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Introduction

The halogenation of an sp³ C-H bond¹ enables direct conversion of an inert motif into a versatile synthetic handle that permits broad reactivity via cross-coupling and substitution.² Generally, C-H halogenation occurs by radical-mediated³ or organometallic⁴ mechanisms. Each approach exhibits complementary reactivity and selectivity - especially for incorporation of the most versatile halide: an iodide (Fig. 1a). In the realm of metal-mediated sp3 C-H iodination, there are just a few methods that can install this reactive handle; they are stoichiometric⁵ or catalytic⁶ in Pd. In the latter cases, only Yu and Rao have reported directed sp³ C-H iodination - employing oxazolines, amides, or oximes as directing groups (Fig. 1b).6 These Pd-catalyzed methods exclusively effect primary C-H conversion to a terminal mono-iodide, which is deactivated to further reactivity. In this mechanism, a second iodination at a distal, primary C-H affords a 1,3-di-iodide.7

Alternatively, radical mechanisms can promote efficient iodination of various types of sp³ C-H bonds via hydrogen atom transfer (HAT).8 Moreover, intramolecular HAT provides unique, & selective C-H functionalizations.9 Yet, non-directed methods¹⁰ surpass the few, pioneering examples of δ (or γ) C-H halogenation.11 Notably, a directed C-H iodination has yet to be developed, despite the key intermediacy of a distal iodide in several δ C-H aminations (or etherification) mediated by 1,5-HAT.¹² Due to the penchant for iodide displacement, intercepting this alkyl iodide intermediate is challenging. As an alternate strategy, we proposed a cascade mechanism -

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 β C–H di-halogenation *via* iterative hydrogen atom transfer*

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A radical relay strategy for mono- and di-halogenation (iodination, bromination, and chlorination) of sp³ C-H bonds has been developed. This first example of β C-H di-halogenation is achieved through sequential C-H abstraction by iterative, hydrogen atom transfer (HAT). A double C-H functionalization is enabled by in situ generated imidate radicals, which facilitate selective N* to C* radical translocation and tunable C-X termination. The versatile, geminal di-iodide products are further elaborated to β ketones and vinyl iodides. Mechanistic experiments explain the unique di-functionalization selectivity of this iterative HAT pathway, wherein the second C-H iodination is twice as fast as the first.

> involving abstraction of the adjacent, α-iodo C-H - might enable geminal C-H di-iodination (Fig. 1c).

> We noted that Suárez observed a minor di-iodide byproduct upon intramolecular δ amination of 8-membered lactams.¹³



Fig. 1 Directed, mono- and di-iodination of sp³ C–H bonds.



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Benzylic tri-iodination mechanisms have also been proposed,¹⁴ but no method yet exists to isolate them.

Given the limited synthetic accessibility (and potential pharmacological value¹⁵) of *gem*-di-iodides – an important, versatile motif (previously only accessible from hydrazones or vinyl iodides)¹⁶ – we sought to design a strategy to harness a directed, iterative HAT mechanism to introduce geminal dihalides at remote carbons. Notably, this new type of double C-H iodination at a single carbon atom is complementary to Pd-catalyzed methods and uniquely possible *via* a radical mechanism (Fig. 1).

To develop a versatile β C–H di-iodination *via* iterative, intramolecular HAT and sequential iodination, we chose to employ imidates as readily accessible, radical relay precursors (Fig. 1c). In our proposed di-iodination mechanism, we envisioned that *in situ* formation of a weak imidate sp² N–I bond would enable its rapid homolysis by visible light. Selective translocation of the ensuing N-centered radical to a β C⁻ can occur *via* thermodynamically favored 1,5-HAT. Finally, either radical recombination with I⁻ (derived from the initial N–I homolysis), or homolytic substitution by I₂ (or N–I), can afford a reactive β iodide. However, we were cognizant of two major challenges (Fig. 1d) for trapping the δ iodide intermediate of HAT mechanisms, including its reactivity: (1) as a leaving group, and (2) towards further oxidative decomposition.

Whereas, we previously observed weak C–H bonds (*e.g.* benzyl, allyl) provide activated iodides that are rapidly displaced (in a formal C–H amination),¹⁷ secondary (2°) C–H bonds yield complete decomposition. Given our knowledge that I_3^-

efficiently mediates HAT of 2° C–H bonds,¹⁸ we hypothesized a β iodide intermediate is formed, yet is prone to further Ioxidation. In this case, decomposition may ensue from the resulting sp³ hypervalent iodide, which is an excellent nucleofuge for elimination or cyclization.¹⁹ Instead, to enable access to *gem*-di-iodides, we proposed an alternate N-selective oxidation may promote a second HAT of the slightly weaker β C–H (103 *vs.* 105 kcal mol⁻¹).²⁰ Importantly, however, this iterative HAT mechanism for directed, di-functionalization is only possible if N-oxidation is more rapid than the previously observed, Ioxidation pathway.

Results and discussion

To our delight, adaptation of our radical relay strategy allowed us to intercept the 2° β iodide intermediate for the first time to access both mono- and di- β C–H iodides. The key factors that enabled discovery of these new reactions included judicious choice of oxidant, increased reaction concentration, and shorter reaction duration – all essential to limit product decomposition. Notably, NIS oxidant was found to favor β mono-iodide **1** formation, while a combination of NaI and PhI(OAc)₂ provides desired β di-iodide **2–17**. For the latter, a strong solvent effect was also observed, wherein greater solubility of NaI (in HFIP or CH₂Cl₂) affords less product (**3**, <30%), while more polar, but less solubilizing MeCN affords a higher yield of β di-iodide **3** (58%). Ultimately, a 3 : 1 mixture of CH₂Cl₂ : MeCN was found to provide the *gem*-di-iodide most efficiently (**3**, 88%, 83% isolated yield) (see ESI† for full details of optimization).



^{*a*} Conditions: C-H mono-iodination: NIS (1 equiv.), MeCN, visible light (26 W CFL). ^{*b*} Conditions: C-H di-iodination: NaI (3 equiv.), PhI(OAc)₂ (3 equiv.), 3 : 1 CH₂Cl₂ : MeCN, visible light (26 W CFL). ^{*c*} Conditions: 2 equiv. NaI and PhI(OAc)₂; <10% distal di-iodide. Isolated yields. ¹H NMR yields in parenthesis.

Having developed the first method for β C–H di-iodination, we next investigated the generality of this radical-mediated transformation with a variety of imidates – derived from base-induced addition of alcohols into Cl₃C–CN. In all cases, we observed efficient formation of β di-iodides with greater than 20 : 1 regioselectivity (Table 1).

Except for the NIS-based conditions that afford mono-iodide 1, di-iodide is always the major product, typically isolated in high yields (2–3). Interestingly, this reaction is tolerant of steric congestion (4–5) and remains β selective even in the presence of weaker C–H bonds adjacent to arenes, halides, ethers, esters, and amides at the γ or δ positions (6–11). Secondary alcohols are also amenable to this di-iodination with selectivity observed for secondary over primary C–H bonds (12) – in contrast to Pd-mediated pathways.⁶ While acyclic 2° alcohols efficiently yield di-iodide (13), cyclic alcohols afford a 2 : 1 mixture of di- and mono-iodide (14) – illustrating conformational constraints for the HAT mechanism. Similarly, an estradiol-derived imidate affords a 1 : 1 mixture of mono- and di-iodide (15). Imidates derived from cholic acid and amino acid, valine, yield *gem*-di-iodides (16–17) efficiently.

Cognizant of the synthetic utility of *gem*-di-halides, we sought to extend this unique di-iodination mechanism to other halides. To this end, we found that the use of NaBr or NaCl (instead of NaI) affords analogous β halogenation (Table 2). These new transformations require slight deviation from standard reaction conditions since NaBr and NaCl are less soluble. In these cases, increased halide concentration *via* phase transfer catalysts (Bu₄N⁺X⁻) and a more solubilizing solvent mixture



^{*a*} C-H di-bromination: NaBr (3 equiv.), Bu_4NBr (1 equiv.), $PhI(OAc)_2$ (3 equiv.), 3 : 1 HFIP : CH_2Cl_2 , visible light (26 W CFL). C-H monochlorination: NaCl (3 equiv.), Bu_4NCl (1 equiv.), $PhI(OAc)_2$ (3 equiv.), 3 : 1 HFIP : CH_2Cl_2 , UV light (300 nm). Isolated yields. ¹H NMR yields in parenthesis.

 $(3:1\ HFIP:CH_2Cl_2)$ are the key factors that enable these new reactions.

Notably, a stronger N–Cl intermediate requires UV light (300 nm) for initiation of the radical relay. It is also noteworthy that C–H chlorination ceases after the first halogenation despite a relative similarity in the α -Cl and α -Br C–H bond strengths (±1 kcal).²¹ The scope is as general as the iodination, with three representative examples shown for each halide (**18–23**). X-ray crystallographic analysis of di-bromide **18** confirms the structure of these distal geminal halides.

Interested in further understanding this exceptionally efficient sequential di-iodination (which provides orthogonal reactivity and selectivity to Pd catalysis), we sought to explore our hypothesis that the weaker α -iodo C–H bond enables this transformation. First, a kinetic study by ¹H NMR illustrates a rapid conversion of the mono-iodide intermediate to the diiodide product (Fig. 2). After an initial induction period (*ca.* 10 min), mono-iodide **24** is formed in ~30% yield, before rapid conversion to di-iodide **2**.

In separate experiments, initial rates of formation of monoiodide 24 and di-iodide 2 were independently measured from their respective starting materials (Fig. 3a), using 1 equiv. of oxidant, for more accurate measurements. A relative rate of 2.2 was observed in the second iodination, supporting the expectation it is more rapid than the first due to a weaker C-H bond. In the course of our studies, we were also interested in comparing the relative rates of reactivity among the various halides. To this end, we performed competition experiments between NaI & NaBr/NaCl (Fig. 3b). In the I/Br competition, a statistical mixture of products is formed (1:1:2 di-iodide 4 : di-bromide 18 : mixed 25) - suggesting both reaction rates are comparable. On the other hand, an I/Cl competition provides greater selectivity. Only mono- and di-iodide products (4) are observed with visible light irradiation (since chlorination requires UV light); yet UV irradiation (which unproductively consumes iodinated species) exclusively affords chlorination (19). Lastly, we exploited the difference in halide reactivity to enable a synthetically useful, iterative C-H halogenation (Fig. 3c). In the sequence, mono C-H chlorination (26) and subsequent C-H iodination affords β geminal halide 27 that contains two different halides (Cl, I).

Equipped with the first method to access β *gem*-di-halides *via* C-H functionalization, we sought to elucidate the synthetic utility of these versatile handles. Fig. 4 illustrates five post-



Fig. 2 Kinetics of mono and di C-H iodination.



Fig. 3 Mechanistic experiments: (a) initial rates of mono vs. di C–H iodination; (b) competitive and (c) iterative C–H halogenation.



Fig. 4 Synthetic versatility of the geminal β di-iodides.

synthetic transformations we investigated to further elaborate the β di-iodide imidates. First, aminolysis with NH₃ affords β diiodo-alcohol **28**. Alternatively, reduction of one of the iodides by Zn in AcOH affords vinyl iodide **29** via imidate elimination. Otherwise, imidate hydrolysis to ester **30** occurs under acidic conditions (HBF₄·H₂O), leaving the di-iodide intact. From the β di-iodo-ester, hydrolysis to α -oxy ketone **31** is possible (AgBF₄, Na₂HPO₄·H₂O); or conversion to allyl alcohol **32**, bearing a vinyl iodide, is realized via addition of AgOTf and K₂HPO₄.

Conclusions

In summary, a radical relay strategy has enabled the one-step conversion of imidates to mono- or di-halides *via* iterative β C-H halogenation. In particular, synthetic access to the versatile, geminal di-halides is uniquely facilitated by an

imidate radical-based 1,5-HAT mechanism. By developing a new strategy to bypass oxidative decomposition pathways, reactive alkyl halide intermediates of a radical relay reaction mechanism were intercepted. Along with new methods for mono- and di-C–H halogenation (X = I, Br, Cl), competitive rates and kinetic profiles have also been investigated. Finally, the versatility of the β di-iodides is showcased in the synthesis of functionally rich molecules – uniquely enabled by an HATbased β C–H functionalization mechanism.

Conflicts of interest

There are no conflicts to declare.

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