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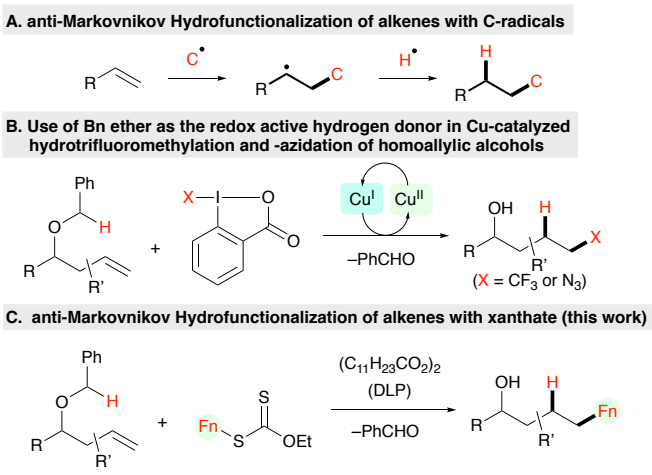
A new protocol for *anti*-Markovnikov hydrofunctionalization of alkenyl alcohol O-Bn ethers was developed using xanthates as functionalizing agents in the presence of lauroyl peroxide as a radical initiator and a stoichiometric oxidant. The benzyl group serves as a traceless hydrogen donor in the remote radical hydrogen atom transfer event during the process.

Chemical processes based on *anti*-Markovnikov hydrofunctionalization of alkenes offer an attractive opportunity for the production of high value fine chemicals. Despite the synthetic potential of this approach and the numerous developments made in this area, there still remain challenges to functionalize non-activated alkenes in a regioselective fashion.[1] One of the methods to realize this goal is to use carbon-centered radicals (Scheme 1A). From a mechanistic point of view, such a process involves the initial addition of a C-centered radical onto the less substituted side of a non-activated alkene, thus generating a new C-C bond in an *anti*-Markovnikov manner. A subsequent delivery of a H atom onto the resulting highly reactive carbon radical is then required to complete the alkene hydrofunctionalization. In this context, the Giese reaction using alkyl halides and their derivatives as a C-radical source, and tin hydrides (typically, Bu_3SnH) as a H atom donor represents one of the most powerful hydrofunctionalization methods.[2] Processes using tris(trimethylsilyl)silane [$(TMS)_3SiH$][3] and borohydrides[4] as a H-atom donor, and those involving photoredox catalysis[5] have proven promising. However, an adequate polarity match is generally required between the C-radical and the alkene in order to favor the formation of the radical adduct and prevent the premature reduction of the initially formed C-radical by the external H-atom donor. As a consequence, most of these intermolecular processes have been conducted with a combination of nucleophilic C-radicals and electron-deficient alkenes. To overcome this defect associated with the intermolecular H-atom delivery step, we recently reported use of a benzyl ether for the precise intramolecular hydrogen atom transfer (HAT) *via* 1,5-radical shift in Cu-catalyzed hydrotrifluoromethylation and hydroazidation of homoallylic alcohols.[6-9] During the redox catalytic process, the benzyl group is removed as a benzaldehyde, thus serving as a traceless protecting group of the corresponding alcohols (Scheme 1B). Despite the general efficiency and selectivity of the method, the employment of hypervalent iodine reagents as C-radical precursors inherently restricted the functional groups that could be introduced on the alkene. To circumvent this limitation, we became interested in the use of xanthates as a carbon radical source in combination with dilauroyl peroxide (DLP) as a radical initiator and a stoichiometric oxidant (Scheme 1C). The design, optimization, and substrate scope of these processes are described herein.



Scheme 1. Hydrofunctionalization of alkenes with radicals

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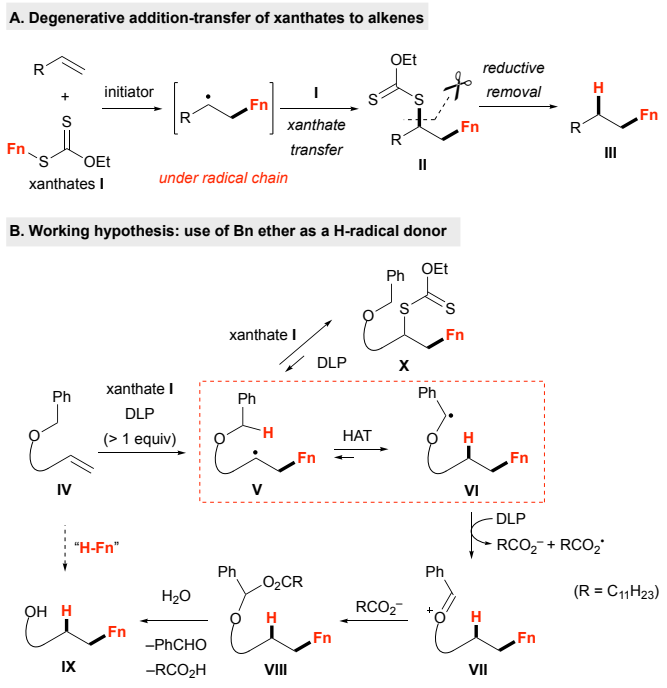
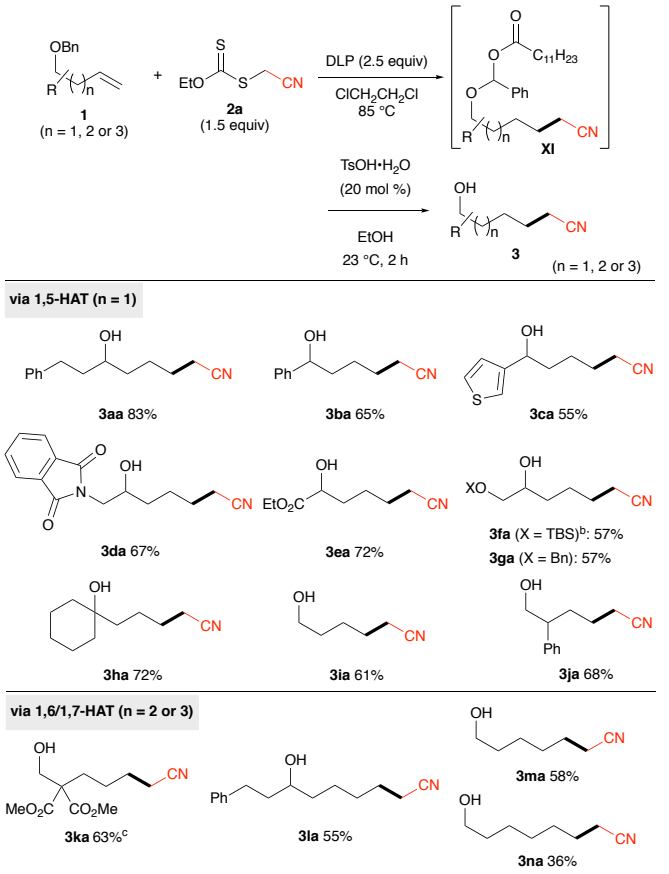
The degenerative addition-transfer of xanthates to alkenes, which has been extensively developed by the group of Zard,[10] represents an extremely powerful synthetic tool for the creation of new C-C bond. This widely applicable protocol enables installation of a variety of functional groups onto alkenes with concomitant transfer of the xanthate moiety following a radical chain mechanism (Scheme 2A). To ultimately obtain a hydrofunctionalized product **III** starting from xanthate **I**, an additional step of reductive removal of the xanthate moiety from the initially formed adduct **II** is required. This can be achieved using an external hydrogen atom donor such as Bu_3SnH or $(TMS)_3SiH$ in combination with AIBN,[11,12] hypophosphorous acid with AIBN,[13] the triethylborane-water system,[14] or more simply isopropanol or cyclohexane in the presence of DLP.[15] We surmised that the presence of a benzyloxy group in an appropriate position of the starting alkene **IV** would facilitate a subsequent HAT to the carbon-centred radical intermediate **V** (Scheme 2B). The resulting α-oxy benzyl radical **VI** could then be further oxidized by DLP to oxocarbenium ion **VII**, that is converted into ketal **VIII**.[16] A subsequent hydrolysis of **VIII** would liberate the hydrofunctionalized product **IX** along with benzaldehyde and lauric acid. Thus, *anti*-Markovnikov hydrofunctionalization of alkenes (**IV**→**IX**) could be accomplished in one-pot fashion. It should be noted that the formation of xanthate adduct **X** would not affect the process as radical **V** should be regenerated in the presence of DLP.



Scheme 2. Hydrofunctionalization of alkenes with xanthates

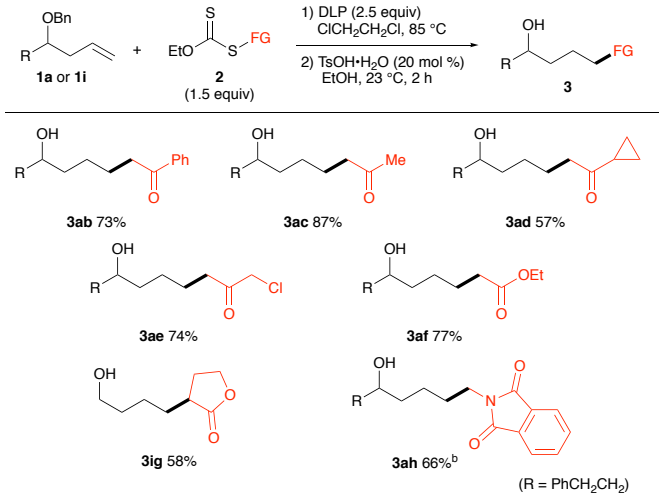
With this working hypothesis, we initiated our studies with the reactions of homoallylic alcohol O-benzyl ether **1a** with cyanomethyl xanthate **2a**. Optimization of the reaction conditions[17,18] revealed that the desired hydrocyanomethylation-debenzylation sequence is enabled by treatment of a mixture of **1a** and **2a** with 2.5 equiv of DLP in 1,2-dichloroethane at 85 °C followed by subsequent acidic solvolysis of the resulting ketal intermediate **XI** with TsOH (20 mol%) in EtOH. This protocol afforded **3aa** in 83% isolated yield (Scheme 3). We then surveyed the substrate scope of alkenes **1** using cyanomethyl xanthate **2a**. As shown in Scheme 3, various secondary alkenyl *O*-benzyl ethers **1b**-**1g** could be transformed into the corresponding hydrocyanomethylated alcohols **3ba**-**3ga** in good to moderate yields. A variety of functional groups such as a thienyl (for **3ca**), a phthalimidoyl (for **3da**), an ethoxy carbonyl (for **3ea**) as well as cleavable ethers (for **3fa** and **3ga**) were tolerated. Notably, the reaction of alkene **1g**, possessing two remote benzyl ether moieties, underwent a selective 1,5-HAT (versus a potentially competing 1,6-HAT) to provide the monobenzyl ether **3ga** in 57% yield. Tertiary (for **3ha**) and primary (for **3ia-3ja**) alcohols could be constructed in good yields. The method also allowed for 1,6- and 1,7-HAT (for **3ka**-**3na**) with moderate efficiency.



Scheme 3. Scope of alkenes **1** with cyanomethyl xanthate **2a**. [a] The reaction were conducted using 0.5 mmol of alkenes **1** and xanthate **2a** (1.5 equiv) with DLP (2.5 equiv) in $ClCH_2CH_2Cl$ (0.5 M) at 85 °C for 2-4 h, followed by solvolysis with TsOH (20 mol%) in EtOH at 23 °C for 2 h. Unless otherwise stated, isolated yields of the products are given based on alkenes. [b] The solvolysis was conducted using AcOH (1.7 equiv) in H_2O at 23 °C. [c] The solvolysis was conducted using TsOH (20 mol%) in MeOH at 23 °C.

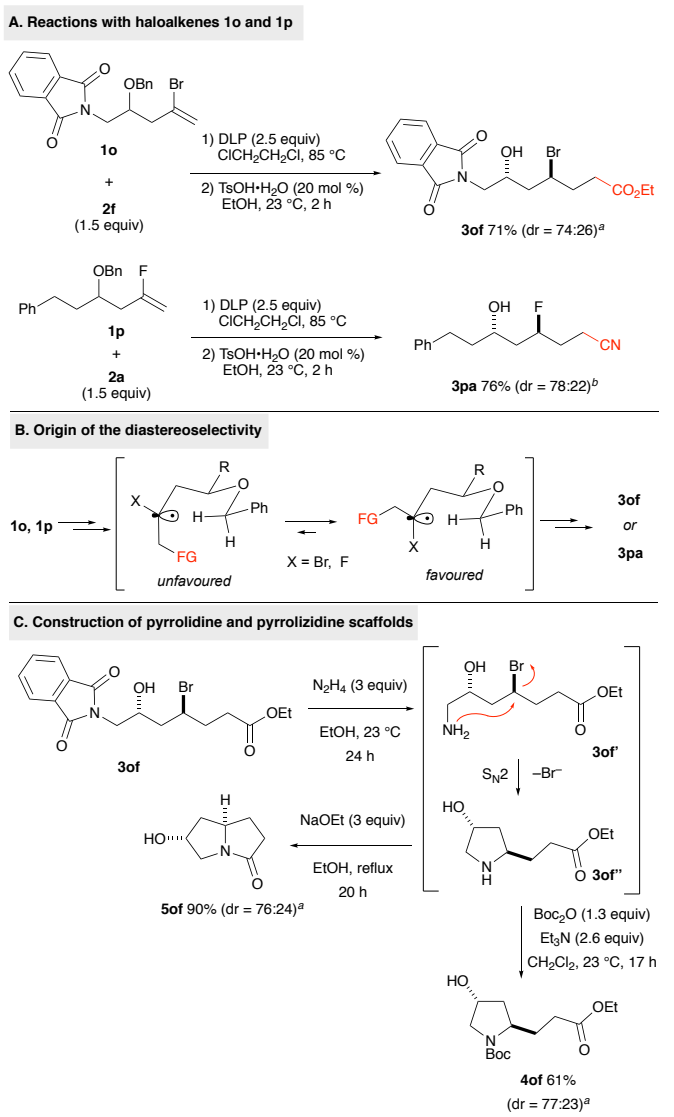
We next investigated compatibility of xanthates using alkene **1a** or **1i** under the optimal reaction conditions. The reactions of ketonyl xanthates having a phenyl (for **2b**), a methyl (for **2c**), a cyclopropyl (for **2d**) or a chloromethyl (for

2e) moiety led to a facile 1,5-HAT/debenzylation sequence, providing the corresponding hydrofunctionalized alcohols (**3ab**-**3ae**) in good to moderate yields. The method also allowed for the installation of an alkoxycarbonyl function as attested by the formation of ester **3af** and lactone **3ig**. The reaction with phthalimidomethyl xanthate **2h**[19] took place smoothly, affording the *N*-protected 1,5-amino alcohol **3ah** in good yield.



Scheme 4 Scope of xanthates **2** with alkene **1a** or **1i**. [a] The reaction were conducted using 0.5 mmol of alkenes **1a** or **1i** and xanthate **2** (1.5 equiv) with DLP (2.5 equiv) in $ClCH_2CH_2Cl$ (0.5 M) under reflux for 2-5 h, followed by solvolysis with TsOH (20 mol%) in EtOH at 23 °C. Unless otherwise stated, isolated yields of the products are given based on alkenes. [b] 3.5 equiv of DLP was used.

The present protocol was also found applicable to diastereoselective HAT in the hydrofunctionalization of either bromoalkene **1o** or fluoroalkene **1p** (Scheme 5A). The hydro-ethoxycarbonylmethylation of **1o** with xanthate **2f** delivered the desired product **3of** in 71% yield with good 1,3-*anti* diastereoselectivity (74:26). A similar behaviour was observed with fluoroalkene **1p**, which could be converted into fluoroalcohol **3pa** (76%, d.r. = 78:22). The observed 1,3-*anti* selectivity could be attributed to the involvement of a chair-like transition state in the HAT process with the more sterically demanding groups preferentially adopting a pseudo-equatorial position.[20] Among the conformers leading to the HAT, that in which the bulkier cyanoethyl or ethoxycarbonylethyl group is located at the pseudo equatorial position would be energetically more favourable (Scheme 5B). It is worth noting that the resulting hydrofunctionalized product **3of** could be further transformed into β-hydroxy *N*-H pyrrolidine **3of''** by treatment with hydrazine. This transformation involved the initial formation of primary amine **3of'** followed by intramolecular cyclization (Scheme 5C). Subsequent protection of the amine moiety in **3of''** afforded the N-Boc pyrrolidine derivative **4of** in 61% yield over two steps.[21] Alternatively, treatment of **3of''** with NaOEt promoted its lactamization into pyrrolizidin-3-one **5of** (90%).[22]



Scheme 5. Diastereoselective HAT onto haloalkenes. [a] The diastereomeric ratio was determined by ^1H NMR analysis. [b] The diastereomeric ratio was determined by ^{19}F NMR analysis.

This work demonstrates the use of a benzyl ether as a traceless redox active hydrogen donor in *anti*-Markovnikov hydrofunctionalization of alkenes with xanthates. This protocol, in which DLP is used both as a radical initiator and an oxidant, allowed for the facile installation of various functional groups onto readily available alkenyl alcohols.

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