

C-H Functionalization : A Holy Grail Transformation

Adapted from Vicinal, Double C-H Functionalization of Alcohols via an Imidate Radical-Polar Crossover Cascade

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Introduction

In nature, form and function are often intertwined. Likewise, increased molecular complexity may increase utility – affording, for instance, more potent and selective medicines.¹ Illustrating this link between value and complexity, Figure 1a includes a series of molecules, each containing a propanol backbone with varying heteroatom substitution. As compared to 1-propanol (< \$0.1/mL), its N-containing analogs [serinol (\$40/mL), 2,3-diaminopropan-1-ol (\$1000/mL), 2-aziridinemethanol (>\$10,000/mL)] are costlier and more challenging to synthesize.² Yet, the latter, N-rich analogs are more likely to be found in medicines,³ and thus methods for synthesizing such densely-oxidized scaffolds remain valuable.¹

Typically, vicinal amino alcohols may be synthesized by alkene difunctionalization of allylic alcohols (Figure 1b).⁴ As a complementary route to access products with α,β,γ heteroatom substitution, we sought to directly employ aliphatic alcohols, without pre-installation of a reactive alkene – via double C-H oxidation.

To access products with three contiguous oxidized carbons, we proposed a radical-polar cascade strategy may address this challenge. Yet, whereas radical-polar crossover mechanisms⁵ are typically initiated by radical addition to alkenes,⁶ we were interested in pursuing a reversed strategy, entailing H• abstraction to first generate an alkene and then harness its polar reactivity. We were inspired by pioneering studies of Barluenga *et al*⁷ converting alkane solvents to iodo-acetates under highly oxidizing conditions via O-radicals, as well as an N₃I-mediated iodo-lactamization by J-Q Yu *et al*.⁸ To extend this approach to enable selective C-H difunctionalization of synthetically useful alcohols, we envisioned a radical chaperone strategy, wherein an alcohol is converted to an imidate N-radical, may allow *in situ* alkene

generation via desaturation (Figure 1c). Amino-halogenation of this transient intermediate would afford an iodo-oxazoline, which may then be readily converted to a family of α,β,γ substituted amino alcohols.

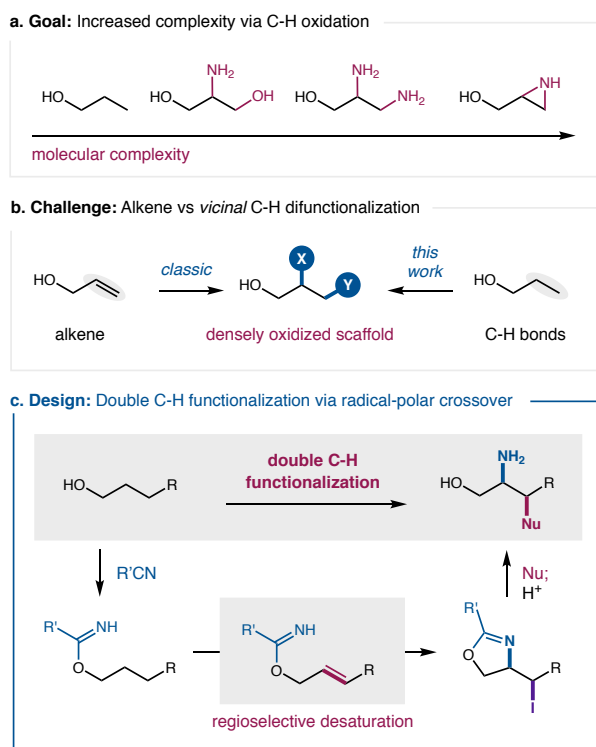


Figure 1. Radical-polar crossover enables synthetically valuable, double C-H functionalization.

Building on our recent work in the area of directed C-H functionalization by 1,5-hydrogen atom transfer (HAT),⁹⁻¹⁰ we were cognizant of the unique ability of imidate radicals to selectively convert alcohols to their β amines¹¹⁻¹² or β

halides.¹³ As shown in Figure 2, this radical chaperone strategy, entails temporary conversion of an alcohol **A** to an imidate by coupling with a nitrile.

Subjecting this imidate radical precursor to AcOI (prepared *in situ* from NaI and $\text{PhI}(\text{OAc})_2$) then affords a transient N-iodo-imidate **B**, whose weak N-I bond is readily homolyzed with visible light.

The resulting N-centered radical **C** is then well-suited to undergo regioselective 1,5-HAT to afford β C-centered radical **D**.

Upon recombination with the caged iodine radical, the key intermediate, β iodo imidate **E**, is formed. In our previous studies, a polar solvent (e.g. MeCN) facilitates *in situ* cyclization to yield oxazoline **F**, which can be hydrolyzed by acidic work-up to afford β amino alcohol **G**.^{11a,c} In non-polar solvents (e.g. PhMe), 4-aryl oxazolines are further oxidized to heretoaromatic azoles.^{11d} Alternatively, β iodo imidate **E** may undergo a second, iterative 1,5-HAT to selectively abstract the remaining β C-H bond, which is weaker by ~ 2 kcal/mol due to C-X polarization, to afford β di-iodide **H**.

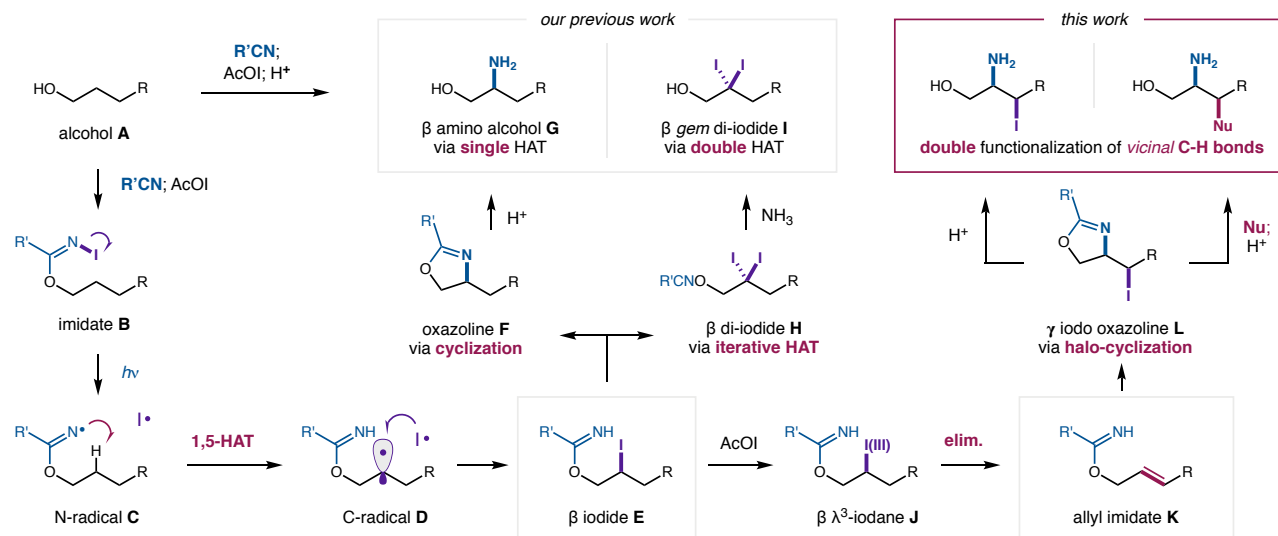


Figure 2. Several single and double C-H functionalization mechanisms enabled by imidate radical chaperone strategy.

Upon aminolysis, *geminal* β di-iodide **I** is obtained – complementing Pd-catalyzed β C-H iodination by J-Q Yu *et al*, which forms distal di-iodides.¹⁴ We have found the key to this divergent reactivity rests in the judicious choice of solvents. For example, whereas MeCN yields cyclization to oxazoline **F**, a MeCN:CH₂Cl₂ mixture affords iterative HAT (to β di-iodide **I**). We anticipate this less polar solvent mixture allows a second N-oxidation to outcompete cyclization. Furthering this hypothesis, we envisioned a solvent that increases NaI (and thus AcOI) concentration without increasing polarity might enable I-oxidation – facilitating an alternate radical-polar

crossover mechanism.

In this third mechanistic possibility, iodine-centered oxidation of β iodo imidate **E** may afford β hypervalent iodane **J**. This alkyl λ^3 -iodane is a hypernucleofuge, which is 10^6 times faster of a leaving group than triflate.¹⁵ For this reason, we anticipated its rapid β elimination would afford allyl imidate **K**. The regioselectivity of this elimination – away from the imidate – was expected based on imidate polarization. Again this reactivity would complement Pd-catalyzed mechanisms, including 1,5-HAT pathways recently developed by Gevorgyan and coworkers

to access enols, enamines, and terminal alkenes via desaturation.¹⁶ Finally, we hoped allyl imidate **K** would directly undergo AcOI-mediated halocyclization in a radical-polar crossover cascade to afford γ iodo oxazoline **L**. We expected this intermediate could also be hydrolyzed to β amino alcohols – with an additional γ iodo functional handle to enable further nucleophilic substitution. With this added versatility, a family of α,β,γ substituted amino alcohols would be rapidly accessible from aliphatic alcohols by a desaturation-mediated cascade.

Results and Discussion

To test our radical-polar crossover cascade hypothesis, we subjected imidate **1**, whose tertiary β iodide intermediate we expected to be prone to oxidative elimination, to excess AcOI (*in situ* combination of NaI and PhI(OAc)₂) in MeCN with visible light irradiation (26W compact fluorescent light) (Figure 3). We were pleased to find the cascade was indeed feasible, affording iodo oxazoline **2** (43% yield) along with des-iodo oxazoline **3** (18% yield). Moreover, substituting a

less polar solvent (CH₂Cl₂) slows cyclization and affords more **2** (63% yield), along with β iodide **4** (18% yield) and oxazoline **3** (12% yield). Extending this trend, non-polar PhCF₃ solvent arrests cyclization and exclusively affords β iodide **4** (60% yield). Alternatively, a more polar 3:1 HFIP:CH₂Cl₂ solvent mixture yields oxazoline **3** (83% yield) selectively. Building on these observations, we tested ^tBuOH, a moderately polar, protic solvent, and were delighted to observe selective *vicinal* C-H difunctionalization to **2** (92% yield). Notably, the proposed intermediate alkene **5** was not recovered from any of these experiments, and ^tBuOH affords < 5% of side-products **3** or **4**. It is worth highlighting the strong solvent effect observed, wherein three divergent transformations are controlled by solvent choice. For example, imidate **1** can be tuned to selectively afford: β C-H iodination (**4**) in PhCF₃, β C-H amination (**3**) in HFIP:CH₂Cl₂, or *vicinal* C-H β -amino- γ -iodination (**2**) in ^tBuOH.

In further probing our hypothesis that ^tBuOH is optimal because it best solubilizes AcOI

precursors and increases oxidant concentration, we switched the iodine reagent from NaI to I₂.

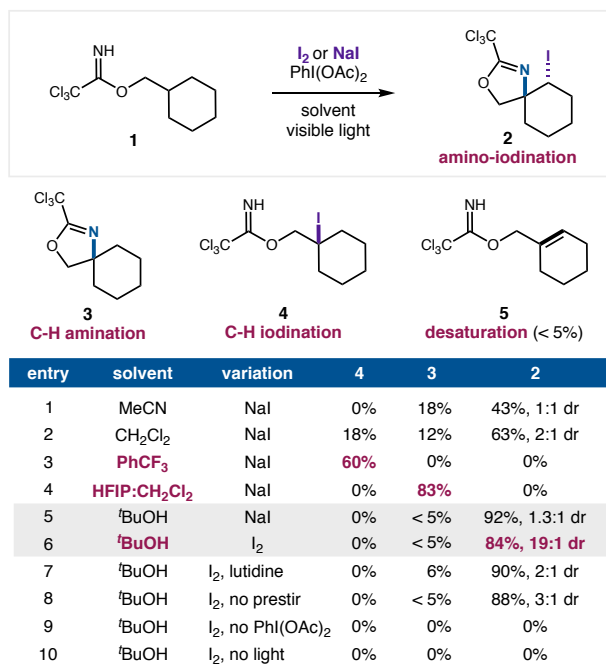


Figure 3. Development of *vicinal*, double C-H functionalization. *Conditions:* 0.2 mmol imide, I₂ or NaI (3 equiv), PhI(OAc)₂ (3 equiv), ^tBuOH [0.3 M], 3 min stir before visible light irradiation for 1 h. Yields and dr determined by ¹H NMR vs internal standard.

Although we previously found I₂ to work well in some cases,^{11c} its photolytic initiation often affords significant side-product formation and poor desired reactivity.^{10a} Thus, we were pleasantly surprised to find that in ^tBuOH, I₂ forms iodo oxazoline **2** efficiently (84% yield) and with high diastereoselectivity (19:1 dr). As reaction controls, we probed the effects of added base (2,6-lutidine) and immediate irradiation (without a 3-

minute pre-stir to ensure I₂ solubility before irradiation). Both changes resulted in significantly lower diastereoselectivity with similar efficiency. Lastly, as expected, absence of PhI(OAc)₂ (to generate AcOI), I₂ (to facilitate iodide elimination), or light (to initiate N-I homolysis) affords no reactivity.

Synthetic Scope

Having developed a regio- and diastereoselective *vicinal*, double C-H amino-iodination of alcohols via an imidate-radical-polar crossover mechanism, we sought to investigate the generality and utility of this cascade reaction (Figure 4). To this end, we found a range of cyclic alcohols are efficiently amino-iodinated to afford spirocyclic oxazolines fused to 4-8 membered carbocycles (**2**, **6-9**). Notably, even cyclobutane (a common motif in medicines and natural products)¹⁷ is amino-iodinated (**9**), likely through a strained cyclobutene intermediate, showcasing the unique utility of this radical-mediated strategy to doubly modify small rings. A variety of functional groups are tolerated under these reaction conditions, including ethers, amides,

esters, and nitriles, affording spiro-fused bis-heterocycles (**10-13**, **19**). In addition to primary alcohols, this cascade is also amenable to secondary alcohols, which selectively undergo radical-polar crossover reactivity to afford spirocyclic oxazolines (**14-15**) rather than distal, iterative HAT products.¹³ Additionally, γ acyclic alcohols afford γ iodo oxazolines as well. In this case, both symmetric (di-Me, di-*n*Bu) or asymmetric (Me, *n*Bu) substituents are tolerated – with the latter affording 8:1 to 20:1 regioselectivity for the more substituted γ iodide (**16-19**).

We have shown the cyclization of intermediate β iodo imidates is challenging in the absence of benzylic activation, and thus, more nucleophilic benzimidates (vs trichloroimidates) are necessary to afford amination in these cases.^{11a} Therefore, to test the limits of this new radical-polar crossover, we investigated such amination-prone imidates. Unexpectedly, a wide range of benzimidates (accessed by addition of alcohols to benzonitriles) are amenable to this cascade. For example, electronically diverse, *para*-aryl substituents,

ranging from -CH₃ to -CF₃ afford iodo oxazolines (**20-24**) with excellent efficiency and diastereoselectivity (>70% yield, >20:1 dr). Additionally, *meta*- and *bis*-halide substitution are tolerated, as well as oxidatively sensitive naphthalenes (**25-28**). Lastly, and perhaps, most surprisingly, alkyl nitrile-derived imidates also efficiently afford spirocyclic oxazolines (**29-30**) despite increased nucleophilicity of these imidates, which may otherwise cyclize to afford mono-amination.

To further probe the functional group tolerance of this radical-polar cascade, a robustness screen was performed.¹⁸ In this investigation of **1** to **2**, we observed medicinally relevant, five- and six-membered N-containing heterocycles (e.g. imidazole, pyridine) are well-tolerated. Interestingly, we observed a slight decrease in diastereoselectivity in the presence of these bases. We attribute this effect to I₂-base complexation,¹⁹ which effectively decreases the concentration of I₂ and rate of the resulting polar amino-iodination pathway (see SI for more details). Next, we were pleased to find alkyl chlorides, which are prone to

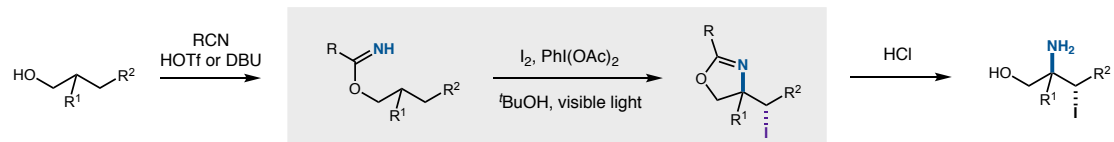
displacement by I⁻ (generated upon alkyl-iodide elimination), are also tolerated. Additionally, alcohols, aldehydes, and amides are preserved, despite the possibility of their consumption under these oxidative conditions (see SI for an extended table of functional group tolerance investigations).

Mechanistic Investigations

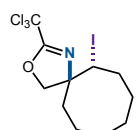
A detailed description of our proposed mechanism is shown in Figure 5a. First, *in situ* generation of AcOI occurs by combination of PhI(OAc)₂ and I₂ via a ligand exchange mechanism.²⁰ Next, an alcohol-derived imidate **I** undergoes N-iodination by displacement of AcOI, which is electrophilic at iodine.²¹ The resulting N-iodo imidate **II** contains a weak N-I bond that is homolyzed under visible light irradiation. The electrophilic, N-centered radical **III** may then undergo a thermodynamically and kinetically driven 1,5-HAT to generate nucleophilic, C-centered radical **IV**. Upon radical recombination with I•, β alkyl iodide **V** is formed – terminating the *radical* component of the radical-polar crossover mechanism. To promote *polar*

elimination, Lewis acidic complexation of I₂ to iodide **V** would form the alkyl triiodide nucleofuge **VI**.²²

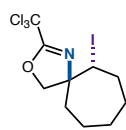
Upon net elimination of HI and I₂, a resulting allyl imidate **VII** is generated and amino-iodinated under these oxidative conditions. This halocyclization may occur by either a *polar*, iodonium (**VIII**) or *radical*, π-addition (5-*exo*-trig cyclization of **IX**) mechanism. The high diastereoselectivity observed for *trans*-iodo-oxazoline **X** suggests a *polar* mechanism is operative – entailing intramolecular cyclization of iodonium **VIII** by the tethered imidate. Nucleophile-induced pre-polarization via this pathway may also account for the observed stereoselectivity.²³



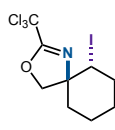
alcohol scope



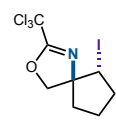
6, 70%, 5:1 dr ^{a,d}



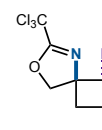
7, 82%, 1.3:1 dr ^{a,d}



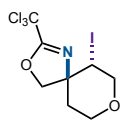
2, 86%, 19:1 dr



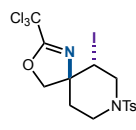
8, 95%, 1:1 dr ^a



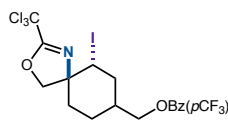
9, 74%, 3:1 dr ^{b,d,e}



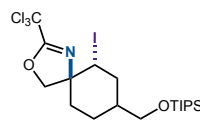
10, 70%, 6:1 dr



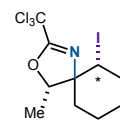
11, 74%, 14:1 dr



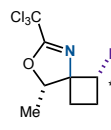
12, 82%, 13:1 dr



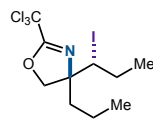
13, 79%, 8:1 dr



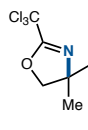
14, 55%, 1:1 dr
> 20:1 dr at (*)



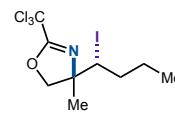
15, 52%, 1:1 dr
3:1 dr at (*)



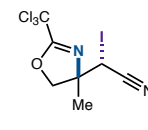
16, 80%, 1.2:1 dr ^a



17 50% ^{a,c}

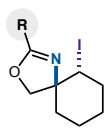


18, 74%, 1:1 dr ^{a,d}
8:1 rr

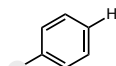


19, 75%, 1.2:1 dr ^{d,e}
> 20:1 rr

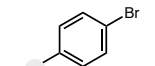
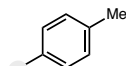
nitrile scope



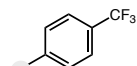
20, 87%, > 20:1 dr



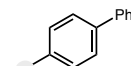
21, 86%, > 20:1 dr



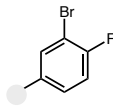
22, 71%, > 20:1 dr



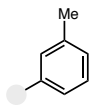
23, 82%, > 20:1 dr



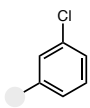
24, 76%, > 20:1 dr



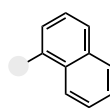
25, 75%, 13:1 dr



26, 89%, 9:1 dr



27, 83%, 9:1 dr



28, 70%, 9:1 dr



29, 79%, 19:1 dr



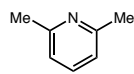
30, 86%, 12:1 dr

functional group tolerance

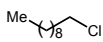
Additive:



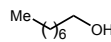
Cascade product (2): 78%, 10:1 dr
Remaining additive: 71%



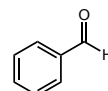
71%, 6:1 dr
100%



78%, 11:1 dr
100%



71%, 6:1 dr
68%



71%, 12:1 dr
84%



60%, 11:1 dr
73%

Figure 4. Synthetic utility of vicinal C-H amino-iodination of alcohols. *Conditions:* 0.2 mmol imidate, I_2 (3 equiv), PhI(OAc)_2 (3 equiv), $t\text{BuOH}$ [0.3 M], 3 min stir before visible light irradiation. ^aNaI (3 equiv). ^b I_2 (2 equiv). ^c PhI(OAc)_2 (5 equiv). ^dNMR yield. ^e PhI(OAc)_2 (4 equiv).

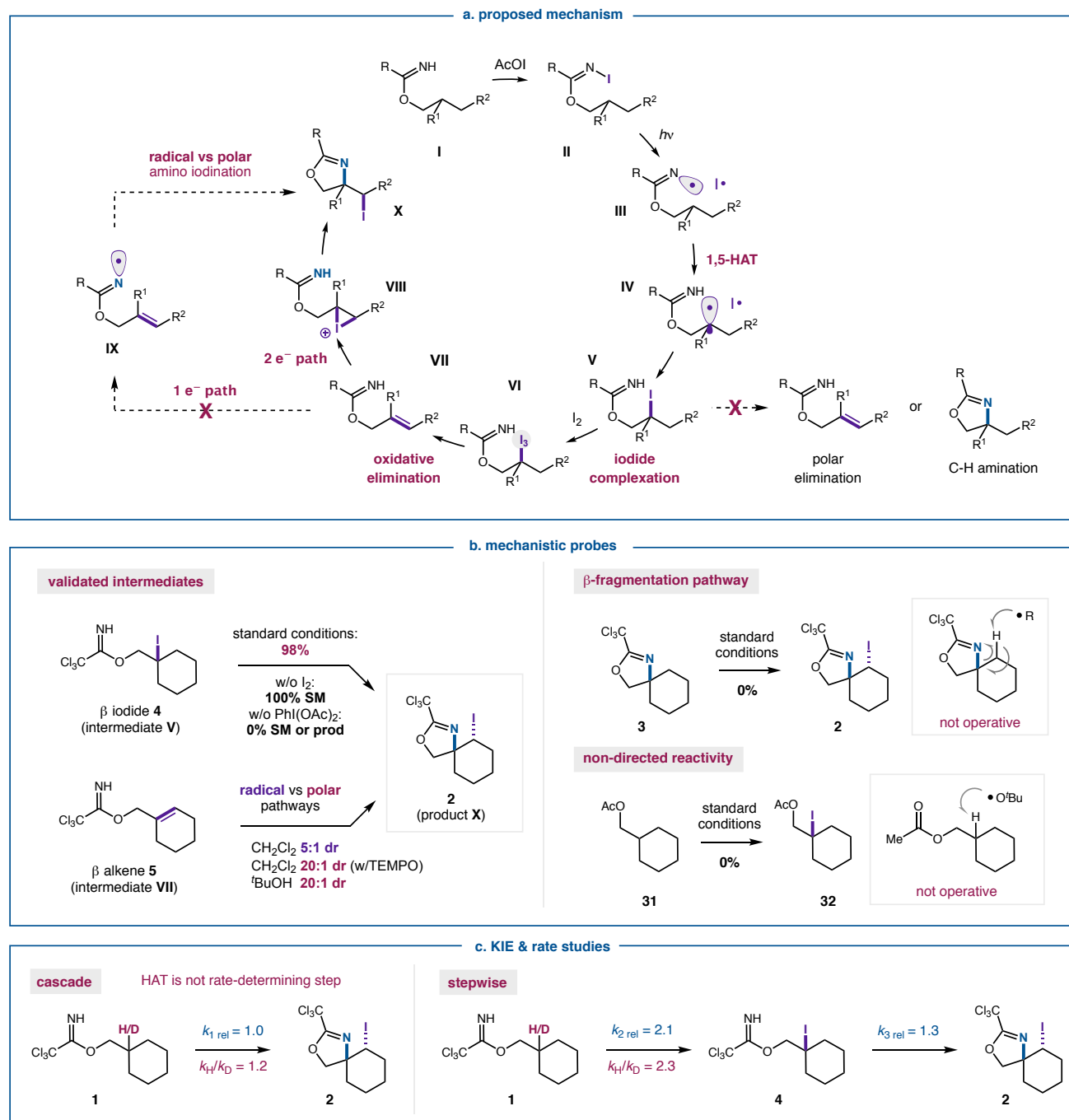


Figure 5. Vicinal C-H aminoiodination via imidate radical chaperone desaturation-addition cascade: (a) Proposed mechanism. (b) Mechanistic probes for various key steps. (c) KIE & rate studies.

To better understand this radical-polar crossover mechanism, we conducted a series of experiments probing the elementary steps of

this cascade. First, two of the key proposed intermediates, β alkyl iodide **4** and β alkene **5** (representing **V** and **VII**, respectively), were

independently synthesized and subjected to the reaction (Figure 5b). Both of these imidates afford iodo oxazoline **2** (up to 98%) – validating their likely intermediacy in the cascade mechanism. As further support, iodide **4** was observed by ¹H NMR during the course of the reaction (alkene **5** is also observed when the reaction is performed in toluene; see SI for details).

We then interrogated the mechanism of β alkyl iodide elimination – an important question, given its similarity to the stable γ iodo product. Since a variety of relevant additives (e.g. NaOAc, HOAc; see SI for full list) do not promote elimination of intermediate **4** (or **V**), we hypothesized the iodide may be first oxidized to a λ^3 -iodane, which is an elimination-prone hypernucleofuge.¹⁵ Upon subjecting **4** to each reaction component (individually or as combinations), the oxidation/elimination/cyclization sequence to form iodo oxazoline **2** was only observed in

the presence of AcOI (98% yield with I₂, PhI(OAc)₂; 36% yield with I₂, NaOAc). Interestingly, PhI(OAc)₂ alone does not oxidize the alkyl iodide, unlike what has been observed in other systems.²⁴ Another notable observation is that I₂ alone provides full consumption of **4**, albeit without formation of **2**. Further discussion of the nature of this β iodide-selective oxidation/elimination is provided in subsequent sections.

As our next line of enquiry, we focused on the proposed β alkene **5** and its ability to afford iodo oxazoline **2** via either a radical or polar pathway. Interestingly, when CH₂Cl₂ is used as solvent (vs ^tBuOH), only 5:1 dr is observed (vs 20:1 dr in ^tBuOH). Suspecting the lower stereoselectivity might be a result of a radical pathway (via **IX**), we added TEMPO to the CH₂Cl₂ reaction and observed a recovery of high stereoselectivity (20:1 dr). Based on this data, we reasoned the stereoselective ^tBuOH conditions suggest a polar mechanism for the amino-iodination of alkene **5** (via *trans*

intramolecular imidate addition to iodonium **VIII**).

Next, we sought to probe if alternate mechanisms, such as β fragmentation or non-directed functionalization, are operative (Figure 5b). In the first case, the C-H amination side-product (oxazoline **3**) could afford amino-iodinated product (iodo oxazoline **2**) by β fragmentation of a γ C-radical (inset). While there is no obvious driving force for γ selective C-H abstraction (or regeneration of an N-centered radical via this pathway), a related mechanism was identified by J-Q Yu and coworkers in their iodo-lactamization.⁸ Nevertheless, when resubjected to reaction conditions, oxazoline **3** remains intact and does not afford iodo oxazoline **2**. Similarly, we sought to investigate if a non-directed pathway, as described by Barluenga *et al.*,⁷ is operative. Noting that AcOI (I_2 , $PhI(OAc)_2$) in t BuOH may form t BuO-I, whose homolysis would generate a reactive HAT reagent (t BuO \bullet),²⁵ we

replaced the imidate directing group with a similarly polar ester. In this case, subjecting acetate **31** to reaction conditions does not form β iodide **32** or any other relevant products. This observation supports our hypothesis that the regioselective cascade is mediated by imidate radical 1,5-HAT rather than non-directed HAT (by t BuO \bullet ; see inset).

Finally, we investigated the role of HAT in the double C-H functionalization by measuring relative reaction rates of individual steps, while also considering the effects of heavy atom labels on these rates (Figure 5c). In the overall reaction, a negligible, primary kinetic isotope effect (KIE) was determined by measuring parallel rates of reactivity of **1** vs β deuterio **1** ($k_H/k_D=1.2$). Interestingly, when rates of formation of intermediate **4** are measured (vs cascade product **1**), a slightly larger primary KIE is observed ($k_H/k_D=2.3$). Together, this data suggests that while HAT is rate-determining for intermediate C-H iodination, it is not the rate-determining step of

the overall amino-iodination cascade. Similarly, comparison of the relative rates of the overall reaction (double C-H amino-iodination; $k_{1\text{ rel}} = 1.0$) to stepwise formation of β iodide **4** (mono C-H iodination; $k_{2\text{ rel}} = 2.1$) and its subsequent conversion to product (elimination/cyclization; $k_{3\text{ rel}} = 1.3$) illustrates the bottleneck in this cascade. Specifically, radical-mediated C-H iodination was found to be 1.6-times faster than subsequent conversion to the iodo-oxazoline, which supports our earlier observation that HAT precedes the rate-limiting step.

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