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Transition-Metal-Free Oxyarylation of Alkenes with Aryl Diazonium Salts and TEMPONa

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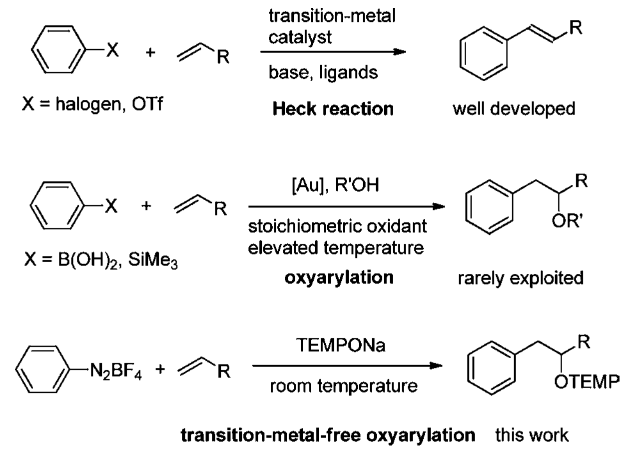
S *Supporting Information*

ABSTRACT: The reaction of readily available TEMPONa with aryl diazonium salts allows for clean generation of the corresponding aryl radicals along with TEMPO. Aryl radical addition to alkenes with subsequent TEMPO trapping provides the corresponding oxyarylation products in good to excellent yields. These experimentally easy to conduct transformations occur in the absence of any transition metal under mild conditions, and the process shows broad functional group compatibility.

Alkenes belong to the most ubiquitous chemical feedstock, and some of them are produced by industry in large scale. Therefore, the development of chemical methods that allow for selective alkene functionalization is an important research field in industry as well as in academia. The Heck reaction, as one of the most important processes for alkene arylation, has been studied intensively during the past decades.[1] In the Heck reaction, the intermediately formed C(sp^3) center generated during the initial C−C bond-forming step is transformed into a C(sp^2) center in the ensuing β-H elimination step (Scheme 1).

Scheme 1. Alkene Arylation



A highly valuable alternative reaction pathway would be oxidation of the intermediately formed alkylpalladium species (or, more generally, alkylmetal species) to give β-aryl-α-heterofunctionalized alkanes. The initial steps in such processes might differ from those of the typical Heck reaction (e.g., oxy- or aminometalation of the alkene rather than carbometalation; C−heteroatom bond formation before C−C bond formation). Whereas intramolecular variants of such processes are rather well investigated,[2,3] reports of intermolecular versions are rare.[4] Recently, oxyarylation of alkenes with arylboronic acids or arylsilanes using cationic Au complexes has been reported independently by Toste[5] and Lloyd-Jones.[6] The addition of a stoichiometric oxidant and elevated temperature are required for these elegant gold-catalyzed oxyarylations. Radical reactions can be conducted under mild conditions and tolerate many functional groups, rendering such processes highly useful in organic synthesis.[7] More than a century ago, it was shown that aryl diazonium salts are valuable precursors of aryl radicals (Sandmeyer reaction).[8] The Meerwein arylation, which involves oxidative addition of aryl radicals derived from aryl diazonium salts to electron-deficient alkenes using copper(I) salts as catalysts, was first reported in 1939.[9] Later it was shown that aryl radical generation from the corresponding diazonium salt can also be achieved with iodide, titanium(III) salts or other metal-based reducing reagents, tetrathiafulvalene, or photocatalysis.[10,11] Heinrich and co-workers reported oxyarylation of alkenes with aryl diazonium salts by using a superstoichiometric amount of an Fe(II) salt for radical generation and the radical 2,2,6,6-tetramethylpiperidine *N*-oxyl (TEMPO)[12] to trap the intermediately generated adduct radical.[13] Compared with the use of aryl halides in combination with tin hydrides for aryl radical generation,[10b] aryl diazonium salts undoubtedly offer a more environment-friendly route toward aryl radicals since toxic tin compounds are not required.[14] Moreover, aryl diazonium salts are easily prepared from the corresponding anilines. Herein we report an unprecedented transition-metal-free oxyarylation of alkenes with aryl diazonium salts and TEMPONa (Scheme 1).

We recently introduced the use of TEMPONa, which is readily generated by reduction of commercially available TEMPO with Na in tetrahydrofuran (THF), as a mild organic single-electron transfer (SET) reagent for generation of the trifluoromethyl radical from a hypervalent CF_3−I(III) compound.[15] On the basis of these results, we envisioned that TEMPONa could also be applied to the generation of aryl radicals upon reaction with the corresponding aryl diazonium salts. In the presence of an alkene, oxyarylation should be feasible. The concept is presented in Scheme 2. TEMPONa would first reduce the aryl diazonium salt via SET[16] to generate the corresponding aryl radical along with the persistent TEMPO radical. Aryl radical addition to the alkene and subsequent selective trapping of the adduct radical with

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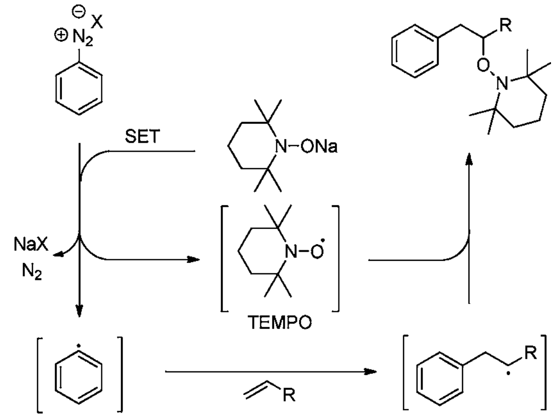
Scheme 2. Oxyarylation of Alkenes with Aryl Diazonium Salts and TEMPONa

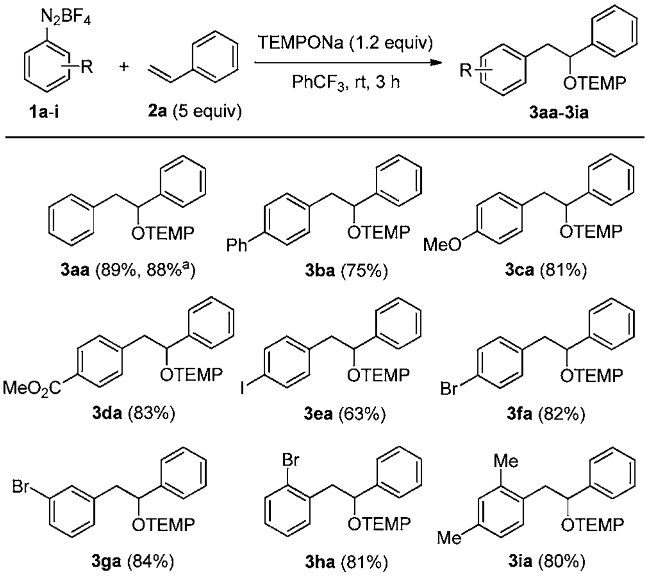


TEMPO should eventually provide the corresponding oxyarylation product. The highly selective cross-coupling of the transient adduct radical with TEMPO would be steered by the persistent radical effect.[17]

Initial experiments were conducted with phenyl diazonium salt **1a** (R = H) and 5 equiv of styrene (**2a**) at room temperature. TEMPONa (1.2 equiv) in THF was added by syringe pump. The solvent and concentration were systematically varied (see the Supporting Information). Optimization studies revealed that reaction was best conducted in α,α,α-trifluorotoluene[18] as the solvent at a concentration of 0.5 M. TEMPONa was added over 3 h, and the oxyarylation product **3aa** was isolated in 89% yield (Scheme 3). Faster or slower addition of the organic SET reagent resulted in decreased yields. Other solvents, such as MeCN (20%), $ClCH_2CH_2Cl$ (52%), and THF (69%), provided worse results. Reducing the amount of styrene did not affect the yield to a large extent (2 equiv, 87%; 1.5 equiv, 88%). Under the optimized conditions, various aryl diazonium salts **1b–i** were reacted with **2a** (5 equiv) to give the oxyarylation products **3ba–ia** in good yields (63–84%). Electron-donating (R = 4-OMe) and electron-withdrawing (R = 4-CO_2Me) substituents on the aryl diazonium salt were tolerated. Moreover, bromo- and iodoaryl diazonium salts reacted equally well, and steric effects due to the installation of ortho substituents were negligible. To document the practicability of our protocol, a gram-scale experiment run with **1a** and **2a** afforded **3aa** in 92% yield (0.93 g of **3aa** was isolated).

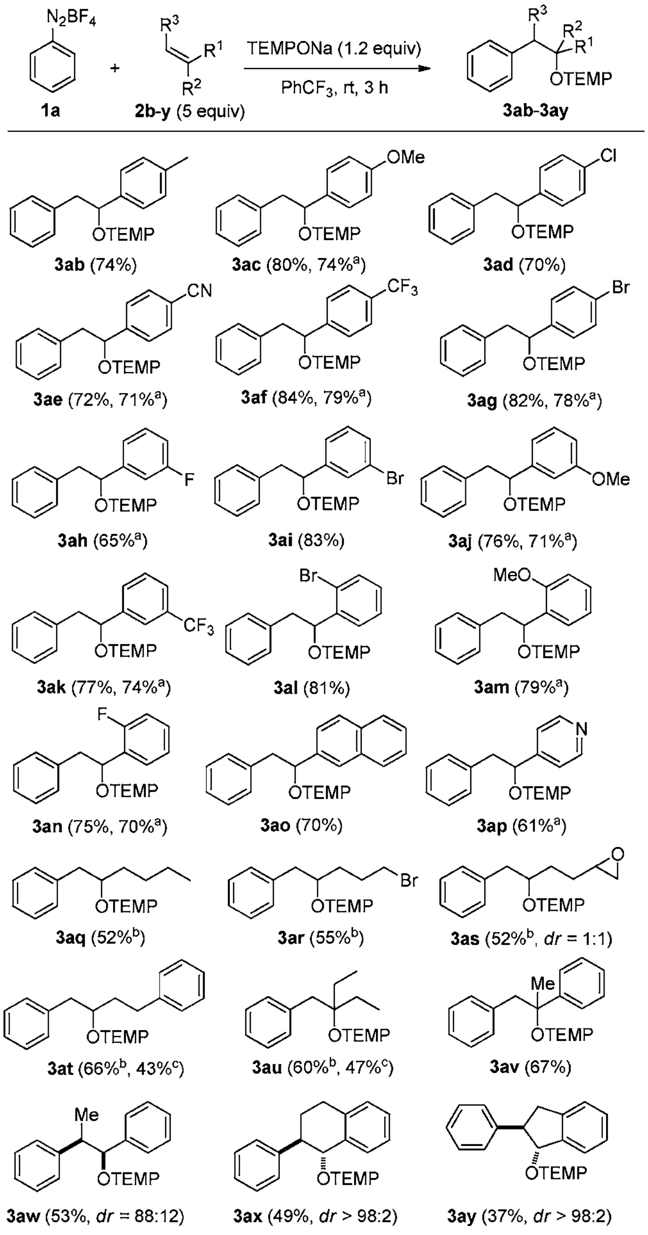
Keeping aryl diazonium salt **1a** as the aryl radical precursor, we varied the aryl radical acceptor. Various styrenes **2b–n** (5 equiv) bearing either electron-donating or electron-withdrawing substituents were successfully converted to the corresponding oxyarylation products **3ab–an** in high yields (Scheme 4). In some cases we repeated the experiment using 1.5 equiv of the vinyl arene and found that the yield decreased only to a small

Scheme 3. Variation of the Aryl Diazonium Salt



[a]With 1.5 equiv of styrene.

Scheme 4. Variation of the Aryl Radical Acceptor



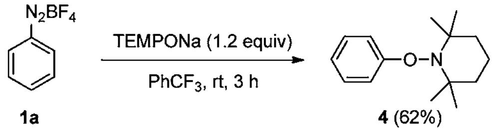
[a]With 1.5 equiv of the styrene derivative. [b]With 10 equiv of the alkene. [c]With 3 equiv of the alkene.

extent. Surprisingly, although the yield of the CN-substituted derivative **3ae** was only slightly lower than that of the MeO congener **3ac**, we found a large difference in the relative reactivity of the corresponding styrene derivatives. Reaction of **1a** with a 1:1 mixture of **2c** and **2e** (5 equiv each) provided **3ac** (65%) along with traces of **3ae** (<2%), showing that phenyl radicals react highly chemoselectively with the more electron-rich styrene derivative **2c**.

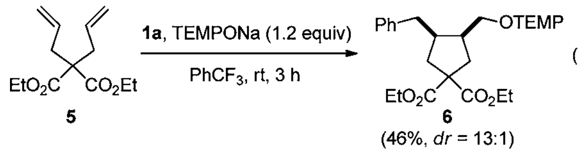
To our delight, oxyphenylation also worked with non-activated aliphatic alkenes, albeit in slightly lower yields (**3aq**–**au**). For these less reactive acceptors, we generally used 10 equiv of the alkene. The yields were slightly lower when 3 equiv of the radical acceptor was used (see **3at** and **3au**). Notably, both terminal bromide and terminal epoxide functionalities were compatible with the reaction conditions. Formation of quaternary C centers was possible by using disubstituted terminal alkenes as radical acceptors (**3au** and **3av**). For all of the terminal alkenes tested, the reaction occurred with complete regioselectivity.

Radical oxyarylation worked also on internal alkenes. Hence, the reaction of *trans-β*-methylstyrene with **1a** provided **3aw** in 53% yield with complete regioselectivity and moderate diastereoselectivity.[19] Perfect regio- and diastereoselectivity were achieved for the transformation of 1,2-dihydronaphthalene and indene (see **3ax** and **3ay**).

To support the mechanism suggested in Scheme 1, we performed two control experiments. The reaction of **1a** with TEMPONa (1.2 equiv) provided TEMPO-Ph (**4**) in 62% yield (eq 1), proving that a phenyl radical is formed under the reaction conditions. Moreover, bis(allyl)malonate **5** reacted with **2a** and TEMPONa to give **6** in 46% yield with high cis selectivity (eq 2).[20] This cascade comprising a 5-exo cyclization represents a typical radical process.



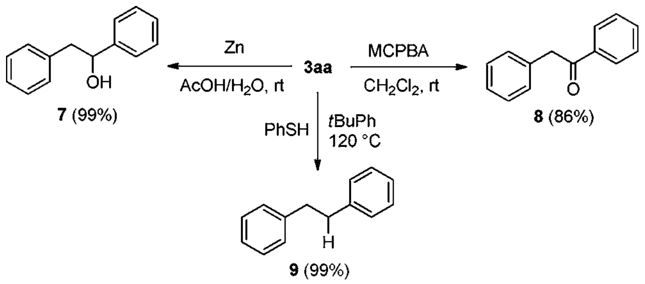
(1)



(2)

It is important to note that these TEMPO-based alkoxyamines can easily be subjected to further chemical manipulation, as documented by three follow-up reactions (Scheme 5).[12] The N–O bond in **3aa** was readily cleaved with Zn at room temperature (rt) to afford benzyl alcohol **7**, which was isolated in quantitative yield (99%). Oxidation of the alkoxyamine to ketone **8** was achieved upon treatment of **3aa** with *m*-chloroperoxybenzoic acid (MCPBA) in CH_2Cl_2 (86%), and radical deoxygenation[21] occurred when the alkoxyamine was heated in the presence of thiophenol, affording bibenzyl (**9**) in quantitative yield.

Scheme 5. Chemical Transformations of Alkoxyamine 3aa



In summary, we have developed a new method for transition-metal-free radical oxyarylation of alkenes. The procedure uses readily available aryl diazonium salts as radical precursors and TEMPONa as a reducing reagent that upon SET is converted to the TEMPO radical, which then acts as an oxidant in the subsequent step. The reactions are experimentally easy to conduct and occur under mild conditions, and the substrate scope is broad.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and characterization data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(16) Aryl radical generation might also occur via N−O bond formation between TEMPONa and the aryl diazonium salt and subsequent N−O bond homolysis:

$$ArN_2^+ + TEMPO^- \longrightarrow Ar{-}N{=}N{-}OTEMP \longrightarrow Ar\cdot + N_2\uparrow + TEMPO$$

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