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

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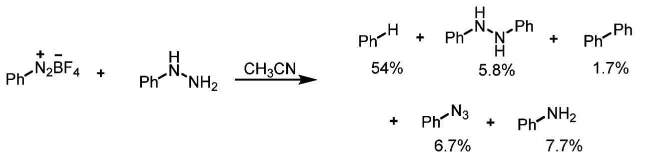
Hydrazines form a new family of low molecular-weight reducing agents for diazonium salts. Using only small amounts of hydrazine catalyst, the coupling of diazonium salts to a variety of reactive partners has been achieved, without the requirement for either metal adjuvants or irradiation with visible 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 arylation[3] or the Sandmeyer[4] and Pschorr reaction families.[5] Since the advent[6] 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 bond forming reactions of diazonium salts, and achieve so without the need for any metal adjuvant or irradiation with light.



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

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 tetrazene 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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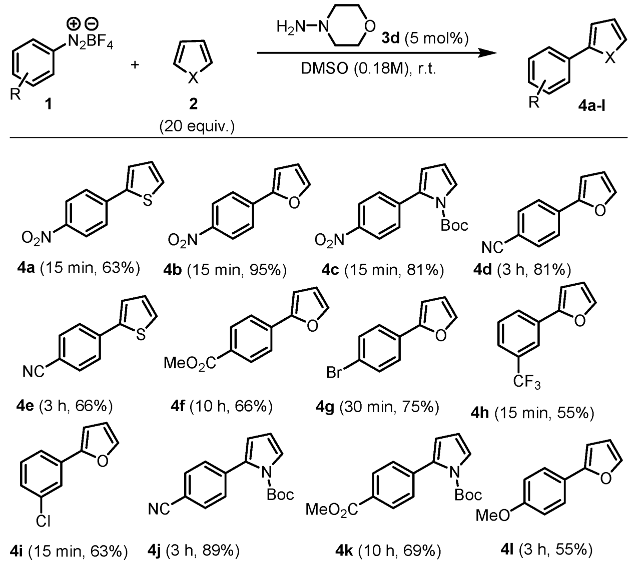
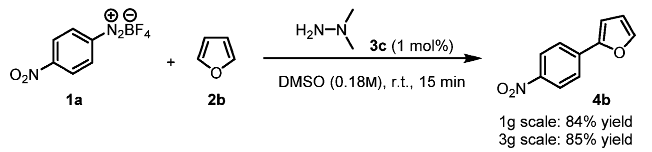


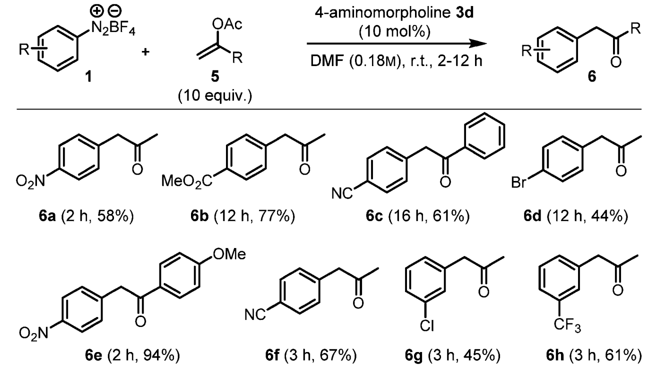
Scheme 2 Scope of the α-arylation of heteroarenes with various diazonium salts using the optimised conditions detailed in the ESI.† The yields are given for the isolated products.

From the outset of our studies on the Meerwein arylation of thiophene, it soon became apparent that hydrazines might have the potential to function as catalysts in such coupling, thus addressing all the above concerns in a fell swoop (detailed optimisation is included as Table S1 of the ESI†). Strikingly, yields of coupling reactions were unchanged when the reaction was performed in the dark, showing that light plays no appreciable role in this transformation. We chose 4-aminomorpholine **3d** to pursue our studies due to practical considerations and its low price. Importantly, the catalyst proved to be essential for the formation of **4a**, as only trace amounts of the desired product were obtained under similar conditions if it was absent from the reaction mixture.[18]

The scope of this hydrazine-catalyzed C–H arylation of heteroarenes with various aryl diazonium salts was then examined using the best conditions found. As shown in Scheme 2, a range of functional groups, such as nitro, cyano, ester, and trifluoromethane, are compatible with the reaction conditions. Notably, the carbon–halogen bonds in **4g** and **4i** were not affected and could serve as reactive handles for further elaboration.[19] A further potential advantage of this system is highlighted in Scheme 3. *N*,*N*-Dimethylhydrazine **3c**, which has a very low molecular weight (M_W = 60 g mol^{-1}, more than 11 times lower than eosin Y), was used to scale up the coupling reaction between nitrobenzene diazonium salt **1a** and furan **2b** to yield **4b** in *ca.* 85% yield in 15 min. Remarkably, only 7.6 mg of the catalyst was used for 12.6 mol of the substrate (3 g scale, 1 mol% catalyst). For the sake of comparison, to achieve the same reaction König's elegant photochemical method would require 87 mg of eosin Y (1 mol%).[10b]



Scheme 3 Scale up of the α-arylation of furan with the *p*-nitrobenzene diazonium salt using *N*,*N*-dimethylhydrazine **3c** as a catalyst.

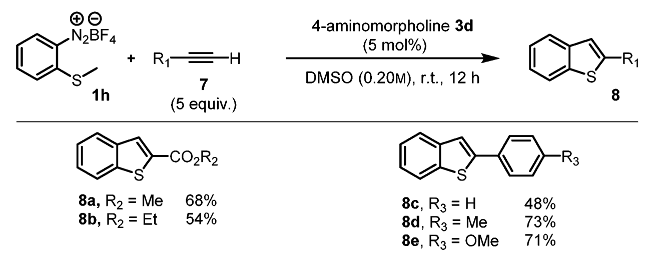


Scheme 4 Preparation of α-aryl ketones *via* hydrazine-catalysed coupling of diazonium salts with alkenyl acetates **5**. Yields refer to isolated products.

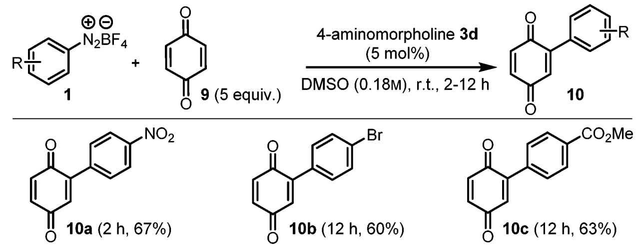
At this juncture, we inquired whether this mode of redox catalysis could be extended to other related transformations. The synthesis of α-aryl ketones is a challenging significant reaction.[20] It was recently shown that the capture of diazonium salts with enolacetates led to this motif.[21] Nevertheless, the reported methodologies mandate the use of transition metal catalysts,[21a] transition metal photocatalysts[21b] or stoichiometric amounts of base.[21c] We thus were intrigued by the possibility of employing hydrazine catalysts for this process (Scheme 4).

Several aryl diazonium salts **1** were therefore treated with alkenyl acetates **5** in the presence of 10 mol% of hydrazine **3d** in dimethylformamide (DMF) to prepare α-arylketone products **6**. A series of α-aryl methylketones and α-aryl arylketones could be synthesized in moderate to good yield. The reaction was tolerant of several functional groups, such as nitro, ester and cyano substituents.

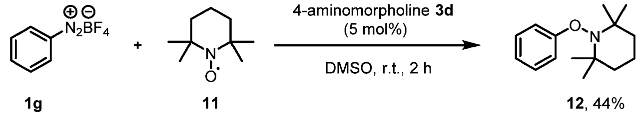
We further applied this catalytic system to the preparation of 2-substituted thiophenes **8** from the corresponding *ortho*-(methylthio) diazonium tetrafluoroborate **1h**. This transformation has been previously reported using transition metal catalysis[22a] or visible light photoredox catalysis with eosin Y.[22b] 4-Aminomorpholine **3d** was able to catalyse this transformation furnishing



Scheme 5 Preparation of 2-substituted benzothiophenes *via* hydrazine-catalysed coupling of diazonium salt **1h** and alkynes **7**. Yields refer to isolated products.



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

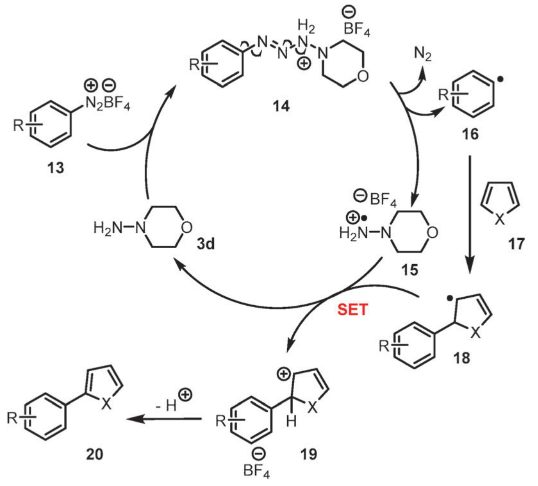


Scheme 7 Trapping the aryl radical intermediate with TEMPO.

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



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

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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