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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

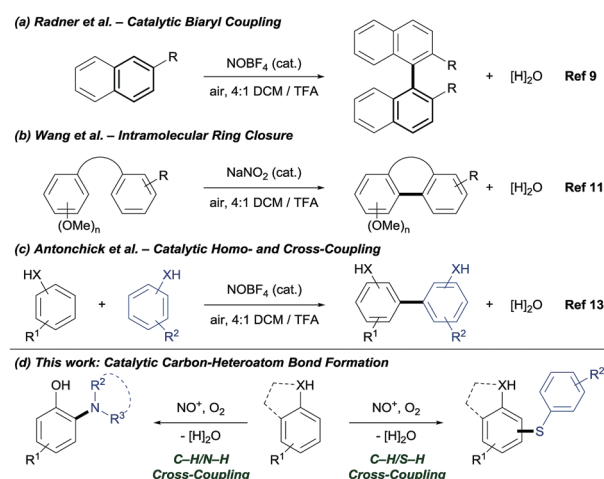


Fig. 1 Prior work on the oxidative carbon–carbon bond formation via C–H bond functionalization and newly developed transformation catalyzed by NO_x^+ .

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).

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

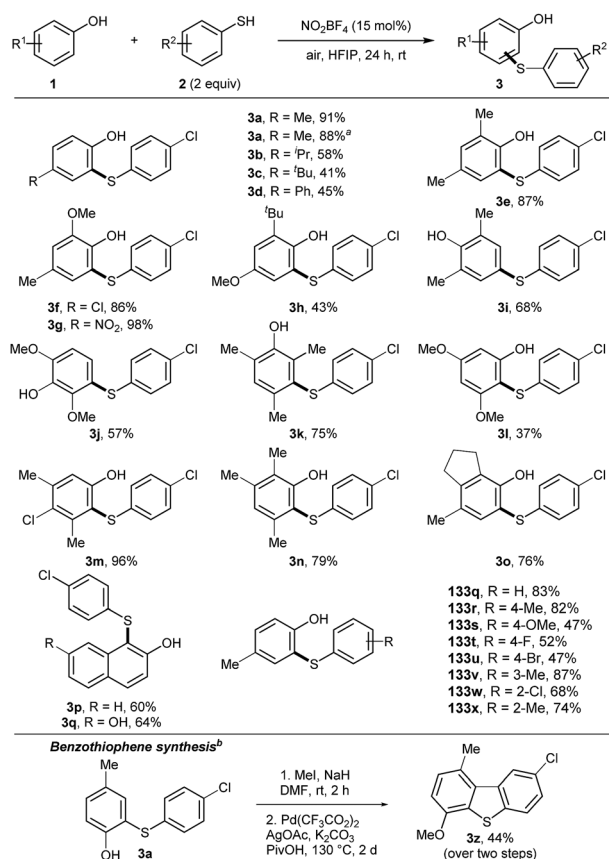
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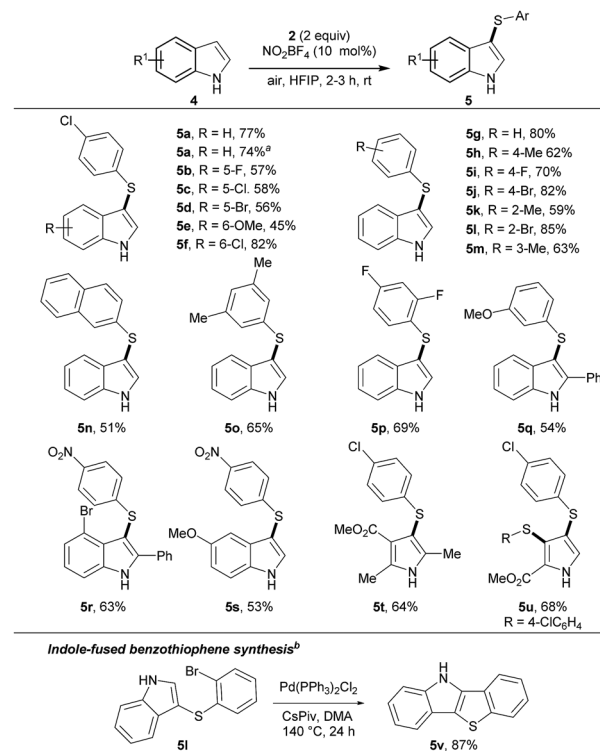
Scheme 1 Scope with respect to phenols (**1**) and thiophenols (**2**). Reaction conditions: **1** (0.1 mmol, 1 equiv.), **2** (2 equiv.), HFIP (0.05 M), at room temperature under air atmosphere. Yields are given for isolated products after column chromatography. ^a Reaction carried out with 1 mmol of phenol **1a**. ^b **3a** (0.3 mmol, 1 equiv.), MeI (1.5 equiv.), NaH (1.2 equiv.) in DMF (0.1 M) at room temperature; 2. (CF₃CO₂)₂Pd (20 mol%), AgOAc (5 equiv.), K₂CO₃ (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-substituted 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 naphthyl 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(PPh₃)₂Cl₂ (5 mol%), CsPiv (2 equiv.) in *N,N*-dimethylacetamide (0.1 M).





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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