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# $\beta$ C-H di-halogenation $\emph{via}$ iterative hydrogen atom transfer†

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A radical relay strategy for mono- and di-halogenation (iodination, bromination, and chlorination) of  $sp^3$  C–H bonds has been developed. This first example of  $\beta$  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  $\beta$  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.

a. Mono- vs Di- C-H iodination

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### Introduction

The halogenation of an sp<sup>3</sup> C-H bond<sup>1</sup> enables direct conversion of an inert motif into a versatile synthetic handle that permits broad reactivity via cross-coupling and substitution.<sup>2</sup> 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 stoichiometric<sup>5</sup> or catalytic<sup>6</sup> in Pd. In the latter cases, only Yu and Rao have reported directed sp<sup>3</sup> 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 sp<sup>3</sup> C–H bonds via hydrogen atom transfer (HAT).<sup>8</sup> Moreover, intramolecular HAT provides unique,  $\delta$  selective C–H functionalizations.<sup>9</sup> Yet, non-directed methods<sup>10</sup> surpass the few, pioneering examples of  $\delta$  (or  $\gamma$ ) C–H halogenation.<sup>11</sup> Notably, a directed C–H iodination has yet to be developed, despite the key intermediacy of a distal iodide in several  $\delta$  C–H aminations (or etherification) mediated by 1,5-HAT.<sup>12</sup> Due to the penchant for iodide displacement, intercepting this alkyl iodide intermediate is challenging. As an alternate strategy, we proposed a cascade mechanism –

involving abstraction of the adjacent,  $\alpha$ -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.<sup>13</sup>

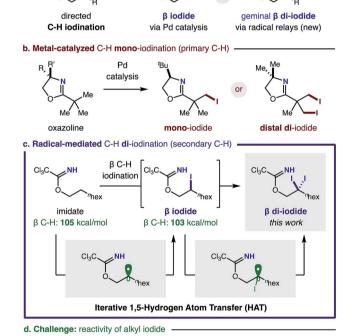


Fig. 1 Directed, mono- and di-iodination of sp<sup>3</sup> C-H bonds.

alkyl iodide

benzylic

mono-amination

(previous work)

secondary

I-oxidation

(decomposition pathway)

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

Given the limited synthetic accessibility (and potential pharmacological value<sup>15</sup>) of *gem*-di-iodides – an important, versatile motif (previously only accessible from hydrazones or vinyl iodides)<sup>16</sup> – 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  $\beta$  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  $sp^2$  N–I bond would enable its rapid homolysis by visible light. Selective translocation of the ensuing N-centered radical to a  $\beta$  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  $I_2$  (or N–I), can afford a reactive  $\beta$  iodide. However, we were cognizant of two major challenges (Fig. 1d) for trapping the  $\delta$  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), <sup>17</sup> secondary ( $2^{\circ}$ ) C-H bonds yield complete decomposition. Given our knowledge that  $I_3^-$ 

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

## Results and discussion

To our delight, adaptation of our radical relay strategy allowed us to intercept the  $2^{\circ}$   $\beta$  iodide intermediate for the first time to access both mono- and di- $\beta$  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  $\beta$  mono-iodide 1 formation, while a combination of NaI and PhI(OAc)<sub>2</sub> provides desired  $\beta$  di-iodide 2–17. For the latter, a strong solvent effect was also observed, wherein greater solubility of NaI (in HFIP or CH<sub>2</sub>Cl<sub>2</sub>) affords less product (3, <30%), while more polar, but less solubilizing MeCN affords a higher yield of  $\beta$  di-iodide 3 (58%). Ultimately, a 3 : 1 mixture of CH<sub>2</sub>Cl<sub>2</sub> : MeCN was found to provide the *gem*-di-iodide most efficiently (3, 88%, 83% isolated yield) (see ESI† for full details of optimization).

Table 1  $\beta$  C-H mono- and di-iodination of imidates via a radical relay strategy

<sup>&</sup>lt;sup>a</sup> Conditions: C-H mono-iodination: NIS (1 equiv.), MeCN, visible light (26 W CFL). <sup>b</sup> Conditions: C-H di-iodination: NaI (3 equiv.), PhI(OAc)<sub>2</sub> (3 equiv.), 3:1 CH<sub>2</sub>Cl<sub>2</sub>: MeCN, visible light (26 W CFL). <sup>c</sup> Conditions: 2 equiv. NaI and PhI(OAc)<sub>2</sub>; <10% distal di-iodide. Isolated yields. <sup>1</sup>H NMR yields in parenthesis.

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Having developed the first method for  $\beta$  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 Cl<sub>3</sub>C–CN. In all cases, we observed efficient formation of  $\beta$  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  $\beta$  selective even in the presence of weaker C–H bonds adjacent to arenes, halides, ethers, esters, and amides at the  $\gamma$  or  $\delta$  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. While acyclic  $2^{\circ}$  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*-diiodides (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  $\beta$  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 (Bu<sub>4</sub>N<sup>+</sup>X<sup>-</sup>) and a more solubilizing solvent mixture

Table 2 β C-H bromination and chlorination

 $(3:1 \text{ HFIP}: CH_2Cl_2)$  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  $\alpha$ -Cl and  $\alpha$ -Br C–H bond strengths ( $\pm 1$  kcal).<sup>21</sup> 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  $\alpha$ -iodo C–H bond enables this transformation. First, a kinetic study by <sup>1</sup>H NMR illustrates a rapid conversion of the mono-iodide intermediate to the di-iodide product (Fig. 2). After an initial induction period (*ca.* 10 min), mono-iodide 24 is formed in  $\sim$ 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  $\beta$  *gem*-di-halides *via* C–H functionalization, we sought to elucidate the synthetic utility of these versatile handles. Fig. 4 illustrates five post-

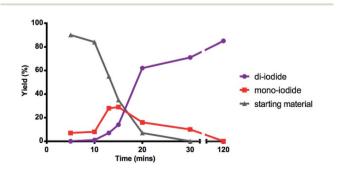


Fig. 2 Kinetics of mono and di C-H iodination.

 $<sup>^</sup>a$  C–H di-bromination: NaBr (3 equiv.), Bu<sub>4</sub>NBr (1 equiv.), PhI(OAc)<sub>2</sub> (3 equiv.), 3:1 HFIP: CH<sub>2</sub>Cl<sub>2</sub>, visible light (26 W CFL). C–H monochlorination: NaCl (3 equiv.), Bu<sub>4</sub>NCl (1 equiv.), PhI(OAc)<sub>2</sub> (3 equiv.), 3:1 HFIP: CH<sub>2</sub>Cl<sub>2</sub>, UV light (300 nm). Isolated yields.  $^1\mathrm{H}$  NMR yields in parenthesis.

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only (4)

only (19)

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  $\beta$  di-iodides.

synthetic transformations we investigated to further elaborate the  $\beta$  di-iodide imidates. First, aminolysis with NH<sub>3</sub> affords  $\beta$  di-iodo-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 (HBF<sub>4</sub>·H<sub>2</sub>O), leaving the di-iodide intact. From the  $\beta$  di-iodo-ester, hydrolysis to  $\alpha$ -oxy ketone 31 is possible (AgBF<sub>4</sub>, Na<sub>2</sub>HPO<sub>4</sub>·H<sub>2</sub>O); or conversion to allyl alcohol 32, bearing a vinyl iodide, is realized *via* addition of AgOTf and K<sub>2</sub>HPO<sub>4</sub>.

#### Conclusions

In summary, a radical relay strategy has enabled the one-step conversion of imidates to mono- or di-halides via iterative  $\beta$  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  $\beta$  di-iodides is showcased in the synthesis of functionally rich molecules – uniquely enabled by an HAT-based  $\beta$  C–H functionalization mechanism.

#### Conflicts of interest

There are no conflicts to declare.

# Acknowledgements

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