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Direct Catalytic Anti-Markovnikov Addition of Carboxylic Acids to Alkenes

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Abstract

A direct catalytic anti-Markovnikov addition of carboxylic acids to alkenes is reported. The catalyst system is comprised of the Fukuzumi acridinium photooxidant (**1**) and a substoichiometric quantity of a hydrogen atom donor. Oxidizable olefins such as styrenes, trisubstituted aliphatic alkenes, and enamides can be employed along with a variety of carboxylic acids to afford the anti-Markovnikov addition adducts exclusively. A deuterium-labeling experiment lends insight to the potential mechanism.

Carboxylic esters are among the most important and prevalent functional groups in small organic molecules and polymers. Classical methods for the introduction of the ester group rely on the reaction of an alcohol and a carboxylic acid or activated derivative. Alternatively, photolytic,[1] Brønsted acid,[2] Au(I),[3] Ag(I),[4] Fe(III),[5] or Ru(II)[6]-catalyzed additions of carboxylic acids to alkene feedstocks provide a direct and simple route to the regioselective formation of esters with high Markovnikov selectivity (eq 1). As a compliment to this reactivity, an anti-Markovnikov-selective variant would offer an important synthetic tool. Despite the potential utility of such a transformation, direct methods for anti-Markovnikov hydroacetoxylations of olefins by carboxylic acids are rare.[7–9] Herein, we describe an anti-Markovnikov addition of carboxylic acids to alkenes catalyzed by the Fukuzumi acridinium salt (**1**)[10] and a hydrogen atom donor.

In seminal work, Arnold[8] and Gassman[9] have each reported single examples of anti-Markovnikov additions of acetic acid to alkenes employing stoichiometric quantities of single electron photooxidants. Despite the use of acetic acid as solvent, single regioisomers of the hydroacetoxylation adducts were obtained, albeit in modest yields. Our laboratory has recently disclosed anti-Markovnikov alkene hydroetherification[11] and hydroamination[12] reactions catalyzed by **1** and either 2-phenylmalononitrile (**2**)[13] or thiophenol[14] as hydrogen atom donors. We sought to take advantage of this generic catalyst platform by applying it to anti-Markovnikov alkene hydroacetoxylation.

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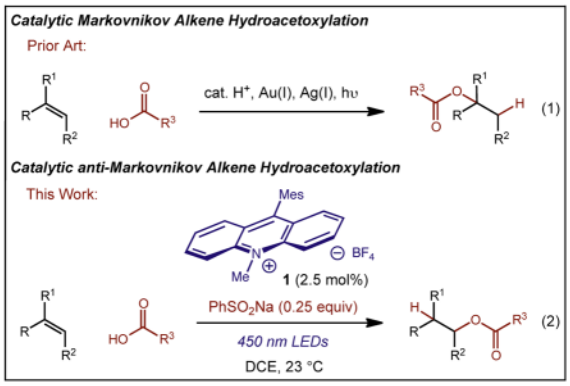
ASSOCIATED CONTENT

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



We began our investigation by examining the reaction of acetic acid with anethole using **1** as the single electron photooxidant. A number of potential hydrogen atom donors were evaluated in the reaction (Table 1, Entries 1, 3–6). In general, C-H hydrogen atom donors **2–5** afforded the desired hydroacetoxylated adduct with complete anti-Markovnikov regioselectivity, however in only modest yields with the remainder of the mass balance attributed to unreacted alkene. A marked increase in reactivity and yield was obtained when employing benzenesulfinic acid (**5**) as a hydrogen atom donor (Entry 6), most likely due to the kinetic advantage gained by the available heteroatom hydrogen bond, given the relative nucleophilicity of the putative benzylic radical intermediate.[15] Given the need for a base to promote the reaction, we were pleased to see that commercially available sodium benzene sulfinate was as effective as the combination of benzene sulfinic acid and sodium acetate. In the absence of hydrogen atom donor (Entry 2), only trace quantities (6%) of the desired acetate were obtained. An increase in catalyst loading had a detrimental effect on the reaction conversion (Entries 8–9) and more concentrated reaction conditions led to an increase in overall reaction efficiency (Entries 10–11).

After determining the optimal reaction conditions, we turned our attention to the reaction scope (Chart 1). A number of β-methyl styrenes bearing a variety of substituents were investigated. Good yields were achieved with both *para* and *ortho* methoxy substitution (71% & 72% yields, respectively, Entries 1 & 2), while slightly diminished yields were observed with the *m*-methoxy isomer (50 % yield, Entry 3). This effect could be due, in part, to less charge density being located on the alkene carbon atoms. Good yields were also observed with the less electron rich *p*-methyl-β-methylstyrene (Entry 4, 52% yield) while the even less electron rich β-methylstyrene resulted in markedly lower yields (Entry 5, 29% yield). To our surprise, *p*-chloro-β-methylstyrene gave elevated yields relative to β-methylstyrene. The reaction also tolerated a phthalimide protected amine and furnished the corresponding ester in good yield. (Entry 7, 75% yield).

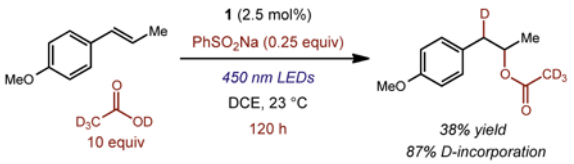
We next turned to investigate the scope of carboxylic acids that could be employed in this reaction, using anethole as a model substrate (Entries 8–12). Unfortunately, the standard conditions outlined above resulted in mixtures of ester products due to the necessary inclusion of acetic anhydride for efficient reactivity. The use of other hydrogen-atom donors, such as 9-cyanofluorene, required prolonged reaction times to reach full conversion and so was deemed unsuitable. Drawing from our recently disclosed anti-Markovnikov hydroamination chemistry, thiophenol was found to be an especially efficient hydrogen-atom donor for this transformation requiring slightly lower loadings than sodium benzene sulfinate (20 mol% versus 25 mol%, respectively), and resulting in high yields of the ester products. Reaction times generally increased with larger carboxylic acids and only modest levels of the pivalic acid adduct were obtained (30% yield, Entry 11). Benzoic acid could be

effectively employed, giving the corresponding benzoyl ester in 94% isolated yield after 30 h (Entry 12).

To further probe the effect of alkene structure on the title transformation, we examined several different classes of alkenes (Entries 13–17). Trisubstituted styrenyl alkenes such as 1-phenylcyclohexene afforded the anticipated anti-Markovnikov adducts in good yield albeit with poor diastereocontrol (67% yield; 1.3:1 d.r., Entry 13). Attempts to increase the diastereoselectivity by examining additional hydrogen atom donors, solvents and bases, were unfortunately fruitless. Nevertheless, we were pleased to find that trisubstituted aliphatic alkenes such as 1-methylcyclopentene and even 2-methyl-2-butene (Entries 14 & 15) were reactive toward the esterification reaction with acetic acid, giving the acetate adducts in respectable levels of chemical efficiency (61% & 74% yields, respectively). This result is further underscored by the fact that these alkenes have oxidation potentials that are quite high (≥+1.4 V vs. SCE)[16,17] and therefore difficult to oxidize by most other chemical oxidants.

Lastly, we questioned whether acid-labile alkenes, such as enamides and enol ethers could be employed in this protocol. We were pleasantly surprised to find that CBz-protected tetrahydropyridines gave the anti-Markovnikov regioisomer exclusively without perturbing the protecting group (82% yield, Entry 16). Only when we examined the more acid-sensitive dihydropyran did we first observe the Markovnikov adduct, in a 2:1 ratio with the desired regioisomer (63% yield). This observation highlights the mildness of the reaction conditions and indicates that the title reaction is competitive with acid-promoted acetal formation.

To lend further insight into the mechanism of the transformation, we examined the reaction of anethole in the presence of d_4-acetic acid (eq 3). The acetate product was obtained with 87% deuterium incorporation at the benzylic position in 38% yield (93% conversion). Since the pK_a values for acetic acid (4.8) and benzene sulfinic acid (2.1) are relatively close and that a 40-fold excess of acetic acid is used relative to the sodium benzene sulfinate, our working hypothesis is that small quantities of d_1-benzene sulfinic acid are generated during the course of the reaction, which acts as the D-atom source. It is also worth noting that the reaction times were significantly longer than the experiments run with protio acetic acid (120 h vs. 24 h) and the yield was far lower due to the presence of significant quantities of unidentifiable byproducts (cf. 71% yield with HO_2CCH_3, Chart 1, Entry 1). We believe this alludes to the possibility of the hydrogen atom transfer step as the rate-limiting process in this mechanism.



(3)

Piecing together these details, we propose the following mechanism (Scheme 1). Oxidation of the alkene by the charge transfer excited state of the Fukuzumi catalyst (**1***) results in the formation of the alkene cation radical (**6**). Addition of the carboxylate nucleophile to the less substituted position of the cation radical provides key intermediate **7**. For the reactions using sodium benzenesulfinate, we propose that a rapid acid-base equilibrium with the excess carboxylic acid generates small quantities of benzenesulfinic acid (**5**), the active hydrogen

atom donor. Based on the results in eq 3, we presume that the hydrogen atom transfer step is rate limiting When d_4-acetic acid is employed, the d_1-benzenesulfinic acid results in a significant kinetic isotope effect that causes buildup of **7** and side reactions to result that are not observed with protio acetic acid. The fate of the resultant benzenesulfinyl radical (**8**) is less clear, however, based on our prior mechanistic hypothesis, we believe that this species acts as an oxidant for acridine radical **9**, to regenerate the catalyst (**1**) and benzenesulfinate. In the presence of thiophenol, a similar mechanism is presumed operational.

In summary, we have described a direct organocatalytic protocol for the anti-Markovnikov addition of carboxylic acids to alkenes. The use of sodium benzene sulfinate or thiophenol as the hydrogen atom donors was necessary for productive reactivity. Further mechanistic experiments to full understand the role of the sulfinate are ongoing.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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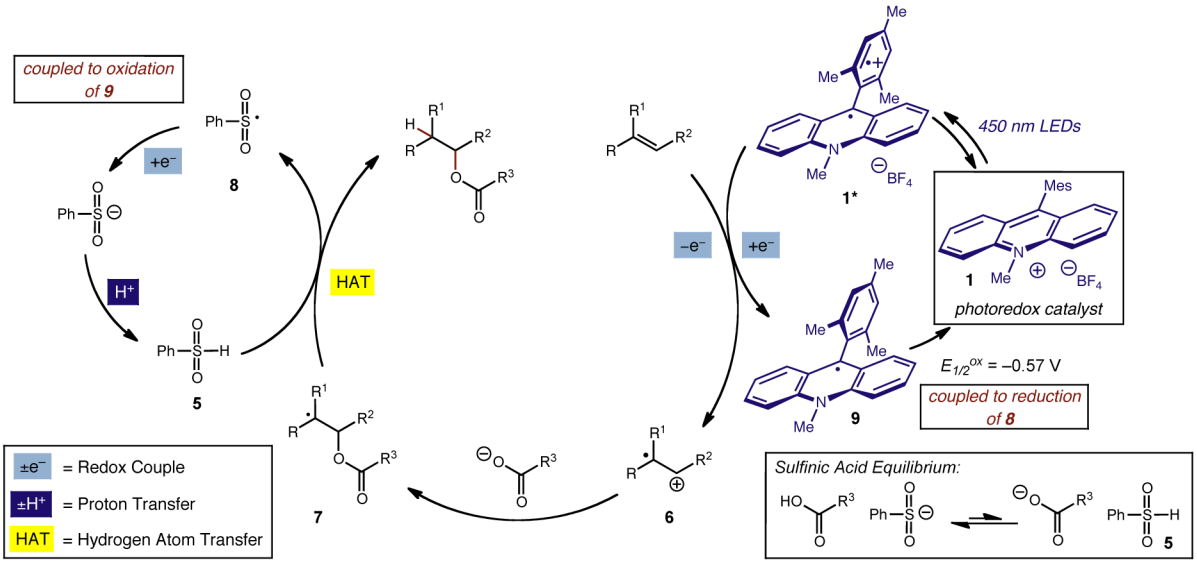


Scheme 1.
Proposed Mechanism for the Anti-Markovnikov Alkene Hydroacetoxylation Reaction

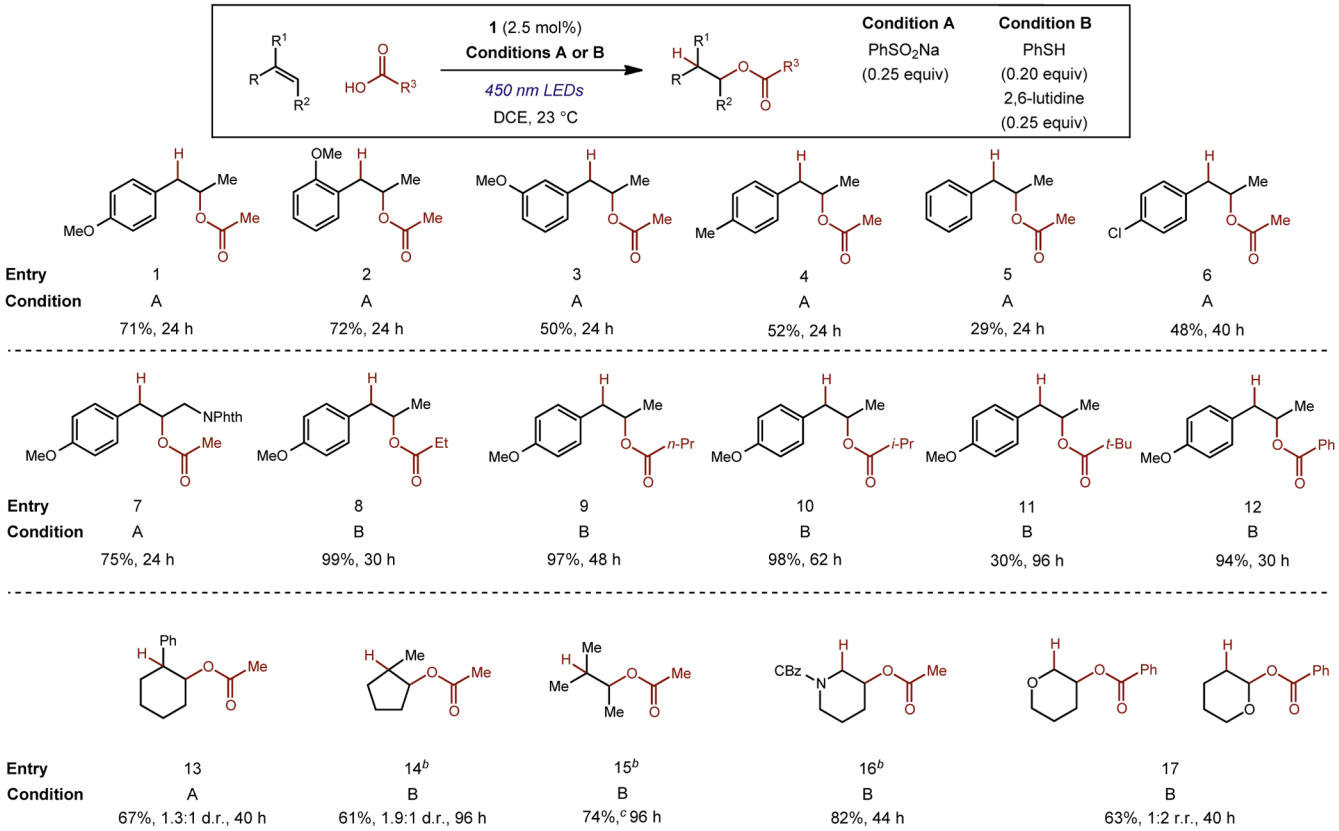
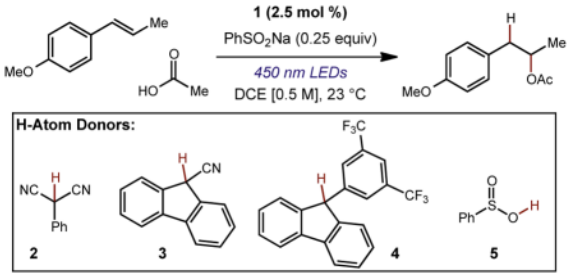


Chart 1. Scope of the anti-Markovnikov Addition of Carboxylic Acids to Alkenes[a]

[a]Isolated yields are averages of two trials. All products observed are single regioisomers unless otherwise noted. [b]Reactions run with 0.25 equiv. of NaOAc instead of 2,6-lutidine. [c]^{1}H NMR yield vs. internal standard.

Table 1

Optimization Studies[a]



Entry	Conditions	Conversion[b]	Yield[b]
1	Standard	100%	70%
2[c]	No H-Atom Donor	22%	6%
3[c]	with 0.25 equiv of **2** instead of $PhSO_2Na$	34%	30%
4[c]	with 0.25 equiv of **3** instead of $PhSO_2Na$	44%	26%
5[c]	with 0.25 equiv of **4** instead of $PhSO_2Na$	24%	10%
6[c]	with 0.25 equiv of **5** instead of $PhSO_2Na$	100%	70%
7[d]	with 0.25 equiv of **5** instead of $PhSO_2Na$	40%	0%
8	5 mol% **1**	100%	70%
9	10 mol% **1**	100%	64%
10	DCE [0.25 M]	100%	58%
11	DCE [0.1 M]	100%	54%

[a]Containing 5 %v/v acetic anhydride.

[b]Determined by ^1H NMR analysis.

[c]With 0.25 equiv. sodium acetate.

[d]Without added base.