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Aerobic, Metal-Free, and Catalytic Dehydrogenative Coupling of Heterocycles: En Route to Hedgehog Signaling Pathway Inhibitors

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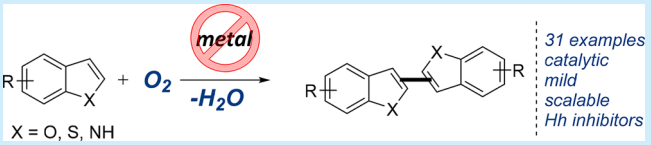
Supporting Information

ABSTRACT: The nitrosonium ion-catalyzed dehydrogenative coupling of heteroarenes under mild reaction conditions is reported. The developed method utilizes ambient molecular oxygen as a terminal oxidant, and only water is produced as byproduct. Dehydrogenative coupling of heteroarenes translated into the rapid discovery of novel hedgehog signaling pathway inhibitors, emphasizing the importance of the developed methodology.



Oxidative coupling through C−H bond functionalization represents one of the most efficient synthetic strategies for the construction of carbon−carbon bonds.[1] Selective functionalization of abundant and inert C−H bonds is in high demand.[2] Various approaches using transition-metal catalysts and directing groups have been widely reported, which often require additional functionalization of the starting materials.[3] Direct oxidative C−C bond formation serves as an alternative strategy.[4] Double C−H bond functionalization offers the unique advantage of making the requirement for prefunctionalization of both coupling partners unnecessary.[5] Early reports demonstrated the oxidative coupling of heterocycles using palladium salts.[6] Mori and co-workers[7] reported the palladium-catalyzed coupling of thiophenes in the presence of AgF and a stoichiometric oxidant (Figure 1A), and Wang and co-workers[8] disclosed the palladium-catalyzed coupling under aerobic conditions. Elevated temperatures, prolonged reaction times, and the stoichiometric use of either palladium salts or oxidants are often drawbacks of double C−H bond functionalization. Kita and co-workers pioneered the metal-free coupling of pyrroles and thiophenes using hypervalent iodine(III) reagents (Figure 1B).[9] The reaction takes advantage of the low oxidation potential and the high intrinsic nucleophilicity of the heteroarene substrates.[10] Radical coupling of arenes was reported using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ).[11,12] Although the described metal-free methodologies represent great improvements in terms of environmental compatibility, the use of high molecular weight oxidants still leads to stoichiometric amounts of waste.

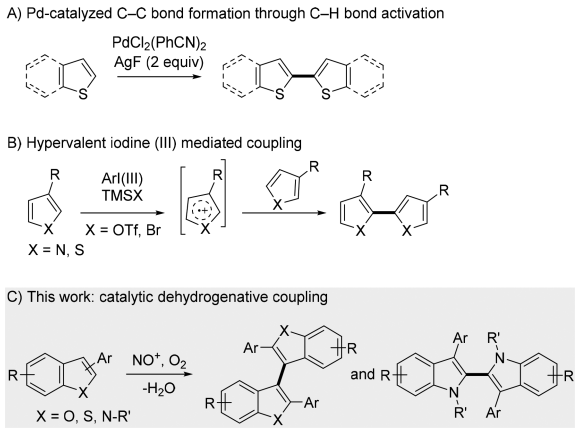


Figure 1. Direct oxidative coupling of heterocycles via C−H bond functionalization.

Early studies by Radner and, later, by Tanaka enlightened Scholl-type reactions through nitrosonium ion-catalyzed coupling.[13] Because of the growing importance of sustainable chemistry, and the ongoing interest of our group in the development of novel metal-free reaction methodologies, nitrosonium salts have attracted our attention.[14] Molecular oxygen is considered the ideal oxidant due to its natural occurrence, inexpensive character, and safe handling.[15] To our surprise, the employment of nitrosonium salts in oxidative C−C bond formation remained almost untouched.[16] Herein, we demonstrate the efficient dehydrogenative coupling of heterocycles under mild reaction conditions using nitrosonium tetrafluoroborate as sustainable catalyst and ambient molecular oxygen as oxidant (Figure 1C).

Initially, we hypothesized an analogy between nitrosonium salts and hypervalent iodine(III) reagents due to a comparable redox potential.[17] We selected an initial set of compounds according to their oxidation potential and were pleased to find 2-phenylbenzofuran (**1a**) as a suitable substrate.[18] We chose **1a** as model substrate, since no methodology was known, which covers metal-free, catalytic, and dehydrogenative coupling conditions at once.[19] 2-Arylbenzofurans and their homodimers are associated with useful biological activities.[20]

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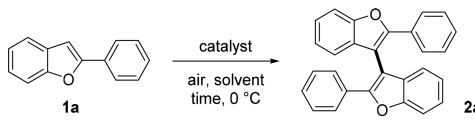
We initiated our systematic optimization by treating **1a** with substoichiometric amounts of nitrosonium tetrafluoroborate ($NOBF_4$) in the presence of trifluoroacetic acid (TFA) (Table 1). Chlorinated solvents yielded the desired product **2a** in 39%

Table 1. Optimization of Reaction Conditions[a]



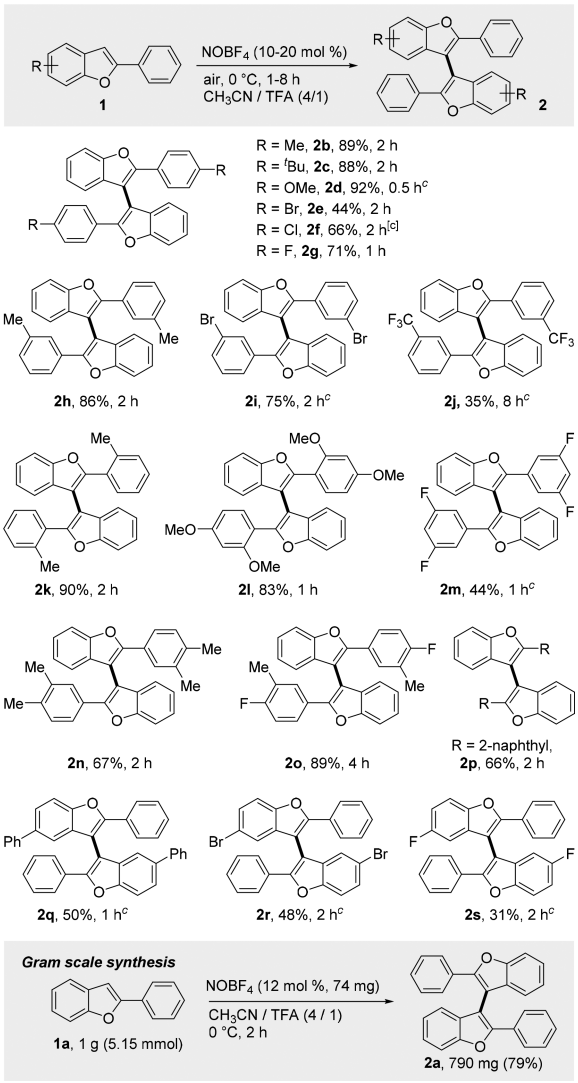
entry	solvent	acid (ratio)	catalyst (mol %)	yield[b] (%)
1	CH_2Cl_2	TFA (4/1)	$NOBF_4$ (10)	39
2	C_6H_5Cl	TFA (4/1)	$NOBF_4$ (10)	80
3	EtOH	TFA (4/1)	$NOBF_4$ (10)	nd
4	THF	TFA (4/1)	$NOBF_4$ (10)	nd
5	CH_3NO_2	TFA (4/1)	$NOBF_4$ (10)	62
6	CH_3CN	TFA (4/1)	$NOBF_4$ (10)	85
7	CH_3CN		$NOBF_4$ (10)	traces
8		TFA	$NOBF_4$ (10)	14
9	HFIP		$NOBF_4$ (10)	31
10	CH_3CN	CF_3SO_3H	$NaNO_2$ (20)	62
11	CH_3CN	CF_3SO_3H	$NOBF_4$ (10)	21
12	CH_3CN	TFA (5/1)	$NOBF_4$ (10)	79
13	CH_3CN	TFA (3/1)	$NOBF_4$ (10)	64
14	CH_3CN	TFA (4/1)	$NOBF_4$ (20)	82
15	CH_3CN	TFA (4/1)	$NOBF_4$ (5)	32
16[c]	CH_3CN	TFA (4/1)	$NOBF_4$ (10)	78

[a]Reaction conditions: **1a** (0.1 mmol, 1 equiv), catalyst (see table), solvent (0.1 M), 0 °C, 2−18 h under air atmosphere (SI for the details). [b]Yields are given for isolated products after column chromatography. [c]Reaction performed at rt. [d]nd = not detected.

and 80% yields, respectively (entries 1 and 2). We were pleased to observe an increased yield of **2a**, when acetonitrile was used as solvent (entry 6), while protic solvents and ethers did not yield any product (entries 3 and 4). Absence of acid yielded traces of **2a** due to electrophilic nitration.[21] A high excess of acid proved to be unfavorable for the course of reaction. Conducting the reaction in HFIP yielded product **2a** in 32%, which underpins the requirement for a strong acid (entry 9). Further screening of solvents in the presence of acid did not improve the outcome of the reaction (Table S1). Cationic nitrosonium species were also generated by treating sodium nitrite with triflic acid, which allowed the isolation of **2a** in 62% yield (entry 10). The yield of **2a** even further decreased when nitrosonium tetrafluoroborate and triflic acid were applied (entry 11). Next, we also examined the amount of acid, which was found to be already optimal (entries 12 and 13). Increased loading of nitrosonium tetrafluoroborate led to a decreased yield of **2a**, and lowering the catalyst loading resulted in an incomplete conversion of starting material (entries 14 and 15). Finally, different temperatures and concentrations were also explored, but no further improvements were found (entry 16 and Table S1).

Having the optimized conditions in hand, we started to explore the scope of this catalytic dehydrogenative coupling reaction. The reaction proved to be robust and versatile and allowed the synthesis of a broad range of bibenzofurans (Scheme 1). Several starting materials suffered from poor solubility in acetonitrile. Changing the solvent to dichloromethane allowed the straightforward isolation of the products in satisfying yield and short reaction times. Functional groups

Scheme 1. Scope of the Catalytic Dehydrogenative Coupling of 2-Phenylbenzofurans



[a]Reaction conditions: **1** (0.2 mmol, 1 equiv), $NOBF_4$ (0.1 equiv), CH_3CN/TFA (0.1 M), 0 °C, 1−8 h under air atmosphere. [b]Yields are given for isolated products after column chromatography. [c]CH_2Cl_2/TFA (4/1) was used as solvent.

on the 2-phenyl group were well tolerated on all accessible positions (Scheme 1, **2b−k**). Next, a set of polysubstituted products was synthesized in good to excellent yield, depending on the electronic properties of the substituents (Scheme 1, **2l−p**). Interestingly, product **2p** was selectively formed, while the naphthalene substituent remained untouched under the reaction conditions. The dehydrogenative coupling of 5-substituted substrates was accomplished (Scheme 1, **2q−s**). To stress the synthetic value of our newly developed reaction, we performed the dehydrogenative coupling using 5 mmol of **1a**. To our delight, product **2a** was isolated in only slightly reduced yield, demonstrating the facile scalability of the coupling reactions.

After confirming the scope of 2-arylbenzofurans, we moved our attention to the dehydrogenative coupling of benzothiophenes and indoles (Scheme 2). Bibenzothiophenes **4a−d** were isolated in good yields and short reaction times, revealing similar trends in functional group compatibility compared,

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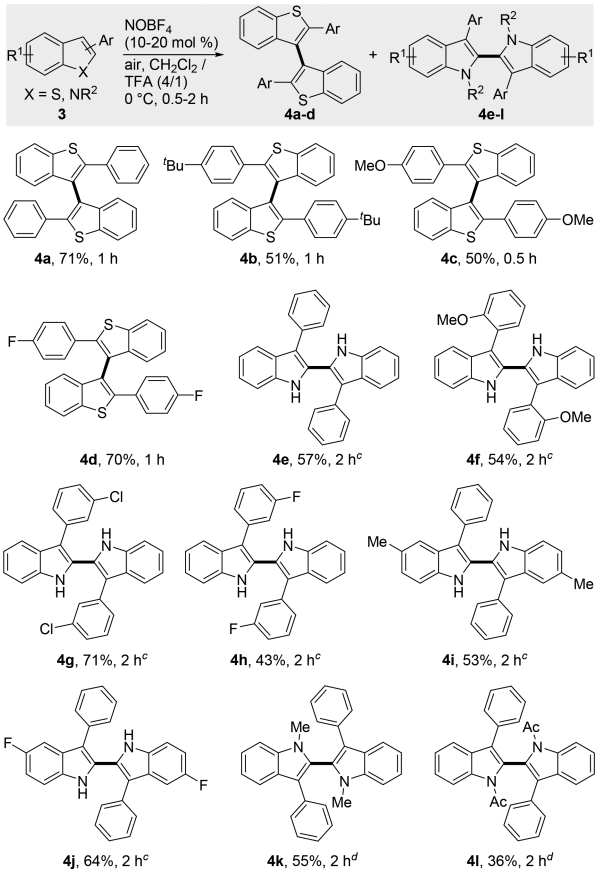
Scheme 2. Scope of the Catalytic Dehydrogenative Coupling of 2-Phenylbenzothiophenes and 3-Phenylindoles



[a]Reaction conditions: **1** (0.2 mmol, 1 equiv), $NOBF_4$ (0.1−0.2 equiv), solvent (0.1 M), 0 °C, 0.5−2 h under air atmosphere. [b]Yields are given for isolated products after column chromatography. [c]CH_3CN was used as solvent. [d]CH_3CN/TFA (4/1) was used as solvent.

although the overall yield was lower. Furthermore, 3-arylindoles were successfully coupled under the developed reaction conditions. Functional groups with electron-donating or electron-withdrawing effects were well tolerated on the 3-phenyl ring and the 5-position of indole (Scheme 2, **4e**−**j**). To our surprise, the coupling of unprotected indole did not require any acid, while products **4k** and **4j** were synthesized using the optimized reaction conditions. To the best of our knowledge, an efficient undirected coupling of 3-arylindoles via C−H bond functionalization has not been described before.

To investigate the course of the reaction, we conducted several control experiments (see the SI for the details). Only traces of products **2a** were detected when the reaction was performed under argon atmosphere. This result underlines the importance of oxygen to maintain the catalytic cycle. In contrast, when the reaction was conducted under oxygen atmosphere, only traces of product were formed as well due to overoxidation of reactive intermediates. Next, a radical-scavenging experiment was performed using butylated hydroxytoluene (BHT). While product **2a** was not detected, formation of a radical scavenging product could be confirmed. Finally, we also performed a competition experiment, but only minor formation of a heterocoupling product was detected. This finding is in accordance to the general tendency that substrates with low oxidation potentials entail higher nucleophilicity and preferentially undergo homocoupling.

On the basis of the conducted control experiments, a reaction mechanism is proposed and outlined in Figure 2.

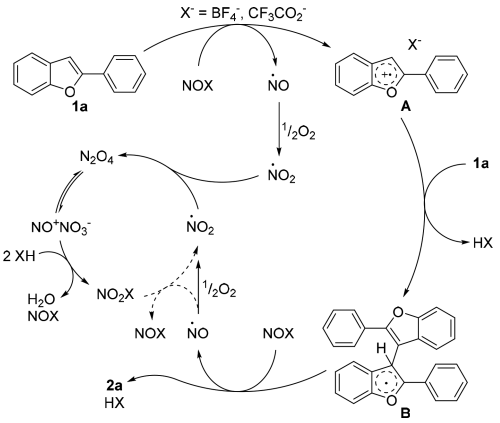
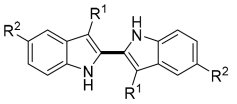


Figure 2. Proposed reaction mechanism.

Initially, **1a** is oxidized via single-electron-transfer (SET), generating radical cation **A** and nitrogen monoxide. Subsequently, **A** reacts with a second molecule of **1a** by means of radical S_EAr to generate intermediate **B**. A second SET leads to rearomatization and formation of product **2a**, while producing a second molecule of nitrogen monoxide. Nitrogen monoxide is oxidized by molecular oxygen generating nitrogen dioxide. Nitrogen dioxide dimerizes to form dinitrogen tetroxide, which is in equilibrium with $NONO_3$ through disproportionation. In the presence of acid water, a nitrosonium and a nitronium ion are released upon protonation. Finally, the nitronium ion is able to oxidize nitrogen monoxide instead of molecular oxygen, maintaining the catalytic cycle.

Dimeric scaffolds can be found in numerous natural products and represent a promising source for the discovery of biologically active compounds.[22] We continued our investigation by testing all substances (**1**−**4**) in cell-based screening assays. To our delight, we discovered the bisindoles **4f**−**i** as potent and novel inhibitors of the hedgehog (Hh) signaling pathway (Table 2 and SI). Inhibition of the Hh signaling pathway is a promising approach for the treatment of cancers, such as basal cell carcinoma and medulloblastoma.[23] A primary structure−activity relationship was observed with IC_{50} values in the low micromolar range, while the monomeric starting

Table 2. Selected Examples of Identified Inhibitors of the Hedgehog (Hh) Signaling Pathway[b]



Monomers inactive
Bisindoles are novel Hh inhibitors

entry	R^1	R^2	**4**	IC_{50} (μM)[b]	viability[c]
1	*o*-$MeOC_6H_4$	H	**4f**	5.42 ± 0.49	inactive
2	*m*-ClC_6H_4	H	**4g**	6.18 ± 1.58	inactive
3	*m*-FC_6H_4	H	**4h**	4.39 ± 0.95	inactive
4	C_6H_5	Me	**4i**	8.11 ± 1.26	inactive

[a]See the SI for biological methods. [b]Mean IC_{50} value for the inhibition of the Hh signaling pathway (see Table S2 for full details). [c]Compound referred to as "inactive" showed more than 80% cell viability at 10 μM.

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materials remained inactive. These findings clearly underline the importance of the developed method, allowing the efficient and selective synthesis of bioactive complex dimeric heteroarenes.

In conclusion, we have developed a regioselective nitrosonium ion-catalyzed dehydrogenative coupling of arylated heteroarenes under mild conditions. The desired products were formed smoothly with a fast reaction rate using molecular oxygen as the stoichiometric oxidant, while water is formed as a single byproduct. A comprehensive scope covering different heterocycles was demonstrated, revealing a good functional group tolerance. We demonstrated that dehydrogenative coupling of heteroarenes allows the straightforward synthesis of dimeric privileged scaffolds, which translated into the rapid discovery of novel Hh inhibitors.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00521.

General experimental procedures, detailed optimization studies, details on control experiments, mechanistic studies and biological methods and characterization of starting materials and products (PDF)

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Notes

The authors declare no competing financial interest.

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