Halonium Catalysis: An Underutilized and Underexplored Catalytic Concept in Olefin Functionalizations

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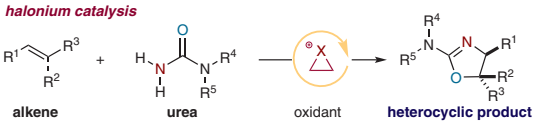
We dedicate this work to the memory of Professor Kilian Muñiz



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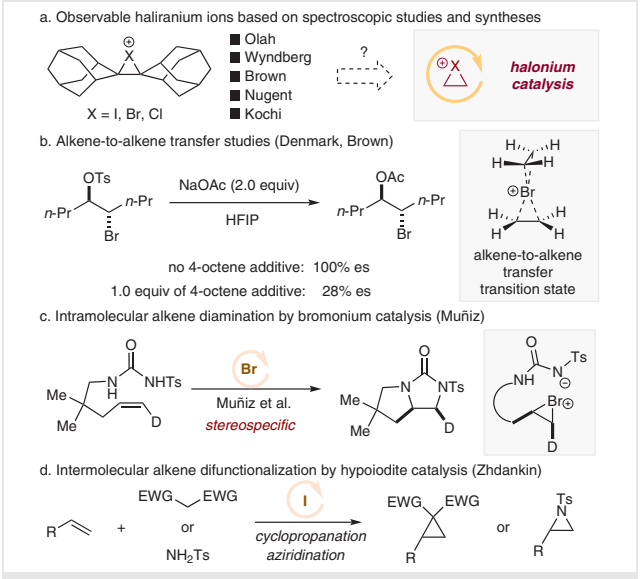
Abstract Iodonium catalysis is described here to accomplish an intermolecular olefin oxyamination reaction. Urea is used as the O- and N-source to add across both activated and unactivated alkenes in a regioselective manner. Mechanistic studies confirm the presence of an iodonium intermediate.

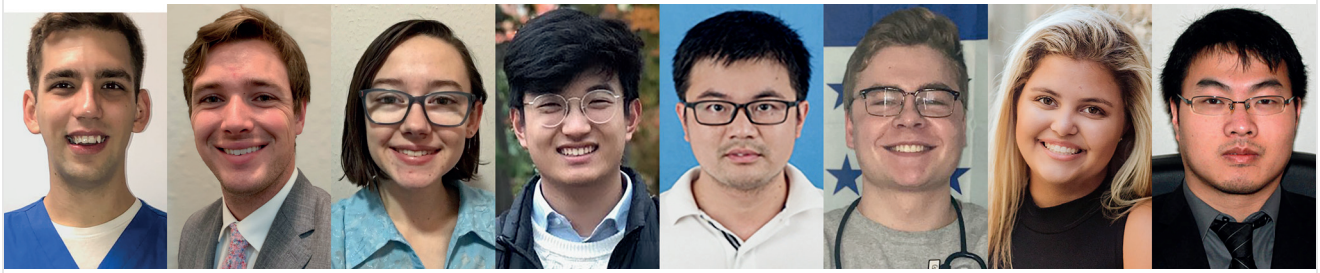
Key words iodonium catalysis, olefin oxyamination, regioselective, N-heterocycles, oxazolines, aminooxygenation

1 Introduction

Three-membered cyclic halonium (haliranium), first proposed by Roberts and Kimball, is a classic intermediate often taught in undergraduate organic chemistry courses to account for the *trans*-addition of a nucleophile and a halogen across an alkene.[2] Structural validation of these intermediates by Olah based on NMR studies, followed by affirmation from Wyndberg, Brown, Nugent, and Kochi based on syntheses from the adamantylideneadamantane system elucidated the distinct structural features and reactivities of the haloniums (Scheme 1a).[3] Later on, variable-temperature ^{1}H NMR studies by Brown and a series of elegant enantiospecific acetolysis experiments by Denmark revealed the existence of an intriguing olefin-to-olefin transfer process that shed light on the challenges often encountered in the development of enantioselective halofunctionalization reactions (Scheme 1b).[4] In conjunction with these excellent works, synthetic utilizations of halonium intermediates have been broadly studied and applied in many chemo-, regio-, and stereoselective settings.[5] An area of research involving halonium that may have been overlooked is its capacity to function as a catalytic intermediate. A distinction must be made between halonium catalysis and the abundant literature of halofunctionalization reactions where the halogen is often incorporated in the final product structure.[6] Halonium catalysis refers to the catalytic generation of a halonium intermediate that proceeds to the product formation without the presence of the halogen in the final product. While this concept was first conceptualized by the late professor Kilian Muñiz, examples in this area are rather rare.[7] To the best of our knowledge, these few examples include the work by Muñiz and coworkers that demonstrated an alkene diamination reaction based on bromonium catal-



Scheme 1 Historical importance and background on halonium and its application as a catalyst in alkene difunctionalizations



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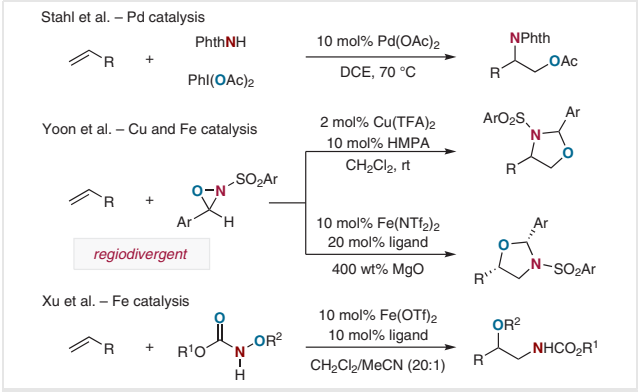
ysis (Scheme 1c).[8] In other cases, Zhdankin and coworkers disclosed the cyclopropanation and aziridination of alkenes using catalytic hypoiodite proceeding via the key catalytic iodonium intermediate (Scheme 1d).[9]

Considering that alkene difunctionalization is a powerful strategy for the rapid assembly of molecular complexity as demonstrated by the recent works from a number of groups, the lack of examples involving halonium catalysis in this area is perplexing.[10] In this regard, alkene oxyamination is among the most studied catalytic reactions due to the prevalence of the resulting vicinal oxyamine products in bioactive molecules and ligand frameworks.[11] Inspired by the venerable osmium-catalyzed Sharpless oxyamination protocol, a range of useful catalytic protocols has been developed to circumvent several inherent challenges encountered in the Sharpless protocols.[12,13] Despite these efforts, regioselectivity for *intermolecular* oxyamination, in general, remains a complex challenge for this class of reactions.[14] While biased alkenes only provide one regioisomeric outcome, unbiased alkenes often result in regioisomeric mixtures. On this subject, limited but notable examples from Stahl, Yoon, and Xu provide useful solutions for regioselective intermolecular oxyamination reactions (Scheme 2).[15] In addition, recent advances in directing group strategies provide another alternative for tackling the regioselectivity challenges; however, undirected olefin substrates remain highly problematic.[16]

2 Hypothesis of Halonium as a Catalytic Template

With these observations in mind, our group is interested in the utilization of halonium as a catalytic and regiochemical template for intermolecular alkene oxyaminations to access nitrogen-containing heterocycles.[17] As documented in a recent literature, N-heterocycles are highly prevalent motifs in pharmaceuticals, natural products, and agrochemicals, which accounted for close to 60% of all the FDA-approved small-molecule drugs.[18] With respect to the research work here, a number of prominent bioactive mole-



Scheme 2 Examples of regioselective intermolecular olefin oxyaminations

cules such as arabinose aminooxazoline, aminooxazoline xanthene, and allosamidin core, all contain an interesting 2-aminooxazoline framework (Figure 1).[19]

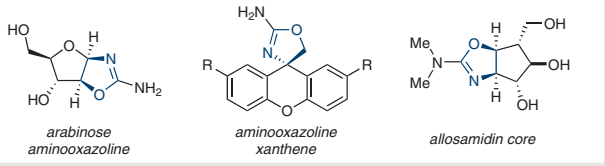
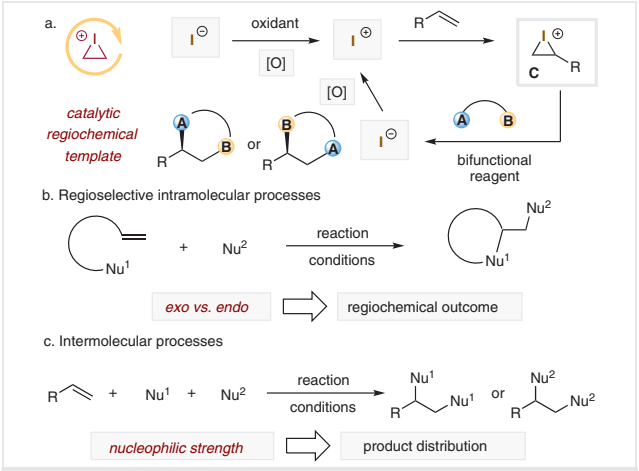


Figure 1 Bioactive 2-aminooxazoline structures

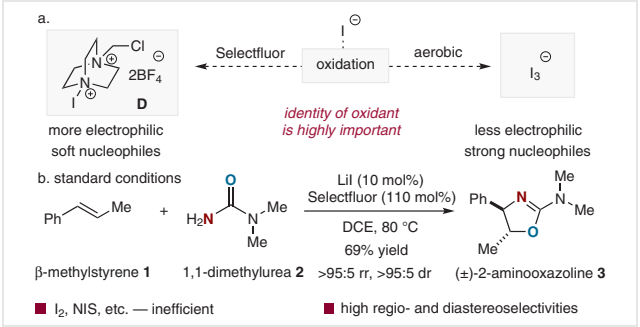
To facilitate the catalytic utilization of the halonium, a key concept that we have developed in our laboratory is the use of a simple bifunctional and soft nucleophile (tethered nucleophiles **A** and **B**, Scheme 3a).[20] The highly electrophilic nature of the halonium **C** renders the initial addition of the soft nucleophile feasible. This initial step also constitutes the crucial regiodetermining step. Following this initiation, an intramolecular cyclization process by the now attached bifunctional nucleophile affords a cyclic product.[21] Meanwhile, the two-step nucleophilic additions return the halide catalyst precursor back into the reaction. To close the catalytic cycle, the halide can undergo oxidation to regenerate the requisite halonium ion. Another critical feature of using the bifunctional reagent is that, ideally, the strength of the two nucleophilic components can be differentiated, thus leading to a regioselective outcome. This provides an interesting solution to the regiochemical challenges often encountered in intramolecular or three-component coupling processes as outlined in Scheme 3b and 3c, respectively.[22] The successful execution of this strategy will therefore provide us an opportunity to recognize halonium as a valuable catalytic and regiochemical template in olefin difunctionalizations.



Scheme 3 Proposed regioselective alkene oxyamination

3 Optimizations and Scope

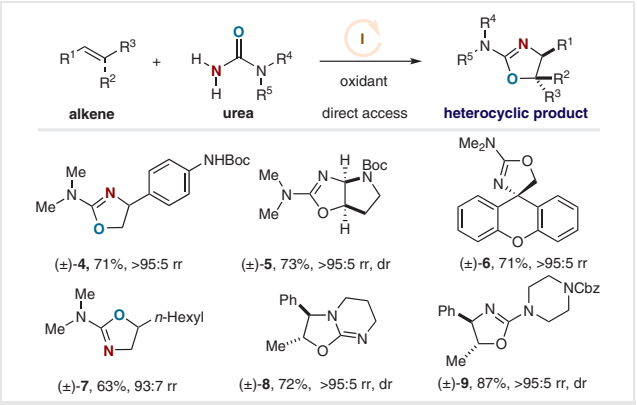
Initially, we tested urea as the bifunctional nucleophile using stoichiometric amounts of simple halogen sources such as I_2 or NIS. In general, these conditions afforded less than 10% yield of the desired product.[23] Our catalytic conditions screening on the other hand revealed that pairing LiI and Selectfluor as the catalyst and oxidant combination was more efficient in affording the product. In this case, a facile salt metathesis would produce a highly electrophilic iodenium ion **D** that can engage soft nucleophiles such as urea as the bifunctional reagent (Scheme 4a). Coincidentally, our previous works suggested that aerobic oxidation of iodide salts often produced the less electrophilic triiodide intermediates.[24] While the less electrophilic triiodide intermediate could tolerate electron-rich amines and carboxylates as nucleophiles in alkene difunctionalizations, softer nucleophiles were often problematic when utilizing such an oxidative approach. With this optimal catalyst and oxidant combination, we carefully evaluated other factors for the standard alkene substrate **1** and urea **2**. Our final conditions are shown in Scheme 4b. The high temperature facilitated the solubility of the LiI catalyst. More excitingly, only one regioisomeric product **3** was observed. In this case, the nitrogen atom of the urea was added to the benzylic position whereas the oxygen atom was added to the homobenzylic position. Furthermore, control reactions revealed the necessity of both the halide catalyst and the oxidant.



Scheme 4 Our rationale for reaction conditions screenings

With these conditions in hand, a range of alkene and urea substrates was tested showing excellent regioselectivity and efficiency (>45 substrate examples). A number of representative substrates **4**–**9** are listed in Scheme 5. In particular, a notable divergent regiochemical feature was observed here. In this case, the electronically activated olefins often afforded a single regioisomeric product, in which the more nucleophilic nitrogen atom of the urea was added to the electronically activated carbon position, and the oxygen atom of the urea was attached to the other carbon atom (Scheme 5, product **4**). Distinctively for the unactivated olefin substrates, the opposite regioisomer relative to N vs. O additions was observed (Scheme 5, product **7**). In this case,

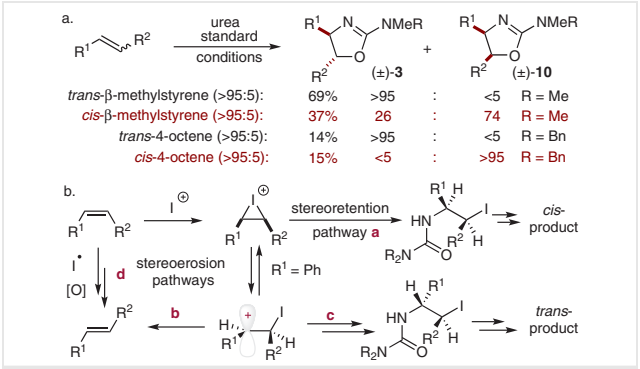
the more nucleophilic nitrogen atom was added to the less sterically hindered carbon (terminal) position and the oxygen atom to the internal position, which suggests that steric hindrance is the predominant regiochemical factor for the key iodonium intermediate. Currently, one limitation for this method is that while monosubstituted olefins provide the products in excellent yields, di- or trisubstituted unactivated olefins are not efficient substrates in this protocol, often resulting in <20% yield. Despite this drawback, this reaction could tolerate olefin substrates with more complex structures (Scheme 5, products **5**, **6**, **8**, **9**).



Scheme 5 Regiochemical analysis of activated vs. unactivated alkenes

4 Mechanistic Probes

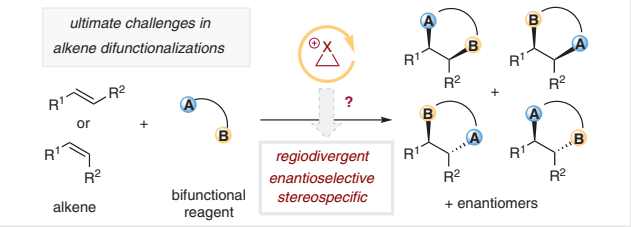
To validate the catalytic involvement of the iodonium in this reaction, we utilized a stereospecificity test, in which the product stereoselectivities of the *trans*- and *cis*-β-methylstyrene substrates were examined in separate reactions (Scheme 6a). For *trans*-β-methylstyrene, >95:5 dr was observed while the *cis*-β-methylstyrene afforded the product in 26:74 dr (*trans* **3**/*cis* **10**). Furthermore, a control reaction with *cis*-β-methylstyrene in the absence of the urea nucleophile resulted in nearly complete stereoerosion under otherwise identical conditions. This control reaction suggests that stereoerosion of the starting material must be taken into consideration. Alarmed by this result, we then examined *trans*- and *cis*-4-octene substrates in these reactions. Although the yields were low, the *cis*-4-octene afforded exclusively the *cis*-product. In addition, control reactions revealed that stereoerosion of *cis*-4-octene had not taken place. These reactions validated that carbocation and radical pathways are unlikely here, as these pathways will afford exclusively the *trans*-products. To account for our findings, the following mechanistic model involving a catalytic iodonium intermediate was proposed to account for both the stereoretention (Scheme 6b, pathway **a**) and stereoerosion (Scheme 6b, pathways **b**, **c**, and **d**). To address the presence of the proposed iodenium intermediate, we pre-synthesized the iodoselectfluor reagent **D** (Scheme 4a). Substituting this reagent in place of the catalyst combination, we observed nearly identical yields and regioselectivity of the desired product, suggesting that it is likely a key intermediate in the reaction.



Scheme 6 Mechanistic probes for the involvement of the key iodonium intermediate

5 Future Outlook

Our work here represents a rare example of the catalytic use of iodonium for regioselective alkene difunctionalization. While tremendous progress has recently been made in regioselective alkene difunctionalizations, *regiodivergent* coupling reactions of π-components remain relatively unexplored.[25] Processes that can effectively control access to both regiochemical outcomes with exceptional selectivity remain an exceptional challenge.[13p,14a–d,26] A parallel illustration of the importance and difficulty in the development of regiodivergent processes can be found in alkene hydrofunctionalizations. While the Markovnikov's rule to predict and guide alkene hydrofunctionalization reactions was discovered as early as 1869, catalytic strategies to access the anti-Markovnikov products remained as one of 'the top 10 challenges in catalysis' until very recently.[27] An interesting direction that our group is currently venturing is the utilization of halonium as both a catalytic and regiocontrol template to design regiodivergent alkene difunctionalization reactions. For example, can we simply control the nucleophilicity of the bifunctional reagent to control the regiodetermining step? What is the role of the halonium in the regiochemical control process? How do we design catalytic solutions to develop regiodivergent processes for more challenging olefin substrates or carbon-based bifunctional nucleophiles? Furthermore, the development of regiodivergent and enantioselective protocols clearly represents an area of significant interest and exceptional challenge to the synthetic community (Scheme 7). For a historically important and valuable synthetic intermediate, haloniums have for a large extent been left in many chemists' hindsight. We believe that our work, and perhaps along with others, will prove such views of haloniums to be unjustified.



Scheme 7 Challenges and outlooks on alkene difunctionalizations

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