Catalytic Alkene Difunctionalization via Imidate Radicals

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Supporting Information Placeholder

ABSTRACT: The first catalytic strategy to harness imidate radicals has been developed. This approach enables alkene difunctionalization of allyl alcohols by photocatalytic reduction of their oxime imidates. The ensuing imidate radicals undergo consecutive intra- and inter-molecular reactions to afford either (i) hydroamination, (ii) aminoalkylation, or (iii) aminoarylation – via three distinct radical mechanisms. The broad scope and utility of this catalytic method for imidate radical reactivity is presented, along with comparisons to other N-centered radicals and complementary, closed-shell imidate pathways.

In pursuit of a new hydroamination reaction, Overman serendipitously discovered a synthetically valuable reaction wherein allyl imidates are rapidly converted to allyl amines by sigmatropic rearrangement.[1-3] Nonetheless, the original goal of converting allyl imidates to 1,2-amino alcohols via hydroamination remains unsolved – likely because the Brønsted, Lewis, and π-acids that could activate alkenes toward amination, efficiently promote rearrangement instead. To solve this ongoing challenge, we proposed an N-centered radical mechanism[4] may bypass the two-electron pathway and afford the long-sought hydroamination[5] to access valuable β-amino alcohols (Figure 1a). Moreover, we anticipated imidate radicals may enable several new classes of reactivity for the synthesis of functionalized amino alcohols.

In developing a catalytic strategy to harness the reactivity of imidate radicals,[6,7] we proposed allyl imidate **A** may be selectively reduced by a single-electron via photocatalysis[8] (Figure 1b). We envisioned that such oxime imidates are readily accessed by the combination of alcohols and imidoyl chlorides in a modular and tunable manner (to access radical precursors with variable N-OR bond strengths). In analogy, the incorporation of weak N-OR bonds within analogs of ketones and amides has afforded other N-centered radicals (e.g. iminyl, amidyl).[9-12] We thus proposed this tunability may enable us to discover a catalytic method to access imidate radicals. In our proposed mechanism, excitation of a photocatalyst (M^n to $*M^n$) precedes reductive quenching by an amine to provide a strong reductant (M^{n-1}). We postulated single-electron reduction of allyl imidate **A** to its radical anion, and subsequent mesolytic cleavage, could then afford imidate radical **B** and regenerated photocatalyst (M^n). Next, rapid, 5-exo-trig cyclization[13] of the N-centered radical would provide **C**, which contains a C• adjacent to the new C–N bond. Upon combination with a variety of intermolecular radical traps, a resulting α-substituted oxazoline **D** may be hydrolyzed under acidic conditions to afford a family of

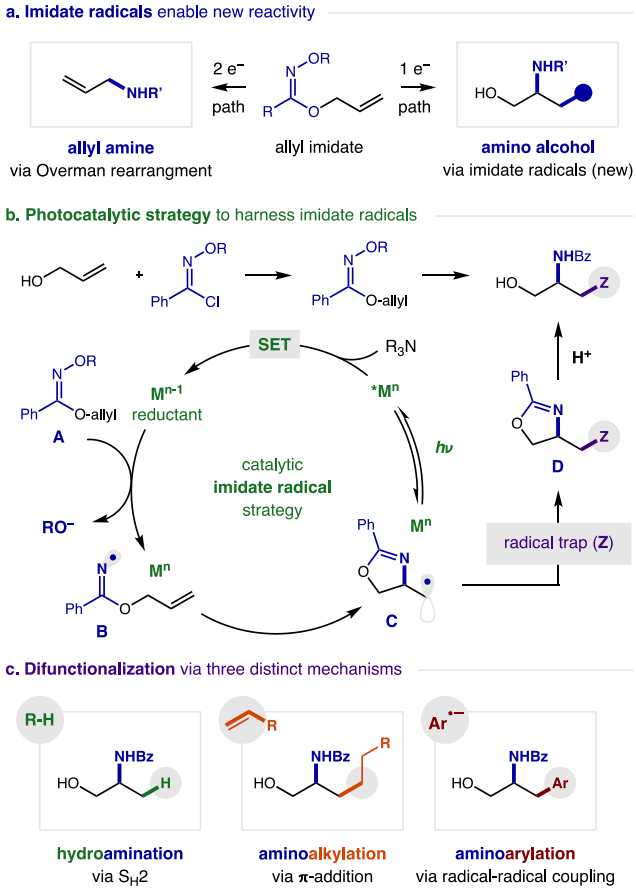
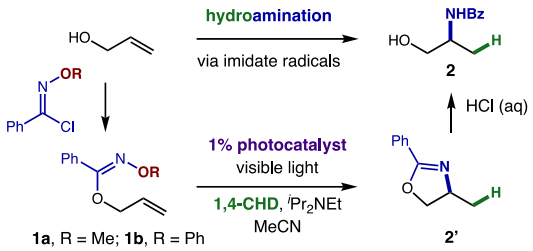


Figure 1. New reactivity modes enabled by imidate radicals.

1,2-amino alcohols. Importantly, we postulated that three distinct mechanisms could be employed to intercept the C-centered radical (Figure 1c). For instance, homolytic substitution (S_H2) of a radical trap containing a weak C–H bond[14] may provide hydroamination. Alternatively, intermolecular radical π-addition of alkenes would afford aminoalkylation.[15] Lastly, a rare, radical-radical coupling mechanism[16] could incorporate γ-arenes in a net, aminoarylation. Crucially, each of these three radical termination mechanisms affords reactivity that is complementary to classic, two-electron strategies.

With this hypothesis in mind, we combined allyl alcohol with a pair of imidoyl chlorides (Figure 2). The resulting allyl imidates

were then subjected to reductive, photoredox catalytic conditions in the presence of a reductant, $^{i}Pr_2NEt$, an H-atom donor, 1,4-



photocatalyst	E_{red}	yield (2') R = Me	yield (2') R = Ph
$Ru(bpy)_3Cl_2$ (I)	–1.3	0%	0%
$Ir(ppy)_2(dtbbpy)PF_6$ (II)	–1.5	0%	80%
$Ir(ppy)_3$ (III)	–2.2	10%	79%

Figure 2. Hydroamination of allyl alcohols via imidate radicals.

cyclohexadiene (CHD), and a blue LED light. Unsurprisingly, the N-OMe oxime **1a**, which has a large reduction potential (E_{red} > –2 V),[17,18] affords minimal hydroamination – yielding 10% oxazoline **2'**, only with a highly reducing catalyst (**III**). Alternatively, the N-OPh oxime **1b** is more easily reduced (–1.6 V) and efficiently provides **2'** (up to 80% yield) with commercially available Ir photocatalysts (**II** or **III**). Notably, subsequent hydrolysis of oxazoline **2'** with HCl (aq) unveils the privileged 1,2-amino alcohol pharmacophore **2**. Interestingly, when imidate **1b** is combined with a Pd catalyst, rearrangement to an allyl amide is observed exclusively, instead (97% yield)[19] – demonstrating the divergent reactivity of one- and two-electron pathways for imidates.

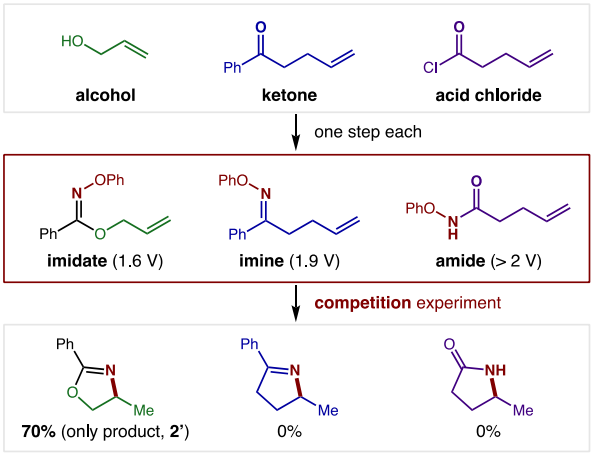


Figure 3. Comparison of N-centered radical precursors.

We were also intrigued by the complementarity of imidate radical reactivity with other N-centered radicals, such as those of imines and amides.[9,10] First, they are synthetically orthogonal, as these imidate-based radicals are accessed from alcohols, whereas iminyl and amidyl radicals are derived from ketones or acid chlorides, respectively (Figure 3). Moreover, we noted each of these N-centered radical precursors reacts differently. For example, when a simple N-OPh is incorporated, a competition between all three radical precursors exclusively results in cyclization of the imidate radical. In this case, only oxazoline **2'** is formed amongst all three possible hydroamination products – with both the imine and amide radical precursors remaining. This competitive hydroamination of the imidate (versus iminyl or amidyl) precursor is also observed with strongly reducing catalyst **III** (–2.2 V).

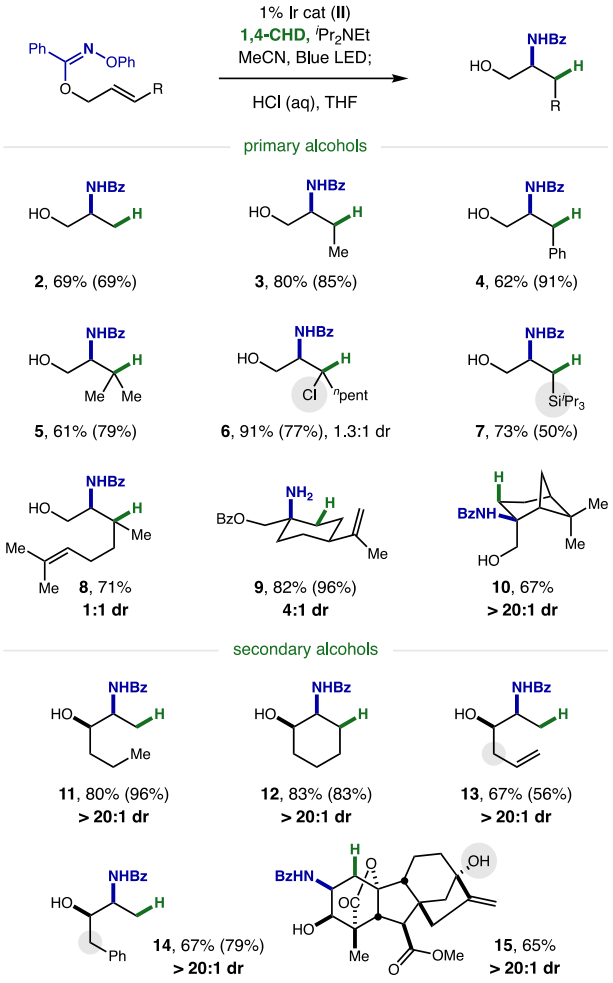


Figure 4. Hydroamination of allyl imidates. Isolated yields of hydroamination (and hydrolysis) are indicated.

Having developed the first catalytic reaction of an imidate radical, we sought to investigate the generality and utility of this hydroamination on a range of allyl imidates (Figure 4). To this end, we found that allyl alcohols with both terminal and internal olefins are hydroaminated smoothly (**2**–**4**), as well as tri-substituted olefins (**5**). These results illustrate that primary, secondary, benzylic, and tertiary radicals are all viable intermediates in the translocation of an imidate N-centered radical to a γ C-radical. If chloro- or silyl-substituted olefins are employed (grey circles), products bearing heteroatom functionality at three adjacent carbons are obtained (**6**–**7**). Several

natural products are also hydroaminated (**8**–**10**), including those containing multiple alkenes – demonstrating chemoselectivity of this protocol for allyl alcohols. In the case of secondary alcohols, exclusive *syn*-diastereoselectivity (> 20:1) is observed in all cases (**11**–**15**), likely due to geometric constraints of the five-membered oxazoline intermediate. Interestingly, and complementary to our previous studies on H-atom abstraction by imidate radicals,[7] hydroamination outcompetes β C–H abstraction – even of weak, allyl or benzyl C–H bonds (**13**–**14**, highlighted with grey circles). Additionally, 5-exo-trig (vs 6-exo-trig) cyclization is solely observed. The imidate of gibberellic ester is also efficiently converted to its β amino-alcohol (**15**) – illustrating chemoselectivity in the presence of esters, lactones, and unprotected allyl alcohols, as well as orthogonal selectivity to other radical-mediated hydroamination methods.[10d]

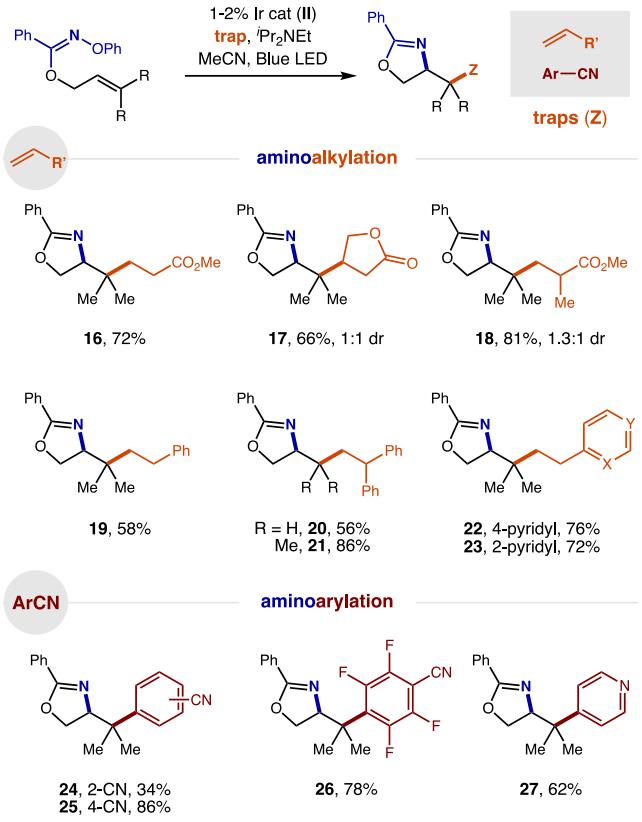


Figure 5. Aminoalkylation and aminoarylation of imidates.

The robust reactivity observed for these imidate radicals in the case of hydroamination via S_H2 led us to question if other trapping mechanisms might also be viable by this catalytic pathway. Replacing CHD with various olefins, we investigated the amino-alkylation of imidates by radical π-addition (Figure 5). Notably, both acrylates (**16**–**18**) and styrenes (**19**–**23**) function as capable partners to effect a three-component radical coupling of imidates, alkenes, and an H-atom. In these cases, both 1,1- and 1,2- di-substitution is tolerated, as well as incorporation of heteroarenes, such as 2- and 4- vinyl pyridines. Although tertiary radicals (from tri-substituted allyl alcohols) afford greater efficiency in this radical π-addition, simple allyl alcohols (that incorporate a primary radical intermediate), are also suitable for this aminoalkylation (e.g. **20** vs **21**).

In the hopes of incorporating an aryl trap within this cascade, we sought to develop an aminoarylation by a radical-radical coupling mechanism (Figure 5). Although such a mechanism is rare, especially in the absence of persistent radicals as traps,[16] we proposed cyanoarenes may selectively combine with the transient, imidate-derived tertiary radicals. This hypothesis was realized by aminoarylation with various aryl precursors, such as di-cyano-benzene (DCB; **24**–**25**), its perfluorinated analog (**26**), and 4-cyano-pyridine (**27**). In these unique couplings, we propose that a radical anion of the arene is photocatalytically generated in parallel with formation of the imidate radicals – both by reductive quenching mechanisms. The ensuing cyclohexadienyl radical and the translocated alkyl radical selectively combine with one another to afford the observed products in preference to dimerization of either radical.

Given the scarcity of such a cascade (radical cyclization terminated by radical-radical coupling), we further probed this mechanism by employing several regioisomers of di-cyanobenzene in the reaction (Figure 6). We proposed if a conjugate addition mechanism is operative, then an arene with reinforcing 1,3-di-substituted electron-withdrawing groups (e.g. CN) should be an especially efficient radical trap. However, no aminoarylation is observed with 1,3-dicyanobenzene. Instead, 1,2- or 1,4- dicyano-benzene, which are more easily reduced (by up to 200 mV),[20] afford significant product formation, likely as a result of a greater concentration of cyclohexadienyl radical anion formed by the Ir photoreductant. Moreover, *ortho*- and *para*- CN di-substitution are not as conducive to conjugate addition as the *meta* isomer, further supporting a radical-radical coupling mechanism.

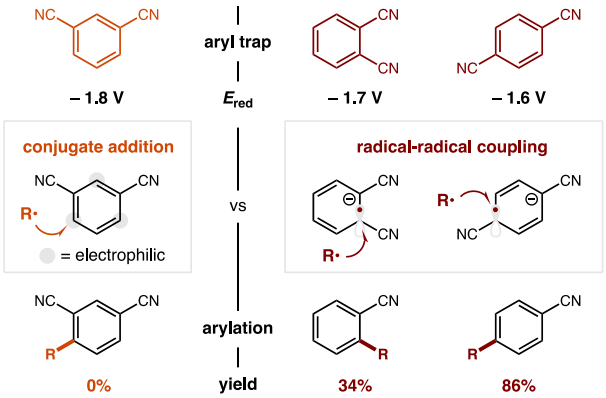


Figure 6. Mechanistic support for radical-radical coupling.

To further investigate the different radical-trapping mechanisms employed in this study, we appended a 1,6-diene on the allyl imidate to serve as a radical clock (Figure 7). In the

presence of CHD, rapid cyclization (k_{cyc} > 1•10^5 s^{-1})[13] precedes trapping, thereby interrupting the hydroamination with an intermediary radical cyclization cascade. However, in the presence of an acrylate trap, aminoalkylation is uninterrupted, indicating intermolecular radical π-addition is faster than intramolecular cyclization.

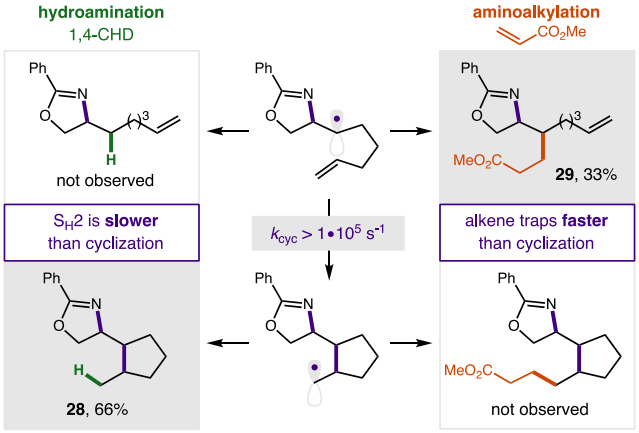


Figure 7. Radical clock experiments for each mechanism indicate the following rates: acrylate addition > cyclization > S_H2.

In summary, a series of catalytic reactions have been developed that harness imidate radicals. Oxime imidates, readily prepared from alcohols, are mildly and selectively reduced by an Ir photocatalyst in the presence of visible-light to generate imidate radicals. Subsequent cyclization and trapping with (a) an H-atom, (b) electronically diverse range of olefins (e.g. acrylates, styrenes), or (c) a cyanoarene enables access to the following transformations: hydroamination, aminoalkylation, and aminoarylation. We expect this strategy will facilitate further development of radical mechanisms that are complementary to classic, two-electron reactivity of imidates.

ASSOCIATED CONTENT

Supporting Information.
The Supporting Information is available free of charge on the ACS Publications website at DOI:
Experimental procedures and characterization for all new compounds (PDF)
^{1}H and ^{13}C NMR spectral data (PDF)

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Notes

The authors declare no competing financial interest.

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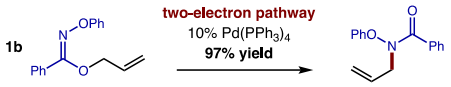

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