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Intermolecular Radical Carboaminohydroxylation of Olefins with Aryl Diazonium Salts and TEMPO

Markus R. Heinrich,* Alexander Wetzel, and Marcel Kirschstein

Lehrstuhl für Organische Chemie 1, Technische Universität München,
Lichtenbergstrasse 4, D-85747 Garching, Germany

markus.heinrich@ch.tum.de

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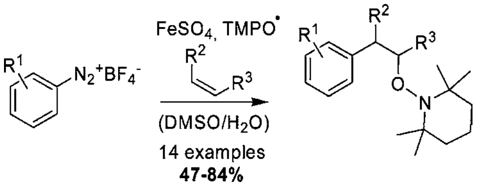
ABSTRACT



Highly reactive aryl radicals can selectively be reacted with a broad variety of activated and nonactivated olefinic substrates in the presence of nitroxyl radicals. Direct recombination of the aryl radical and the nitroxide as well as telomerization of the olefin is successfully suppressed by the reaction conditions.

Aryl and vinyl radicals represent the most unstable and highest reactive species in the group of carbon-centered radicals. Due to this reactivity, conversions of aryl radicals are often complicated by numerous side reactions, and their application in organic synthesis has remained limited to a number of processes. Sandmeyer[1] and Meerwein[2] reactions as well as iodine-transfer[3] based conversions are efficient methods since the rate constants for the reaction of the aryl radical with the desired target molecule are sufficiently high so that side processes such as hydrogen abstraction or biaryl coupling are suppressed.

More recently, aryl radicals have been successfully employed by Porta for selective hydrogen transfer from tetrahydrofurans[4] as well as for addition reactions to iminium ions.[5] In contrast to the classical Meerwein reaction, where aryl radicals add to activated electron-deficient olefins, similar conversions with nonactivated alkenes were believed to be troublesome due to significantly lower addition rates.[6] Low velocity can be counterbalanced by shifting to an intramolecular reaction type. The synthetically useful 5-*exo*-cyclization of 2-(allyloxy)phenyl radicals,[7] for example, has been used as a radical clock reaction.[8]

In this Letter, we would like to present a new reaction that relies on the efficiency of *intermolecular* aryl radical addition to a wide range of olefinic substrates. Our interest in this field was driven by previous results from carbodiazenylation reactions[9] as well as by competition experiments.

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* To whom correspondence should be addressed. Fax: +49-89-289-13329.

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[8] Determination of $k \cong 6 \times 10^9$ M^{-1} s^{-1} for the 5-*exo*-cyclization of 2-(allyloxy)phenyl radicals: Johnston, L. J.; Lusztyk, J.; Wayner, D. D. M.; Abeywickreyma, A. N.; Beckwith, A. L. J.; Scaiano, J. C.; Ingold, K. U. *J. Am. Chem. Soc.* **1985**, *107*, 4594−4596.

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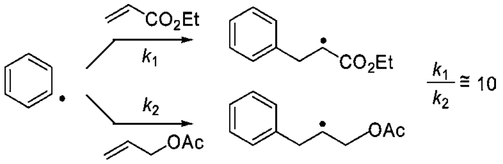
In these experiments we compared the addition rates of aryl radicals toward different types of olefins and found that in aqueous DMSO aryl radicals add to allyl acetate only ten times slower than to the activated alkene ethyl acrylate (Scheme 1, see also the Supporting Information). The persistent tetramethylpiperidine-oxyl radical TEMPO was used to trap the intermediates arising from the addition step.[10−13] From these results one can estimate rate constants of $k \cong 3 \times 10^7$ M^{-1} s^{-1} (23 °C) for the addition of aryl radicals to nonactivated, monosubstituted olefins.[14] This finding correlates well with the values found by Ingold and Lusztyk ($k \cong 2 \times 10^7$ M^{-1} s^{-1}),[15] but the rate is far higher than reported elsewhere (values starting from $k \cong 10^5$ M^{-1} s^{-1}).[6,14] Ingold and Lusztyk[15] moreover pointed out that aqueous solvents are a critical element for controlled reactions of aryl radicals.[3c] All observations from our recent studies fully support this statement.

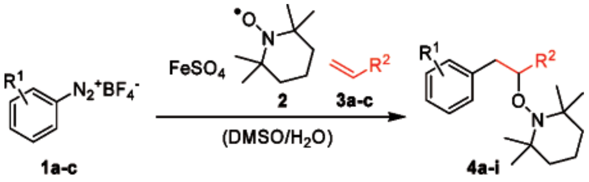
Scheme 1. Competitive Addition of Aryl Radicals to Ethyl Acrylate and Allyl Acetate



Surprisingly good overall yields (50−70% based on the diazonium salt used as the source of the aryl radical) and only small amounts (<15%) of aryl-TEMPO adducts were formed in the competition reactions.

At this point, we felt that the significantly reduced reactivity of nitroxyl radicals in polar hydrogen-bonding solvents,[16] which allows olefins to act as competing substrates, could advantageously be used for the development of a new synthetic method. The type of functionalization that results from the competition reactions can be described as carboaminohydroxylation. While previous methodology developed by Studer[17,18] is based on the persistent radical effect (PRE),[19] the process described herein depends on the reduced reactivity of nitroxyl radicals. To determine the scope and limitations of the reaction, we conducted the following diversity-oriented study including different types of aryldiazonium salts **1**, TEMPO (**2**), and various olefins **3** (Table 1).

Table 1. Scope and Limitations of Carboaminohydroxylation[a,b]



diazonium salts **1**	olefins **3** **3a**: R^2 = CO$_2$Et	 **3b**: R^2 = CH$_2$OAc	 **3c**: R^2 = OAc
1a: R^1 = *p*-OMe	**4a** (68%)	**4b** (48%)	**4c** (60%)
1b: R^1 = *p*-F	**4d** (62%)	**4e** (64%)	**4f** (62%)
1c: R^1 = *o*-CO$_2$Me	**4g** (63%)	**4h** (47%)	**4i** (48%)

[a] Reactions conducted according to the standard procedure (see ref 20). [b] Yields after purification by column chromatography.

The yields obtained from the nine experiments show that all combinations led to synthetically useful results. Addition of ascorbic acid to the reaction mixture prior to workup significantly facilitated product isolation.[7]

Interestingly, the reactions including ethyl acrylate (**3a**) (Table 1, column 2) do not generally give the best yields, although they are favored in two ways: first by the fast addition of the aryl radical to the olefin and second by the fact that carbodiazenylation (radical trapping by an aryl diazonium salt) is not a competing process.[3a,21] The carbodiazenylation accounts for the slightly decreased yields of **4h** and **4i**, as it is favored by both the reactive diazonium

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(20) To a degassed 2:1 mixture of DMSO and water (3 mL) under argon were added the olefin (3 mmol for activated, 10 mmol for nonactivated substrates), FeSO$_4$ × 7H$_2$O (834 mg, 3 mmol), and TEMPO (313 mg, 2 mmol). A solution of the arenediazonium salt (1 mmol) in 2:1 DMSO−water (1 mL) was added dropwise over a period of 10 to 15 min and the resulting mixture was left to stir at rt for another 10 min before ascorbic acid (528 mg, 3 mmol) was added. After 10 min more, the mixture was diluted with water (50 mL) and extracted with Et$_2$O (3 × 30 mL). The combined organic phases were washed with satd NaCl and dried over Na$_2$SO$_4$. Concentration and purification by column chromatography furnished the carboaminohydroxylation products.

(21) Electrophilic radicals (e.g., in the α-position of a carbonyl, ester, or cyano group) are unreactive toward diazonium salts: (a) Minisci, F.; Coppa, F.; Fontana, F.; Pianese, G.; Zhao, L. *J. Org. Chem.* **1992**, *57*, 3929−3933. (b) Blank, O.; Heinrich, M. R. *Eur. J. Org. Chem.* **2006**, 4331−4334.

salt **1c** and the nucleophilicity of the intermediate alkyl and alkoxy radicals arising from aryl radical addition to allyl acetate (**3b**) and vinyl acetate (**3c**).[21a]

We then applied the carboaminohydroxylation conditions to additional substrates, which further proved the general applicability. The products **4j−n** obtained from the reactions of the aryldiazonium salts **1a** and **1b** with acrylonitrile, *N*,*N*-dimethylacrylamide, and styrene are shown in Figure 1. Carboaminohydroxylation of vinylcarbonate proceeded with moderate diastereoselectivity (**4m**, dr = 72:28), but with methyl 1-cyclohexene-1-carboxylate only one product isomer was dectected in the ^{1}H NMR spectrum before purification (**4n**, dr >90:10). The attempted addition to phenylacetylene failed and furnished the unstable benzoine derivative **5** instead of the expected stilbene.

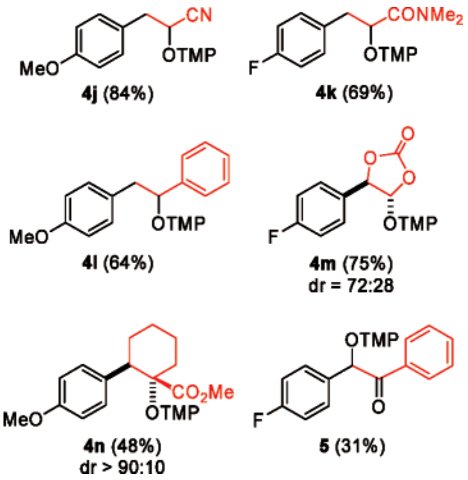
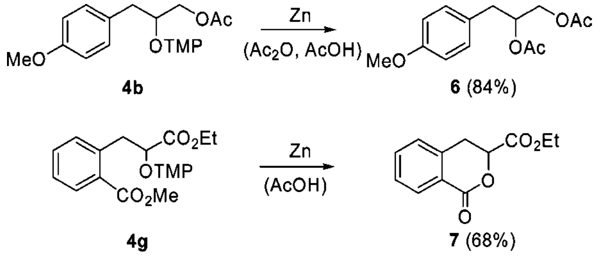


Figure 1. Products from the carboaminohydroxylation of acrylonitrile, *N*,*N*-dimethylacrylamide, styrene, vinylcarbonate, methyl 1-cyclohexene-1-carboxylate, and phenylacetylene (TMP = 2,2,6,6-tetramethylpiperidine).

Carbohydroxylation[22] products can be obtained from the hydroxylamines **4** by reduction with zinc in acetic acid.[23] We exemplified this by converting **4b** and **4g** to bisacetate **6** and oxoisochromane **7**, respectively. Lactones of type **7** are known as core structures of a number of bioactive natural products (Scheme 2).[24]

Scheme 2. Conversion of Alkoxyamines to Carbohydroxylation Products



In summary, we have shown that aryl radicals can be used as carbon equivalents in carboaminohydroxylation reactions due to the decreased reactivity of nitroxide radicals in polar solvents. The described process significantly enlarges the product pattern of radical olefin functionalizations. The broad variety of olefinic substrates which are tolerated and the mild reaction conditions show that this newly developed methodology is of general value for synthetic organic chemistry.

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Supporting Information Available: Experimental procedures and characterization data for compounds **4a−n**, **5**, **6**, and **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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