



Cite this: *Chem. Commun.*, 2018, 54, 13022

Received 17th October 2018,
Accepted 31st October 2018

DOI: 10.1039/c8cc08328b

rsc.li/chemcomm

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

Luis Bering,^{ab} Laura D'Ottavio,^{ac} Giedre Sirvinskaite^a and
Andrey P. Antonchick^{ab}★

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

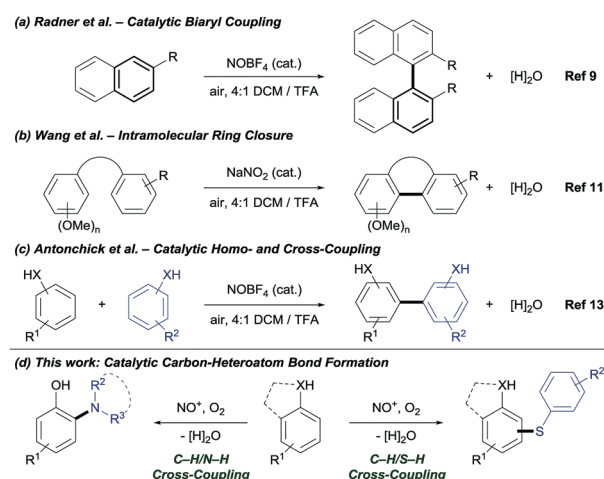


Fig. 1 Prior work on the oxidative carbon–carbon bond formation via C–H bond functionalization and newly developed transformation catalyzed by NO_x^+ .

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

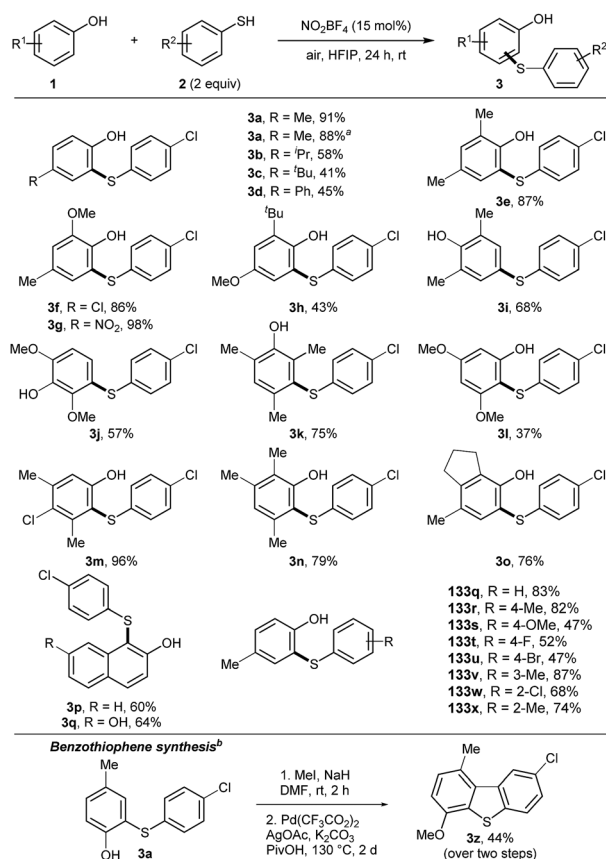
^a Department of Chemical Biology, Max-Planck-Institute of Molecular Physiology, Otto-Hahn-Straße 11, 44227 Dortmund, Germany.
E-mail: Andrey.Antonchick@mpi-dortmund.mpg.de

^b Faculty of Chemistry and Chemical Biology, TU Dortmund University, Otto-Hahn-Straße 4a, 44227 Dortmund, Germany

^c University of Bologna, Department of Pharmacy and Biotechnology, Via Belmeloro 6, 40126 Bologna, Italy

† Electronic supplementary information (ESI) available. See DOI: 10.1039/c8cc08328b





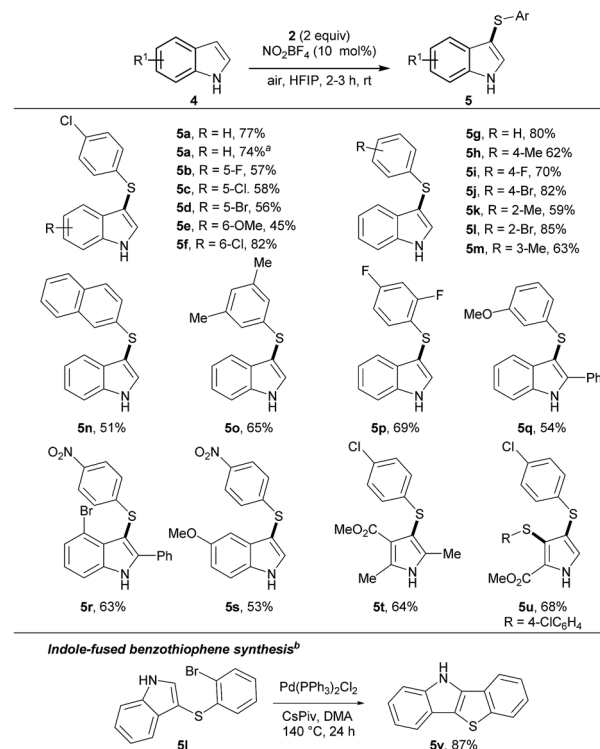
Scheme 1 Scope with respect to phenols (**1**) and thiophenols (**2**). Reaction conditions: **1** (0.1 mmol, 1 equiv.), **2** (2 equiv.), HFIP (0.05 M), at room temperature under air atmosphere. Yields are given for isolated products after column chromatography. ^a Reaction carried out with 1 mmol of 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.

A. P. A. acknowledges the support of the DFG (AN 1064/4-1) and the Boehringer Ingelheim Foundation (Plus 3). L. B. is supported by the Verband der Chemischen Industrie e.V. We gratefully acknowledge Ms R. Perinbarajah for assistance. Open Access funding provided by the Max Planck Society.

Conflicts of interest

There are no conflicts to declare.

Notes and references

- (a) J. F. Hartwig, *Nature*, 2008, **455**, 314; (b) A. K. Yudin and J. F. Hartwig, *Catalyzed Carbon-Heteroatom Bond Formation*, Wiley-VCH, Weinheim, 2010.
- (a) S. A. Girard, T. Knauber and C.-J. Li, *Angew. Chem., Int. Ed.*, 2014, **53**, 74; (b) J. F. Hartwig and M. A. Larsen, *ACS Cent. Sci.*, 2016, **2**, 281.
- (a) I. P. Beletskaya and V. P. Ananikov, *Chem. Rev.*, 2011, **111**, 1596; (b) J. Bariwal and E. Van der Eycken, *Chem. Soc. Rev.*, 2013, **42**, 9283; (c) L. Chin-Fa, L. Yi-Chen and B. S. Singh, *Chem. – Asian J.*, 2014, **9**, 706; (d) M.-L. Louillat and F. W. Patureau, *Chem. Soc. Rev.*, 2014, **43**, 901; (e) Y. Park, Y. Kim and S. Chang, *Chem. Rev.*, 2017, **117**, 9247.
- (a) C.-L. Sun and Z.-J. Shi, *Chem. Rev.*, 2014, **114**, 9219; (b) R. A. D. Arancon, C. Sze Ki Lin, C. Vargas and R. Luque, *Org. Biomol. Chem.*, 2014, **12**, 10; (c) V. P. Mehta and B. Punji, *RSC Adv.*, 2013, **3**, 11957.
- (a) R. Samanta, K. Matcha and A. P. Antonchick, *Eur. J. Org. Chem.*, 2013, 5769; (b) R. Narayan, K. Matcha and A. P. Antonchick, *Chem. – Eur. J.*, 2015, **21**, 14678; (c) L. Bering, S. Manna and A. P. Antonchick, *Chem. – Eur. J.*, 2017, **23**, 10936.
- (a) Y. Liu, Y. Zhang, C. Hu, J.-P. Wan and C. Wen, *RSC Adv.*, 2014, **4**, 35528; (b) S. K. R. Parumala and R. K. Peddinti, *Green Chem.*, 2015, **17**, 4068; (c) Z. Huang, D. Zhang, X. Qi, Z. Yan, M. Wang, H. Yan and A. Lei, *Org. Lett.*, 2016, **18**, 2351; (d) S. Song, Y. Zhang, A. Yeerlan, B. Zhu, J. Liu and N. Jiao, *Angew. Chem., Int. Ed.*, 2017, **56**, 2487; (e) L. T. Silva, J. B. Azeredo, S. Saba, J. Rafique, A. J. Bortoluzzi and A. L. Braga, *Eur. J. Org. Chem.*, 2017, 4740; (f) R. Rahaman, S. Das and P. Barman, *Green Chem.*, 2018, **20**, 141; (g) H.-H. Wang, T. Shi, W.-W. Gao, Y.-Q. Wang, J.-F. Li, Y. Jiang, Y. S. Hou, C. Chen, X. Peng and Z. Wang, *Chem. – Asian J.*, 2017, **12**, 2675; (h) P. Wang, S. Tang, P. Huang and A. Lei, *Angew. Chem., Int. Ed.*, 2017, **56**, 3009; (i) R. Ohkado, T. Ishikawa and H. Iida, *Green Chem.*, 2018, **20**, 984; (j) H. Iida, R. Demizu and R. Ohkado, *J. Org. Chem.*, 2018, **83**, 12291.
- (a) M.-L. Louillat-Habermeyer, R. Jin and F. W. Patureau, *Angew. Chem., Int. Ed.*, 2015, **54**, 4102; (b) R. Jin and F. W. Patureau, *Org. Lett.*, 2016, **18**, 4491; (c) Y. Zhao, B. Huang, C. Yang and W. Xia, *Org. Lett.*, 2016, **18**, 3326; (d) M. Goswami, A. Konkel, M. Rahimi, M.-L. Louillat-Habermeyer, H. Kelm, R. Jin, B. de Bruin and F. W. Patureau, *Chem. – Eur. J.*, 2018, **24**, 11936; (e) R. Jin, C. L. Bub and F. W. Patureau, *Org. Lett.*, 2018, **20**, 2884; (f) S. Tang, S. Wang, Y. Liu, H. Cong and A. Lei, *Angew. Chem., Int. Ed.*, 2018, **57**, 4737.
- (a) K. Y. Lee, D. J. Kuchynka and J. K. Kochi, *Inorg. Chem.*, 1990, **29**, 4196; (b) G. A. Olah, G. K. S. Prakash, Q. Wang and X.-Y. Li, Nitrosonium Tetrafluoroborate, *Encyclopedia of Reagents for Organic Synthesis*, John Wiley & Sons, New Jersey, 2001; (c) G. I. Borodkin and V. G. Shubin, *Russ. Chem. Rev.*, 2001, **70**, 211; (d) I. B. Gennady and G. S. Vyacheslav, *Russ. Chem. Rev.*, 2017, **86**, 18.
- F. Radner, *J. Org. Chem.*, 1988, **53**, 702.
- (a) M. Tanaka, H. Nakashima, M. Fujiwara, H. Ando and Y. Souma, *J. Org. Chem.*, 1996, **61**, 788; (b) M. Tanaka, E. Muro, H. Ando, Q. Xu, M. Fujiwara, Y. Souma and Y. Yamaguchi, *J. Org. Chem.*, 2000, **65**, 2972.
- (a) B. Su, L. Li, Y. Hu, Y. Liu and Q. Wang, *Adv. Synth. Catal.*, 2012, **354**, 383; (b) B. Su, M. Deng and Q. Wang, *Org. Lett.*, 2013, **15**, 1606.
- (a) Y. E. Lee, T. Cao, C. Torruellas and M. C. Kozlowski, *J. Am. Chem. Soc.*, 2014, **136**, 6782; (b) A. Libman, H. Shalit, Y. Vainer, S. Narute, S. Kozuch and D. Pappo, *J. Am. Chem. Soc.*, 2015, **137**, 11453; (c) M. Koji, S. Kazuma, O. Takao, D. Toshifumi and K. Yasuyuki, *Angew. Chem., Int. Ed.*, 2016, **55**, 3652; (d) H. Shalit, A. Libman and D. Pappo, *J. Am. Chem. Soc.*, 2017, **139**, 13404; (e) A. Wiebe, B. Riehl, S. Lips, R. Franke and S. R. Waldvogel, *Sci. Adv.*, 2017, **3**, eaao3920; (f) H. Kang, Y. E. Lee, P. V. G. Reddy, S. Dey, S. E. Allen, K. A. Niederer, P. Sung, K. Hewitt, C. Torruellas, M. R. Herling and M. C. Kozlowski, *Org. Lett.*, 2017, **19**, 5505; (g) S. R. Waldvogel, S. Lips, M. Selt, B. Riehl and C. J. Kampf, *Chem. Rev.*, 2018, **118**, 6706.
- (a) L. Bering, F. M. Paulussen and A. P. Antonchick, *Org. Lett.*, 2018, **20**, 1978; (b) L. Bering, M. Vogt, F. M. Paulussen and A. P. Antonchick, *Org. Lett.*, 2018, **20**, 4077.
- (a) T. Itoh, N. Tsutsumi and A. Ohsawa, *Bioorg. Med. Chem. Lett.*, 1999, **9**, 2161; (b) A. S. Demir, I. A. Cigdem and A. S. Mahasneh, *Tetrahedron*, 1999, **55**, 12399; (c) N. Tsutsumi, T. Itoh and A. Ohsawa, *Chem. Pharm. Bull.*, 2000, **48**, 1524; (d) J.-M. Lü, J. M. Wittbrodt, K. Wang, Z. Wen, H. B. Schlegel, P. G. Wang and J.-P. Cheng, *J. Am. Chem. Soc.*, 2001, **123**, 2903.
- (a) M. I. de Heer, H.-G. Korth and P. Mulder, *J. Org. Chem.*, 1999, **64**, 6969; (b) Y.-D. Wu and D. K. W. Lai, *J. Org. Chem.*, 1996, **61**, 7904.
- (a) L. Ebersson, M. P. Hartshorn and O. Persson, *J. Chem. Soc., Perkin Trans. 2*, 1995, 1735, DOI: 10.1039/P29950001735; (b) M. Lucarini, V. Mugnaini, G. F. Pedulli and M. Guerra, *J. Am. Chem. Soc.*, 2003, **125**, 8318; (c) J.-P. Bégué, D. Bonnet-Delpont and B. Crousse, *Synlett*, 2004, 18.
- C. Rui, W. Zhiqing, L. Zhengkai, X. Haifeng and Z. Xiangge, *Chem. – Eur. J.*, 2014, **20**, 7258.
- P. Saravanan and P. Anbarasan, *Org. Lett.*, 2014, **16**, 848.
- (a) M. Lucarini, P. Pedrielli, G. F. Pedulli, L. Valgimigli, D. Gigmes and P. Tordo, *J. Am. Chem. Soc.*, 1999, **121**, 11546; (b) L. A. Farmer, E. A. Haidasz, M. Griesser and D. A. Pratt, *J. Org. Chem.*, 2017, **82**, 10523.

