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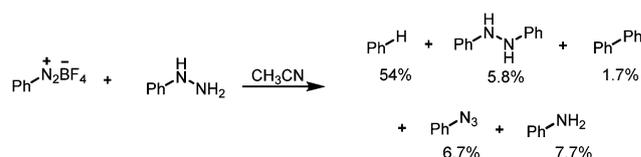
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A family of low molecular-weight, organic catalysts for reductive C–C bond formation†

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Hydrazines form a new family of low molecular-weight reducing agents for diazonium salts. Using only small amounts of hydrazine catalyst, the coupling of diazonium salts to a variety of reactive partners has been achieved, without the requirement for either metal adjuvants or irradiation with visible or ultraviolet light. The generality of the concept proposed herein as well as its advantages in the preparative scale is outlined and discussed.

Diazonium salts are well-known highly reactive species in organic synthesis.¹ Despite their commercially important application in the dye industry,² diazonium salts function as ideal sources of organic radicals that engage in several important transformations such as the Meerwein arylation³ or the Sandmeyer⁴ and Pschorr reaction families.⁵ Since the advent⁶ and renaissance of photoredox catalysis,⁷ many photocatalysts have been shown to catalyse the single electron transfer reduction of diazonium salts to organic radicals. In particular, ruthenium(II) and iridium(III) complexes have been successfully applied in many reactions that exploit their remarkable reactivity in either reductive or oxidative quenching pathways upon visible light (440 nm) excitation.⁸ The relatively high price of those noble/precious metal complexes has subsequently led to the development of alternatives. Namely, several organic dyes proved to be efficient photocatalysts upon excitation with visible light.⁹ For instance, eosin Y,¹⁰ acridinium salts^{9a,11} and perylene diimides (PDI)¹² were all successfully used in photocatalytic organic transformations. A recurrent structural feature of these organic dye catalysts is the presence of extended π -surfaces (mandated by the need to effectively absorb visible light) and high molecular-weight frameworks.¹³ Recently, Carrillo *et al.* described the use of ascorbic acid as an initiator for C–H arylation of anilines.¹⁴ Herein we describe a family of low-molecular weight organic catalysts that promote a range of C–C



Scheme 1 Reaction of the phenyldiazonium salt with phenylhydrazine as reported by Shevlin *et al.*¹⁵

bond forming reactions of diazonium salts, and achieve so without the need for any metal adjuvant or irradiation with light.

We were inspired by the work of Shevlin *et al.*¹⁵ who aimed to isolate stable tetrazenes by reacting phenyldiazonium tetrafluoroborate with phenylhydrazine (Scheme 1). However, those authors were not able to isolate the tetrazeno intermediate but instead observed a complex mixture that featured benzene as the major component in 54% yield and several other minor compounds. The formation of most of the components of the mixture was attributed to the intermediacy of free radicals, as supported by spectroscopic studies (CIDNP).

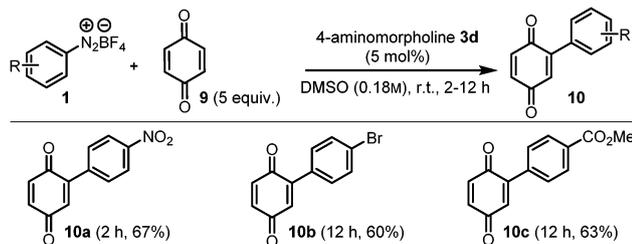
Arylated heteroarenes have proved to be of interest for various applications, such as material sciences and biomedicine.¹⁶ One efficient route to install the aryl–heteroaryl bond is the Meerwein arylation, a cross-coupling reaction between heteroarenes and diazonium salts that is assumed to proceed by a free radical mechanism.¹⁷

We hypothesized that a hydrazine such as phenylhydrazine (employed in the work of Shevlin) could function as a novel reducing agent towards aryl diazonium salts. However, it was crucial to generate the radical intermediate under conditions which would (a) avoid the occurrence of either homocoupling or hydrogen abstraction (as seen by Shevlin), (b) enable its efficient trapping by the heteroarene partner, (c) prevent unwanted disproportionation reactions (such as, *e.g.* leading to an azide and an aniline, as originally also observed by Shevlin) and, most importantly, (d) allow rebound electron-transfer from the coupling adduct to generate the final, neutral biaryl product.

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Scheme 6 Hydrazine-catalysed C–H arylation of quinones with diazonium salts. Yields refer to isolated products.

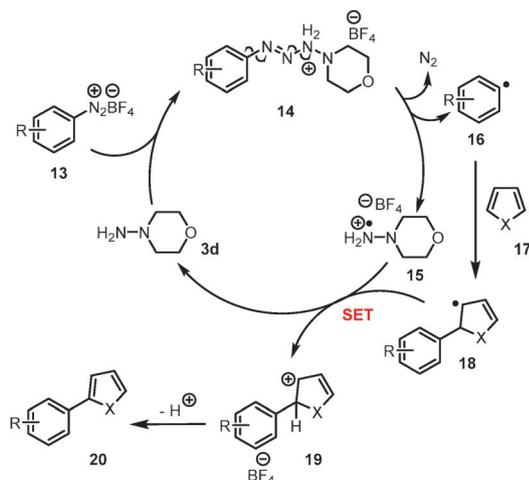


Scheme 7 Trapping the aryl radical intermediate with TEMPO.

the corresponding benzothiophenes in good to moderate yields (Scheme 5).

Furthermore, the arylation of quinones with diazonium salts is an interesting transformation due to the important role of functionalized quinones in medicinal chemistry and biologically active compounds. Bearing this in mind, this reaction was also achieved employing 4-aminomorpholine **3d** as a catalyst and the results are summarized in Scheme 6.²³

Finally, we attempted to trap the putative aryl radical intermediate, presumably formed upon diazonium salt reduction, with TEMPO **11**. As shown in Scheme 7, phenyldiazonium salt **1g** was exposed to a catalytic amount of 4-aminomorpholine **3d** in the presence of 2 equiv. of TEMPO. The expected covalent adduct, 2,2,6,6-tetramethyl-1-phenoxypiperidine **12**, was isolated in 44% yield. Additional experiments (see ESI† for details) reveal that the hydrazine catalyst is present in the reaction mixture (by both LC-MS and NMR analysis) after full conversion has been reached, thus establishing catalytic behaviour. Based on the above observations and previous literature,^{3b,10b,15} a general mechanism



Scheme 8 Proposed catalytic cycle for the hydrazine-catalysed coupling of diazonium salt **13** and heteroarene **17**.

for the couplings of diazonium salts catalysed by 4-aminomorpholine (typified by the Meerwein arylation) is proposed in Scheme 8.

We believe that formation of tetrazene **14**,¹⁵ via reaction of diazonium salt **13** with the hydrazine catalyst **3d**, will generate aryl radical **16** and diazenium radical cation **15** and is driven by the release of nitrogen gas. Radical **16** is subsequently intercepted by reactive unsaturation typified by **17**, to form radical adduct **18**. Oxidation of **18** via SET of **15**²⁴ to the corresponding carbocation **19** regenerates the hydrazine catalyst **3d** and aryl radical **16**, enabling turnover.

In summary, we have shown that simple hydrazines form a new family of low molecular weight reducing agents that allow the catalytic coupling of diazonium salts to electron-rich heteroarenes, enol acetates, alkynes or benzoquinones under simple conditions. Notably, these catalysts' low molecular weight ensures unrivalled practicality when one considers the upscaling of this type of chemistry. The observation that hydrazines can function as catalytic activators for diazonium salts, shown by their presence after full conversion has been achieved, is a new type of reactivity bound to inspire the development of further transformations.

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