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Anti-Markovnikov Hydrofunctionalization of Alkenes - Use of a Benzyl Group as a Traceless Redox-active Hydrogen Donor

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Abstract: A protocol for the *anti*-Markovnikov hydrofunctionalization of alkenes, that utilizes a benzyl group as a traceless redox-active hydrogen donor, has been developed. Under copper catalysis and in the presence of CF₃- or N₃-containing hypervalent iodine reagents, a series of homoallylic alcohol derivatives could be regioselectivity hydrofunctionalized. A similar principle was also applied to the hydrofunctionalization of alkenols.

The ability in hydrofunctionalization of alkenes in a regioselective manner is of prime importance for the development of chemical processes to produce high value fine chemicals. Despite the recent remarkable progress in this area,^[1] a number of challenges still remain for the *anti*-Markovnikov hydrofunctionalization of non-activated alkenes.^[2] One of the most reliable ways to achieve the *anti*-Markovnikov hydrofunctionalization involves the use of carbon- or heteroatom centered radicals which can indeed add on the less hindered/substituted side of an unactivated alkene, thus generating a new C-C or C-heteroatom bond in an *anti*-Markovnikov manner (Scheme 1A). Subsequent delivery of a H atom onto the resulting highly reactive C-centered radical is then required to complete the transformation. This last step often appears to be a key issue to realize an efficient hydrofunctionalization.^[3] In this context, we wondered if a simple benzyl ether moiety, that would be introduced in an alkenyl substrate **I** possessing a hydroxyl group at a suitable position (Scheme 1B, **I**→**II**), could be used after the radical functionalizing event (**II**→**III**) for the precise intramolecular H-delivery *via* a remote H radical shift (**III**→**IV**).^[4,5] We reasoned that this H-radical shift could be driven by the formation of a more stable α -oxy benzyl radical **IV**, which could be, if the suitable redox reaction conditions are set, readily converted into an oxonium cation **V** in a subsequent single-electron-oxidation step (**IV**→**V**). The cationic intermediate **V** could finally be degraded by hydrolysis/solvolysis to release the original hydroxyl group with formation of benzaldehyde as a co-product

(**V**→**VI**). Overall, the temporarily introduced benzyl moiety would function both as a redox active traceless H-donor and as a protecting group for the hydroxy moiety. Herein, we demonstrate the feasibility of this concept with the Cu-catalyzed hydrotrifluoromethylation^[6] and hydroazidation^[7,8] of readily accessible homoallylic alcohols (Scheme 1C). The design, optimization, and substrate scope of these processes are described herein.

A. *anti*-Markovnikov Hydrofunctionalization of alkenes with radicals

B. Use of Bn ether for the redox active hydrogen radical source

C. Cu-catalyzed hydrotrifluoromethylation and -azidation of homoallylic alcohols (this work)

Scheme 1. Anti-Markovnikov hydrofunctionalization of alkenes

We initiated our investigations by studying the possibility to perform the hydrotrifluoromethylation of the readily accessible homoallylic alcohol benzyl ether **1a** (Scheme 2A). The use of Togni's reagent **2**^[9] as a source of trifluoromethyl radical along with a copper salt as a redox catalyst was considered as a potentially suitable set of reagents to achieve the desired transformation.^[10] An extensive screening of the reaction conditions (see SI for details) revealed that the *anti*-Markovnikov hydrotrifluoromethylation of **1a** could be efficiently performed in the presence of CuI (10 mol%) and Togni's reagent **2** (1.2 equiv) in dioxane-MeOH (9:1) solvent system at 60 °C. Under these conditions, **1a** was completely consumed after 12 h of reaction,

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and subsequent treatment of the reaction mixture with TsOH (20 mol%) in MeOH for 1 h led to isolation of the hydrotrifluoromethylated alcohol **3a** in 92% yield (Scheme 2A).^[11]

As shown in Scheme 2B, the catalytic process is initiated by a single-electron reduction of Togni's reagent **2** by the Cu(I) species. This allows for the generation of a CF₃-radical along with a higher-valent Cu(II) species and a 2-iodobenzoate ion. The CF₃-radical then undergoes an *anti*-Markovnikov addition onto the alkene moiety of **1a** to produce a secondary carbon centered radical **VII**. A subsequent 1,5-H radical shift leads to the formation of an α -oxy benzyl radical **VIII**,^[12,13] which is then oxidized by the Cu(II) species, thus producing the oxonium carbocation **IX** while maintaining the redox catalytic turnover with regeneration of the active Cu(I) species. Trapping of oxonium **IX** with MeOH produces acetal **X**,^[14] which is finally degraded in the presence of TsOH in MeOH to provide **3a**.

A. Optimized reaction conditions: hydrotrifluoromethylation of **1a**

B. Proposed catalytic cycle

Scheme 2. Cu-catalyzed hydrotrifluoromethylation of **1a** with Togni's reagent **2**.

With optimized reaction conditions in hands, we next investigated the scope and limitation of this *anti*-Markovnikov hydrotrifluoromethylation. As shown in Scheme 3, the transformation could be applied to a variety of homoallylic alcohols **1b-k** with good efficiency in general. Various functional groups such as silyl ether (**3c**), cyclopropyl (**3d**), phosphonate (**3e**), and thienyl (**3g**) moieties were tolerated. A quaternary carbon center could be introduced at position α to the alcohol with high efficiency (**3h**). In addition to secondary alcohols **3b-h**, tertiary alcohols **3i** and **3j** could be afforded in good yields, while the yield of **3k**, derived from camphor, was moderate. Moreover,

the present method was found applicable to the synthesis of primary alcohol such as **3l**. It could also be employed for the hydrotrifluoromethylation of *N*-benzylamine derivatives **1m** and **1n** to deliver amines **3m** and **3n** in 59% and 49% yields, respectively.

Scheme 3. Substrate scope for the Cu-catalyzed hydrotrifluoromethylation. [a] The reactions were conducted using 0.2–0.3 mmol of **1** with 10 mol% of CuI in 1,4-dioxane-MeOH (0.3 M) for 12–24 h followed by treatment with TsOH (20 mol%) in MeOH for solvolysis and isolated yields were noted above unless otherwise stated. [b] ¹H NMR yield based on the internal standard (**3d** was volatile and **3m** was not very stable). [c] 20 mol% of CuI was used. TBDPS = *tert*-butyldiphenylsilyl; PhthN = phthalimido; PMP = *para*-methoxyphenyl.

The method was not limited to the introduction of a CF₃ group onto alkenes. As proof of the synthetic potential of our approach, hydroazidation of alkenes **1** with hypervalent iodine reagent **4** as a source of the azido radical was developed by slightly modifying the reaction conditions (Scheme 4).^[15] Treatment of alkene **1a** with **4** (1.5 equiv) in the presence of CuBr₂^[16] (20 mol%) as the catalyst in 1,2-dichloroethane at 60 °C delivered, after the acidic work-up, the hydroazidation product **5a** in 57% isolated yield. Notably, this product is a precursor of 1,5-diamino-2-pentanol in which the two amino functionalities are orthogonally protected. The hydroazidation protocol could be applied to other homoallylic alcohol benzyl ethers **1**, which were converted into the corresponding azidoalcohols **5** in moderate to good yields. Given the versatile

reactivity of organic azides,^[17] the products obtained using this protocol would be of high value in various applications.

Scheme 4. Cu-catalyzed hydroazidation. [a] The reactions were conducted using 0.2 mmol of **1** with 20 mol% of CuBr₂ in ClCH₂CH₂Cl (0.3 M) for 10–20 h followed by treatment with TsOH (20 mol%) in MeOH for solvolysis and isolated yields were noted above unless otherwise stated. [b] ¹H NMR yield based on the internal standard.

We also sought for the possibility to apply the current protocol to 1,1-disubstituted alkenes. As shown in Scheme 5A, the Cu(I)-catalyzed hydrotrifluoromethylation of methyl substituted alkene **1o** delivered the desired adduct **3o** in 72% yield but with poor diastereoselectivity (60:40). The replacement of the methyl group by a bromine (for **1p**), a chlorine (for **1q**) or a fluorine (for **1r**) atom did not alter the reactivity, affording **3p**, **3q**, and **3r** in 73%, 65%, and 55% (65% brsm) yields, respectively, and more fascinatingly, we observed an enhancement of the diastereoselectivity (84:16 for **3p**, 85:15 for **3q**, and 85:15 for **3r**). A similar level of selectivity was obtained in the hydroazidation of bromoalkene **1p**, that afforded **5p** in decent 47% yield with a good diastereoisomeric ratio (80:20). The origin of the diastereoselectivity likely stems from the transition states in the 1,5-H shift process.^[18] In the possible chair-like transition states **XI** and **XII** (Scheme 5B), both the phenyl group of the benzyl moiety and the phthalimidomethyl group would preferentially adopt a pseudo-equatorial position. Considering that a trifluoroethyl group or an azidomethyl group would be more sterically demanding than a halogen atom,^[19] the reaction would more favourably proceed via transition state **XII**, in which the halogen atom stands in a pseudo-axial position. As a result, the major isomer from **1p-r** would be the one having the resulting hydroxyl group and the halogen atom in a relative 1,3-*anti*-configuration (see Scheme 5A). We took advantage of the high density of functional groups present in **3p** and **5p** to derivatize them. They could be readily converted into the valuable pyrrolidines **6p** and **7p** through a sequence of hydroxyl group protection as a TBS ether, removal of the phthalimide moiety with hydrazine followed by spontaneous intramolecular substitution of the secondary bromide by the resulting primary amine (Scheme 5C).

A. diastereoselective hydrofunctionalization of 1o-1q

B. Origin of the diastereoselectivity

C. Derivatization of 3p and 5p to pyrrolidines 6p and 7p

Scheme 5. Hydrofunctionalization of 1,1-disubstituted alkenes. [a] Diastereomeric ratio was determined by ¹H NMR spectroscopy. [b] Diastereomeric ratio was determined by ¹⁹F NMR spectroscopy. [c] 65% yield based on recovery of **1r** (brsm). [d] i) TBSOTf, 2,6-lutidine, CH₂Cl₂, 0 °C, 95% yield; ii) aq. NH₂NH₂, EtOH, 60 °C, 97% yield of **6p** as an inseparable mixture of two diastereomers. [e] i) TBSCl, imidazole, DMF, 23 °C, 68% yield of the single diastereomer derived from the major isomer of **5p**; ii) aq. NH₂NH₂, EtOH, 60 °C, 96% yield of **7p** as the single diastereomer.

We also envisaged using the present concept to perform the hydrotrifluoromethylation of a simple alkenol **XIII** (Scheme 6). In this case, a suitably located alcohol moiety in **XIII** would play the role of a redox-active hydrogen donor. We considered that the 1,n-H shift step (**XIV**→**XV**) would proceed favourably from the α-H of the hydroxyl group to the reactive C-centered radical, while the resulting hydroxy-substituted C-centered radical intermediate **XV** could be subsequently oxidized into ketone **XVI**. Overall, this transformation would be a combination of *anti*-Markovnikov hydrotrifluoromethylation and alcohol oxidation.

Scheme 6. Cu-catalyzed hydrotrifluoromethylation of alkenes using alcohols as redox active hydrogen donor groups

Gratifyingly, we found that the treatment of 1-aryl-5-hexenols **8a-k** with **2** (2 equiv) in the presence of Cu(OAc)₂ (10 mol%)^[16] and 2,2'-bipyridine (10 mol%) in 1,4-dioxane at 60 °C resulted in the formation of the hydrotrifluoromethylated ketones **9a-k** in generally good yields (Scheme 7). Notably, the cyclopropyl moiety in **9k** could be kept intact during the redox radical process probably due to a higher oxidation rate of the α -hydroxy radical **XV** to ketone **9k** than the radical ring-opening. The method could be extended to the synthesis of benzene-tethered carbonyl compounds **9l** and **9m** as well as aliphatic ketones such as **9n**. Interestingly, the reaction of 1-phenyl-6-heptenol **8o**, which has a linker with an additional carbon unit (as compared to **8a-n**), proceeded smoothly via a probable 1,6-hydrogen shift to furnish **9o** in 66% yield. The method also allowed for the use of substituted alkenes. The reaction of 1,1-disubstituted alkene **8p** was shown to be highly efficient affording the desired hydrotrifluoromethylated ketone **9p** in 89% yield. The reaction of **8q** possessing a styryl moiety (as an example of internal alkene substrate) provided the γ -trifluoromethyl ketone **9q** in 57% yield via benzylic radical **XVII** intermediately formed by a regioselective addition of the CF₃ radical onto the styryl moiety.

In summary, this work demonstrated that a simple benzyl protecting group can be employed as a traceless redox-active hydrogen radical donor for the *anti*-Markovnikov alkene hydrofunctionalization of homoallylic alcohols and their derivatives. The hydrotrifluoromethylation and azidation developed herein are easy to set up, relatively efficient and exhibit a high functional group tolerance. This concept has been successfully extended to the hydrotrifluoromethylation of 5-hexenol and 6-heptenol derivatives. Application of this general concept to develop other types of catalytic redox molecular transformations is the subject of our ongoing investigations.

Scheme 7. Cu-catalyzed sequence of hydrotrifluoromethylation/oxidation of alkenols. [a] The reactions were conducted using 0.5 mmol of **8** in 1,4-dioxane (0.1 M) at 60 °C for 2–61 h and isolated yields were noted above. [b] The reaction was run at 80 °C. [c] brsm = based on recovery of the starting material.

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Keywords: *anti*-Markovnikov alkene functionalization • trifluoromethylation • azidation • radicals • copper catalysis

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