Carbohydroxylation

Thermally Induced Carbohydroxylation of Styrenes with Aryldiazonium Salts

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Abstract: *The radical carbohydroxylation of styrenes with aryldiazonium salts has been achieved under mild thermal conditions. A broad range of aryldiazonium salts was tolerated, and the reaction principle based on a radical–polar crossover mechanism could be extended to carboetherification as well as to a two-step, metal-free variant of the Meerwein arylation leading to stilbenes.*

Over the last decade, the Meerwein arylation has become a broadly applicable reaction for the functionalization of alkenes.[1] The product scope has been increased through the introduction of new radical acceptors and aryl radical sources. Besides this, the reaction conditions have been improved through the development of catalytic,[2] photocatalytic,[3] and metal-free versions.[4] Seminal examples are the TEMPO/sodium-mediated carboaminohydroxylation by Studer et al.[5] and the remazol-catalyzed hydroperoxyarylation by Leow et al. (Scheme 1).[6–8] Inspired by new carboamination reactions,[9] we investigated whether basic conditions—which have so far mainly been applied in Gomberg–Bachmann reactions[1e,10,11]—could also add to the attractiveness of Meerwein-type carbohydroxylations.
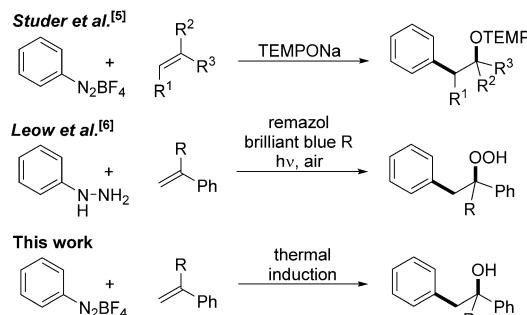
Scheme 1. Meerwein-type carbooxygenation reactions.

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Supporting information for this article can be found under:
http://dx.doi.org/10.1002/anie.201601656.

The results from a series of optimization experiments with 4-chlorophenyldiazonium tetrafluoroborate (**1a**) and α-methylstyrene (**2a**) are summarized in Table 1. To avoid the attack of aryl radicals onto unconverted diazonium ions, slow addition of **1a** was combined with elevated reaction temper-

Table 1: Optimization of reaction conditions.
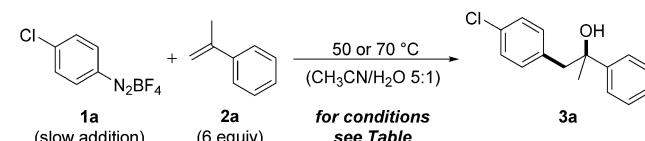
Entry	Reaction conditions[a]	Yield **3a** [%][b]
1	Na₂CO₃, 50°C	60
2	Na₂CO₃, 50°C, under oxygen atmosphere	56
3	Na₂CO₃, 70°C	72
4	Na₂CO₃, 70°C, **2a** (3 equiv)	61
5	Na₂CO₃, 70°C, **2a** (12 equiv)	58
6	KOAc, 70°C	85 (82)[c]
7	KOAc, CH₃CN/H₂O (1:1)	81
8	KOAc, under nitrogen atmosphere	78
9	No base, 70°C	83 (86)[c]

[a] General reaction conditions: **1a** (1.0 mmol) in CH₃CN/H₂O (5:1, 4 mL) added slowly over 5 min to a mixture of the base (1.5 mmol) and **2a** (3–12 mmol) in CH₃CN/H₂O (5:1, 5 mL) under air. [b] Yield determined by ¹H NMR spectroscopy using dimethyl terephthalate as an internal standard. [c] Yield after purification by column chromatography.

atures, as both measures reliably decrease the concentration of **1a** in the reaction mixture. Potassium acetate[10b] (Table 1, entries 6–8) was found to be a better suited base than sodium carbonate (Table 1, entries 1–5), and in the former case the reaction under nitrogen gave a slightly lower yield of alcohol **3a** than that under air (Table 1, entries 6 and 8). The lower yield obtained under oxygen atmosphere (Table 1, entry 2) already indicated at an early stage that radical trapping by oxygen is—in contrast to many other carbooxygenations[6,7g,k]—at least not the major mechanistic pathway. The use of twice as much alkene **2a** (12 equivalents) did not further increase the yield, as the reaction was then complicated by phase separation (Table 1, entry 5). The strong base sodium hydroxide, which largely converts aryldiazonium ions into aryl diazotates,[11d] led to low yields in the range of 16–41% (see the Supporting Information), thus suggesting that a certain amount of free diazonium ions is required for the desired reaction course. Finally, a control experiment in the absence of base provided **3a** in 86% yield and revealed thermal initiation as a useful alternative to weakly basic conditions.[1e]

With optimized conditions **A** and **B** available (Table 1, entries 6 and 9, respectively), we then explored the scope and limitations regarding the substitution pattern on the diazonium salt (Scheme 2). Good to high yields of the racemic alcohols **3** were obtained with few exceptions. The 4-

3a R = 4-Cl, 82% (86%)[a]
3b R = 4-F, 5% (76%)[a]
3c R = 3-F, 77%
3d R = 3-Cl, 68%
3e R = 2-Cl, 75%
3f R = 3,5-Cl$_2$, 62%
3g R = 4-Br, 70% (87%)[a]
3h R = 3-Br, 63%
3i R = 2-Br, 72%

3j R = 4-I, 63%
3k R = 4-H, 23% (0%)[a]
3l R = 4-OMe, 6% (0%)[a]
3m R = 4-NO$_2$, 55% (74%)[a]
3n R = 4-CF$_3$, 57%
3o R = 4-CN, 53% (72%)[a]
3p R = 3-CN, 59%
3q R = 4-COMe, 67%
3r R = 4-CO$_2$Me, 73%

3s R = 2-CO$_2$Me, 90%[b]
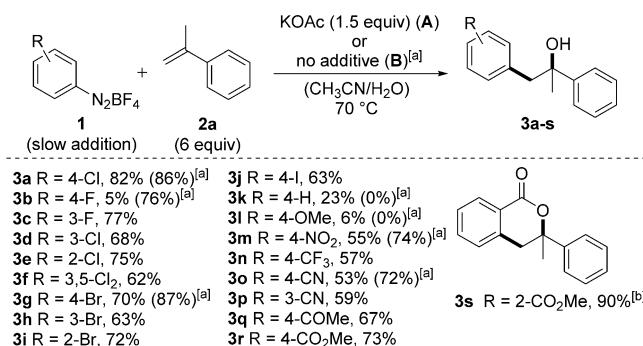
Scheme 2. Carbohydroxylation: variation of substituents on the aryldiazonium salt. See the Experimental Section for general procedures **A** and **B**. Yields determined after purification by column chromatography. [a] Yield from reaction under base-free conditions **B**. [b] Reaction time: 18 h.

fluorophenyldiazonium salt used for the synthesis of **3b** is likely to undergo nucleophilic aromatic substitution under conditions **A** rather than enter the radical reaction,[12] so that a good yield could only be achieved under base-free conditions **B**. Reactions of the unsubstituted phenyldiazonium ion, such as that leading to alcohol **3k**, appear under some conditions to be complicated by effects like aggregation.[13] The low yield obtained for **3l** can be explained by the underlying mechanism (Scheme 3), in which the donor-substituted 4-methoxyphenyldiazonium ion (**1**, R^1 = OMe) is unable to effectively propagate the radical chain through oxidation of radical **4** to cation **5**.[14] In a tandem reaction combining carbohydroxylation and lactonization, the 2-methyloxycarbonyl-substituted diazonium salt directly provided isochromanone **3s**. A repetition of the synthesis of **3a** on a larger scale (10 mmol, conditions **A**) led to a yield of 66% (1.39 g).

The radical–polar crossover step[15] in the assumed reaction mechanism (Scheme 3), in which basically an electron acts as a catalyst to form the new aryl radical **6**,[16] was further supported by the results obtained with different styrenes (Scheme 4). Substituents leading to a comparable or increased stabilization of cation **5**, such as R^3 = OMe (**3t**), R^3 = Cl (**3u**), and R^2 = Ph (**3w**), support product formation. Destabilizing substituents like R^3 = NO$_2$ (**3v**) and R^2 = H (**3x**), on the other hand, lead to low yields. The lack of the methyl group in R^2 is not counterbalanced by a more reactive diazonium ion (**3y**, R^1 = NO$_2$), but is counterbalanced by a donor substituent R^3 (**3z**–**3cc**, R^3 = OMe). Donor substitution (R^3 = OMe) then even allowed a successful reaction with the electron-rich 4-methoxyphenyldiazonium salt (R^1 = OMe) to give alcohol **3bb**. Furthermore, the

reaction scope could be extended to a substituted naphthalene **3dd**, tetrahydronaphthalene **3ee**, and thiophene **3ff**. If one compares conditions **A** and **B**, it appears that the main advantage of potassium acetate (conditions **A**) is to protect acid-labile alcohols **3**. Reactions in the absence of base (conditions **B**) were found to be strongly acidic (pH ≈ 1) after the complete addition of **1**, so that donor-substituted alcohols (e.g. **3t**, **3z**, R^3 = OMe) can decompose via their related cations **5**. Acid-stable alcohols **3**, as is the case in Scheme 2, benefit from base-free conditions **B** as more free diazonium ions **1** are then available for chain propagation.[10a] Radical arylations in which solely the diazonium ions act as chain carriers have been described so far for only enol ethers, enol esters, and some aromatic systems.[17] In related carboamination reactions of styrenes reported by König et al.,[7e] an additional photocatalyst is required.[3d]

Extension of the reaction principle to obtain the carbo-etherfication product **7**[7f] was possible in two ways, either by exchanging the cosolvent acetonitrile for methanol (Path I, Scheme 5) or by treating alcohol **3a** with catalytic amounts of acid in methanol (Path II).[18] The latter sequence did not require intermediate purification of **3a**. The synthesis of stilbenes **8a**–**e**, which offers an attractive alternative to known transition-metal-catalyzed[19] and radical reactions,[3d,20] could
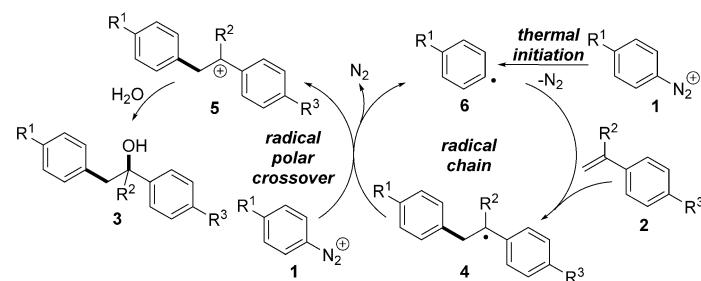
Scheme 3. Plausible reaction mechanism.

3t R^3 = OMe, 68% (31%)[a]
3u R^3 = Cl, 66% (56%)[a]
3v R^3 = NO$_2$, 10%[b]

3w R^1 = Cl, R^2 = Ph, 52%
3x R^1 = Cl, R^2 = H, 10%[b] (0%)[a,b]
3y R^1 = NO$_2$, R^2 = H, 10%[b] (12%)[a,b]

3z R^1 = Cl, 78% (3%)[a,b]
3aa R^1 = Br, 60%
3bb R^1 = OMe, 56%
3cc R^1 = NO$_2$, 55%

3dd 65%

3ee 83%

3ff 62%
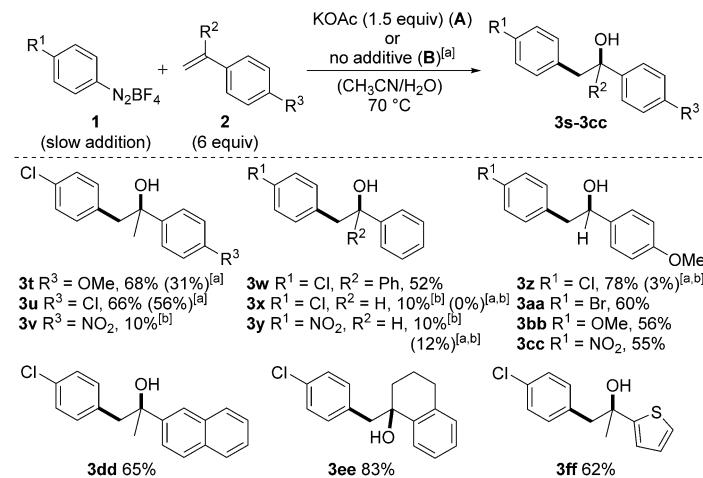
Scheme 4. Carbohydroxylation: variation of the alkene. See the Experimental Section for general procedures **A** and **B**. Yields determined after purification by column chromatography. [a] Yield from reaction under base-free conditions **B**. [b] Yields determined by ^{1}H NMR spectroscopy.
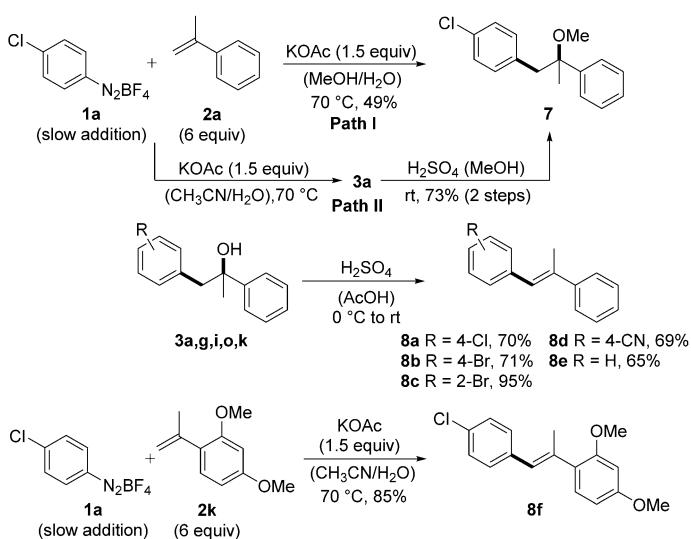
Scheme 5. Carboetherification and synthesis of stilbenes.

be achieved after some optimization with sulfuric acid in acetic acid.[21] With the doubly donor-substituted styrene **2k**, stilbene **8f** was directly obtained under carbohydroxylation conditions.

In summary, we have shown that carbohydroxylation of styrenes is feasible via a mild thermally induced Meerwein arylation, in which the diazonium ion itself acts as an oxidant to propagate the radical chain. Through trapping with water, this reaction directly provides the corresponding alcohols, and in this way it can be extended to carboetherification and to the synthesis of stilbenes. Regarding the manifold substitution patterns on the diazonium ion, this strategy represents a valuable alternative to reactions of benzylic organometallic compounds with benzophenones.[22]

Experimental Section

General procedures **A** and **B** for the carbohydroxylation of styrenes with aryldiazonium tetrafluoroborate salts: A stirred solution of styrene **2** (6.00 mmol) and KOAc (147 mg, 1.50 mmol, only for conditions **A**, no base is added for conditions **B**) in CH$_3$CN/H$_2$O (5:1, 5 mL) at 70 °C was treated by the dropwise addition of a solution of the aryldiazonium tetrafluoroborate salt **1** (1.00 mmol) in CH$_3$CN/H$_2$O (5:1, 4 mL) over 5 min. After stirring for 10 min at 70 °C, the reaction mixture was diluted with water (10 mL), cooled to room temperature, and extracted with diethyl ether (3 × 30 mL). The combined organic layers were washed with aqueous acetate buffer (only for conditions **B**) and brine (30 mL), and dried over Na$_2$SO$_4$. The solvents were removed under reduced pressure and the product was purified by column chromatography on silica gel.

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