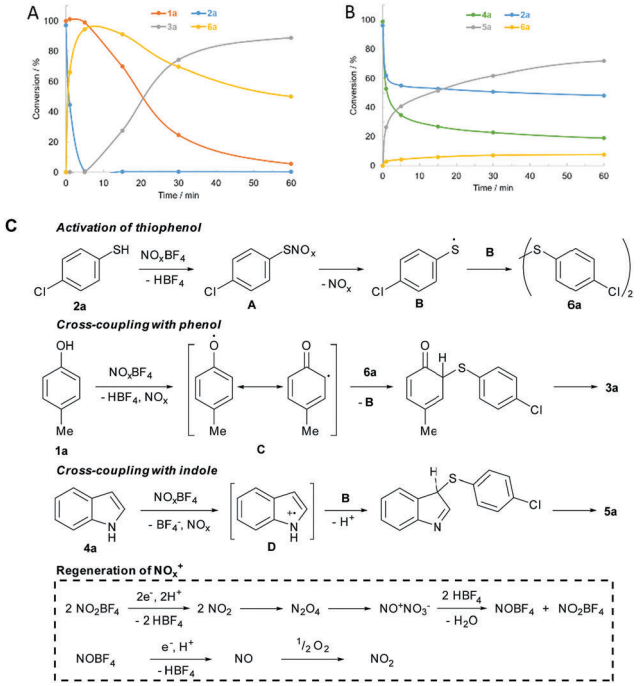


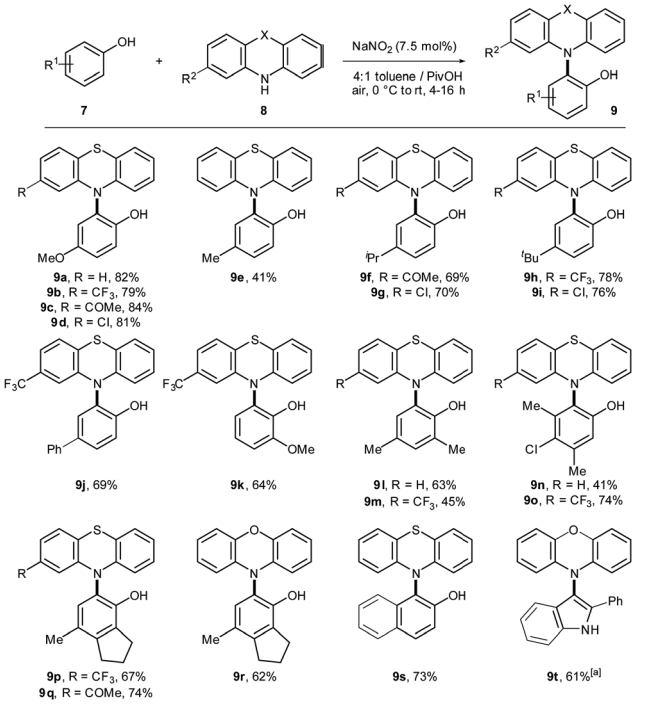
Fig. 2 Reaction profiles and proposed mechanism. (A) Reaction profiles for the thioarylation of phenol **1a** with thiophenol **2a**. (B) Reaction profiles for the thioarylation of indole **4a** with thiophenol **2a**. (C) Reaction mechanism.

formation of **6a** (Fig. 2B). Conducting the coupling reaction with disulfide **6a** confirmed the discrete recombination selectivities (Schemes S2 and S5, ESI†). Consequently, disulfide **6a** is an intermediate for the coupling with phenol, but indoles undergo direct recombination with thiophenols. Further control experiments were conducted (ESI† for the details). No product was formed in the presence of radical trap butylated hydroxytoluene (BHT) and the product formation was inhibited under inert gas atmosphere (Schemes S2 and S4, ESI†). Ambient oxygen was crucial to maintain the catalytic activity. Initiation of the coupling reaction through oxidation of weak heteroatom–hydrogen bonds was studied by methylating the starting materials. Drastically reduced conversion was observed, which excludes a direct single-electron-transfer (Schemes S2 and S4, ESI†). Thiophenol **2a** was quantitatively oxidized to disulfide **6a** in the presence of $NOBF_4$ (Scheme S3, ESI†). Conversion to disulfide **6a** was tied to the presence of air and did not take place in the presence of BHT (Scheme S3, ESI†).

Based on the control experiments, a mechanism for the cross-coupling of phenol **1a** and indole **4a** with thiophenol **2a** was proposed (Fig. 2C). Initially, intermediate **A** is formed by *S*-nitrosylation of **2a**. Homolytic cleavage releases radical **B**, which forms disulfide **6a** by recombination with itself. Phenol **1a** is oxidized to form a phenoxy radical. Delocalization of the phenoxy radical (**C**) and attack at the disulfide bond leads to release of radical **B**. Rearomatization furnishes product **3a**. Oxidation of indole **4a** gives intermediate **D**, which undergoes recombination with **B**. Oxidation of indole **4a** and thiophenol **2a** occurs synchronously, leading to the formation of **5a** before disulfide **6a** begins to form. Further, NO_2BF_4 oxidizes the starting materials to form NO_2. NO_2 dimerizes to form N_2O_4, which undergoes disproportionation to $NONO_3$.[11a] Water is released upon protonation by HBF_4 and nitrosonium and nitronium tetrafluoroborate are regenerated. $NOBF_4$ is capable of oxidizing the substrates in the same way as the nitronium salt. Oxidation of substrates results in the formation of nitrogen monoxide, which has to be oxidized by ambient oxygen, in order to maintain the catalytic cycle.

Based on the revealed radical mechanism, we hypothesized that phenothiazines represent suitable substrates for the radical recombination with phenols, due to the low N–H BDE and the unique ability to stabilize radical intermediates.[19] Multi parameter optimization was performed (Table S2, ESI†). Sustainable C–H bond amination of phenols with phenothiazines was achieved using $NaNO_2$ as catalyst, omitting halogenated reagents and solvents. The developed conditions overcome environmental issues of known methods.[7]

Next, the scope of the catalytic C–H/N–H cross-dehydrogenative coupling was studied (Scheme 3). Initially, the cross-coupling of 4-methoxyphenol (**7a**) and different phenothiazines was performed. Products **9a–d** were isolated in good yields. Different 4-substituted phenols yielded the desired cross-coupling products in moderate to excellent yields (**9e–j**). Cross-coupling with differently substituted phenothiazines was achieved for several phenols. Product **9k** was isolated in good yield as single regioisomer. Polyfunctionalized products **9l–q** were isolated in moderate to good yields. Phenoxazine proved to be compatible



Scheme 3 Scope for the cross-dehydrogenative C–H bond amination. Reaction conditions: **8** (0.2 mmol, 1 equiv.), **9** (3 equiv.), 4 : 1 toluene/PivOH (0.05 M), 0 °C to rt under air atmosphere. Yields are given for isolated products after column chromatography. [a] $NOBF_4$ (0.02 mmol, 10 mol%) was used as catalyst.

for the cross-coupling reaction (**9r**). 2-Naphthol yielded the desired product **9s** in 73% yield. Finally, the cross-coupling of 2-phenylindole and phenoxazine was successfully performed. However, synthesis of **9t** worked superior if $NOBF_4$ was used as catalyst. The underlying mechanism for the aerobic C–H bond amination proceeds analogously as described before *via* direct radical–radical recombination under aerobic conditions (Scheme S8, ESI†).

In summary, we have reported the first application of NO_x^+ as efficient and environmentally friendly catalyst for carbon–heteroatom bond formation. The operationally simple and sustainable protocol enables the C–H/S–H and C–H/N–H CDC. Ambient oxygen serves as stoichiometric oxidant and water is generated as by-product. A broad scope was demonstrated in good yields and regioselectivities. The reported methodology offers mild reaction conditions and does not require an excess of reagents or any specialized equipment.

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Conflicts of interest

There are no conflicts to declare.

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