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Letter

Benzophenothiazine and Its Cr(III)-Catalyzed Cross Dehydrogenative Couplings

Christina L. Bub, Vinzenz Thönnißen, and Frederic W. Patureau*

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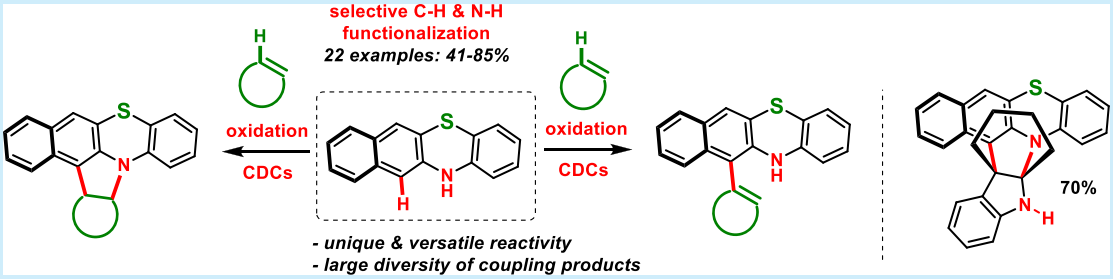


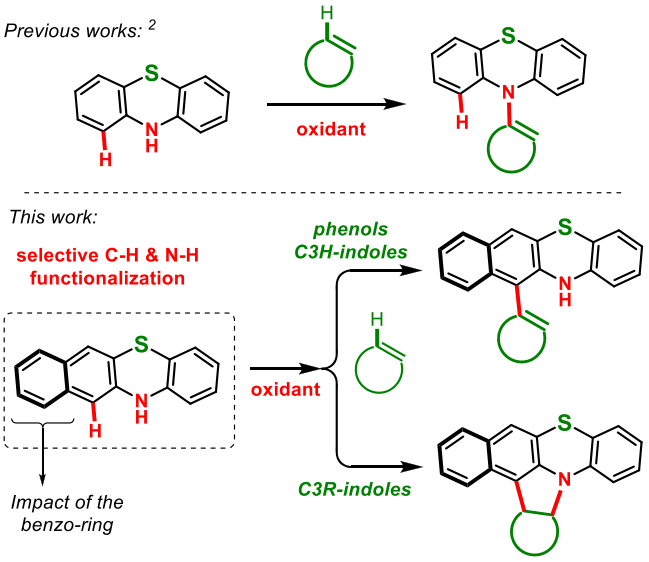
ABSTRACT: In stark contrast to phenothiazines and their prevalence for cross-dehydrogenative amination reactions, benzophenothiazine has a pronounced preference for cross-dehydrogenative C−C bond-forming reactions. Moreover, the substrate is very versatile, leading to several new classes of C−C bond-forming reactions and many new oxidative coupling product architectures, including unprecedented indole fused paddlewheel-like structures.

Phenothiazines have proven to be unique cross-dehydrogenative amination substrates due to their ability upon simple oxidation to accommodate a persistent N-centered neutral radical.[1] The latter furnishes a versatile platform for the N-phenothiazination of a wide range of organic scaffolds.[2] But what happens if one alters the backbone of that N-centered neutral radical? This can be easily achieved, for example, by incorporating an additional fused benzene ring such as in benzophenothiazine, thus modifying its radical properties. This letter reports our surprising findings in terms of cross dehydrogenative coupling (CDC)[3] reactivity for the benzophenothiazine scaffold (Scheme 1).

The title compound, benzophenothiazine, has a number of interesting applications, for example, as a visible-light photoredox catalyst for metal-free atom transfer radical polymerization,[4] a metal-free organic dye for visible-light-driven dye-sensitized photocatalytic hydrogen production,[5] or as a photosensitizer for triarylsulfonium salt cationic photoinitiators (Figure 1).[6] Thus, the direct, cheap, step and atom economical C−H and/or N−H functionalization of benzophenothiazine should be of interest for the development of sustainable technologies based on these new organic materials and their derivatives. Moreover, making new scaffolds easily available, which are derived from benzophenothiazine, may provide physical organic chemists with new facile solutions for future and/or more efficient technologies.

Benzophenothiazine can be accessed through the condensation of 2-aminothiophenol onto 2,3-dihydroxynaphthalene at 200 °C.[7] With the compound in hand, we investigated its cross-dehydrogenative coupling reactivity under a number of oxidative conditions and in combinations with a series of aromatic

Scheme 1. Phenothiazines and Benzophenothiazine CDCs



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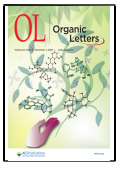

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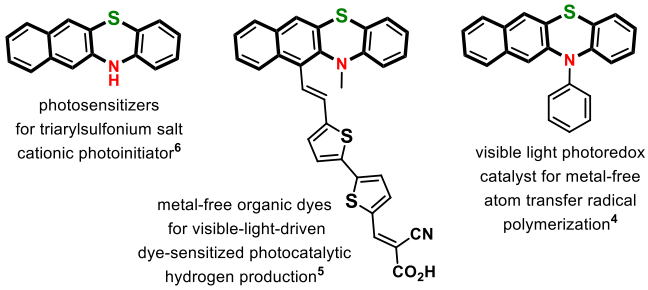
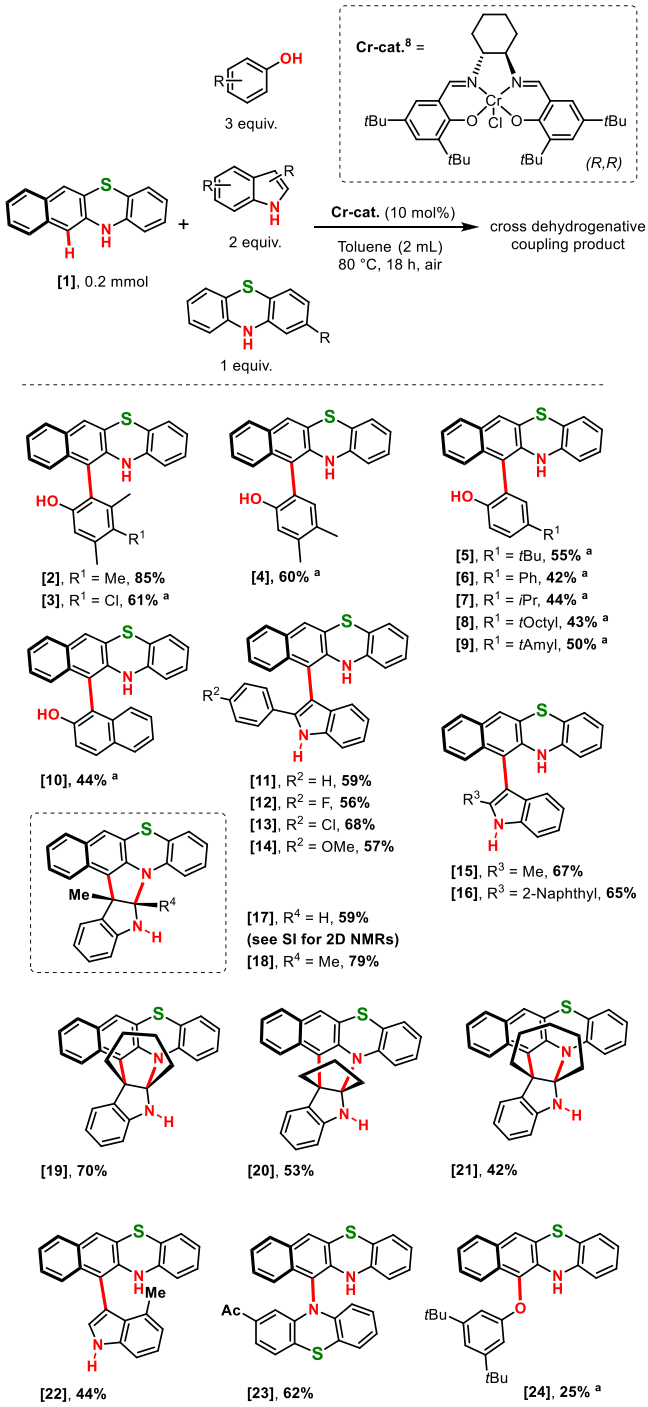


Figure 1. Benzophenothiazine applications.

coupling partners.[2] Eventually, we settled for an oxidative procedure based on an (enantiopure) Jacobsen-type $Cr^{(III)}$ Lewis acid catalyst,[8] which we adapted from a recently reported and inspiring oxidative coupling of 2-naphthylamines by Kozlowski and Paniak.[9] A few adjustments in terms of temperature and solvents allowed us to access a very diverse number of scaffolds in good yields (Scheme 2). In some cases, toluene was found to be a superior solvent. In some other cases it was hexafluoroisopropanol (HFIP).

We then explored the dehydrogenative substrate scope with a number of important phenols[10] and indoles.[11] Several phenols were well accommodated in the cross-dehydrogenative coupling to benzophenothiazine, affording C−C biaryl coupling products with yields up to 85% (structures [**2**−**10**]). Likewise, C3−H indoles delivered the expected C3−C cross dehydrogenative coupling products with yields up to 68% (compounds [**11**−**16, 22**]). Importantly, when the C3 position is blocked by a functional group, thus preventing re-aromatization, the cross-dehydrogenative coupling reaction still occurs. However, an additional subsequent C2−N bond-forming cyclization event then takes place, yielding unique highly functionalized paddlewheel-like scaffolds (structures [**17**−**21**]) with yields up to 79%. Standard COSY, NOESY, HSQC, and HMBC NMR techniques easily confirmed the structural assignments (see the SI). Moreover, interestingly, some small enantiomeric excess could be observed for structure [**2**] (ee = 13%). Decreasing the reaction temperature, however, did not significantly improve the ee (20%), associated with a decrease in conversion. Some of the coupling products did not display any ee at all ([**19**] and [**23**], ee = 0%). Our efforts at optimizing the enantioselectivity of this method have failed so far, but are continuing in our laboratory. Mechanistically, the reaction is assumed to proceed in a radical fashion. Indeed, while the addition 1.5 equiv of TEMPO did not significantly alter the reaction, BHT as well as α-methylstyrene completely suppressed the formation of product [**2**] (see the SI). In the latter cases, some benzophenothiazine homocoupling product could then be detected. Finally, the facts that 2-acetylphenothiazine and Nonhebel's phenol (3,5-di-*tert*-butylphenol)[12] are competent N- and O-coupling partners (structures [**23**−**24**]), respectively, are also in line with a radical mechanism. It should, moreover, be noted that ordinary phenothiazine (**PTZH**) also converted well in those reaction conditions with 3,4,5-trimethylphenol. The latter substrate, however, delivered only the classical dehydrogenative C−N bond-coupled product [**25**] (86%, Scheme 3). In contrast, the C−C bond-coupled product [**25′**] could not be detected. Thus, the herein described Cr(III) catalyzed method merely accelerates the pre-existing intrinsic tendency of benzophenothiazine to couple in a C−C bond forming fashion.[13] The latter propensity for C−C bond formation would be due to the benzo unit affecting the radical

Scheme 2. Method and Scope, Isolated Yields



[a]Toluene was replaced with HFIP.

behavior of benzophenothiazine compared to that of **PTZH**[1] (see Scheme 3, proposed mechanism).

In summary, we investigated the cross-dehydrogenative reactivity of benzophenothiazine with indoles and phenols and found it to be at odds with that of ordinary phenothiazines. In particular, benzophenothiazine strongly favors C−C over C−N cross-dehydrogenative couplings. Moreover, benzophenothiazine easily furnishes paddlewheel-like structures with indoles, thus yielding interesting scaffolds in the chemistry of benzophenothiazine-derived materials.

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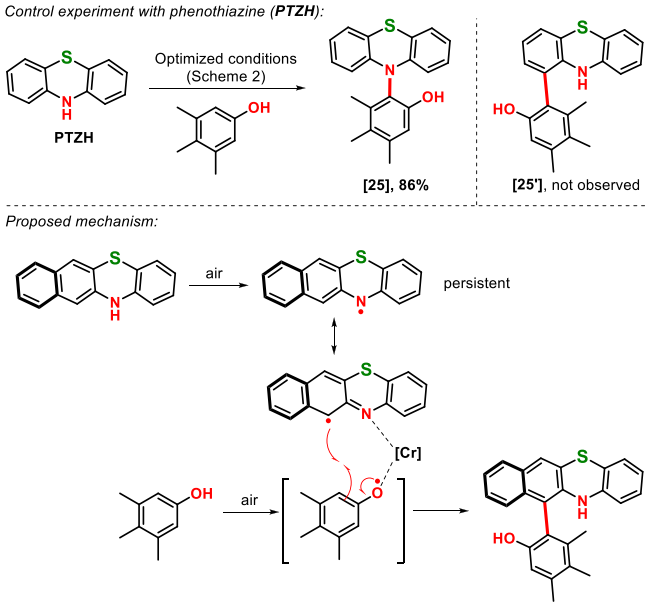
Scheme 3. Control Experiment and Proposed Mechanism



■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03354.

Experimental procedures and characterization of new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Frederic W. Patureau − *Institute of Organic Chemistry, RWTH Aachen University, 52074 Aachen, Germany;* orcid.org/0000-0002-4693-7240; Email: frederic.patureau@rwth-aachen.de

Authors

Christina L. Bub − *Institute of Organic Chemistry, RWTH Aachen University, 52074 Aachen, Germany*

Vinzenz Thönnißen − *Institute of Organic Chemistry, RWTH Aachen University, 52074 Aachen, Germany*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.0c03354

Notes

The authors declare no competing financial interest.

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