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Direct access to 2-imidazolines from unactivated alkenes

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The formation of carbon–nitrogen bonds is crucial for the discovery of pharmaceuticals, materials, and agrochemicals. Nitrogen-containing functional groups, especially heterocycles, are common motifs in biologically active compounds. Among these, 2-imidazolines have emerged as important scaffolds with their own class of biological targets. Herein, we report the development of an oxidative amination process to directly convert unactivated alkenes into 2-imidazolines. The combination of ammonia and a commercially available hypervalent iodine reagent achieves the cleavage of the carbon–carbon double bond. Subsequent interception of the resulting imine by ethylenediamine and oxidation furnishes 2-imidazolines in high yields. The reaction is rapid and tolerates a wide range of functional groups, showcasing its potential for late-stage diversification of complex molecules.

Introduction

Nitrogen-containing heterocycles are prevalent scaffolds in biologically active molecules and functional materials.[1,2] Among these, imidazolines represent an important class, with 2-imidazoline being the most frequently occurring isomer.[3] 2-Imidazolines interact with a distinct set of biological targets[4–7] and function as more lipophilic bioisosteres of amidines.[8] They also serve as synthetic intermediates for accessing imidazoles, which rank among the most prevalent nitrogen heterocycles in U.S. FDA-approved drugs.[9] Besides their biological application, 2-imidazolines have also been widely used as ligands for transition metal catalysts.[10] Over the past years, numerous strategies for the synthesis of 2-imidazolines have been developed. Most approaches rely on the reaction of carbonyl derivatives, such as carboxylic acids, esters, or aldehydes, with diamines, followed by oxidation,[10,11] or the use of nitriles[12–16] (Fig. 1Ai). However, these methods mostly require harsh conditions or include transition metal catalysis. Synthetically, an interesting alternative approach to the use of those classical carbonyl derivatives would be to directly employ easily accessible alkenes as starting materials in an oxidative diamination process.

Alkenes are valuable precursors for nitrogen-containing molecules due to their prevalence in petrochemical feedstocks, natural products, and wide use as synthetic intermediates.[17,18] To date, however, there is a dearth of methods realizing the desired direct transformation of alkenes into 2-imidazolines (Fig. 1Aii).[19–23] The first example converts electron-deficient alkenes to 2-imidazolines using ethylenediamine *via* carbon–carbon bond cleavage, yet it is limited to activated substrates.[20] Another method is the iridium-catalyzed photoredox functionalization using *N*-Ts-protected 1-aminopyridinium and acetonitrile as nitrogen sources.[21] However, this operationally complex procedure furnishes *N*-tosylated products, which are challenging to deprotect; additionally, the method produces substituted 2-imidazolines. Thus, the development of a simple method that would directly convert unactivated alkenes to unprotected 2-imidazolines to expedite the incorporation of this motif in biologically relevant molecules is needed.

In our design, we aimed to use commercially available reagents to develop an operationally simple transformation of

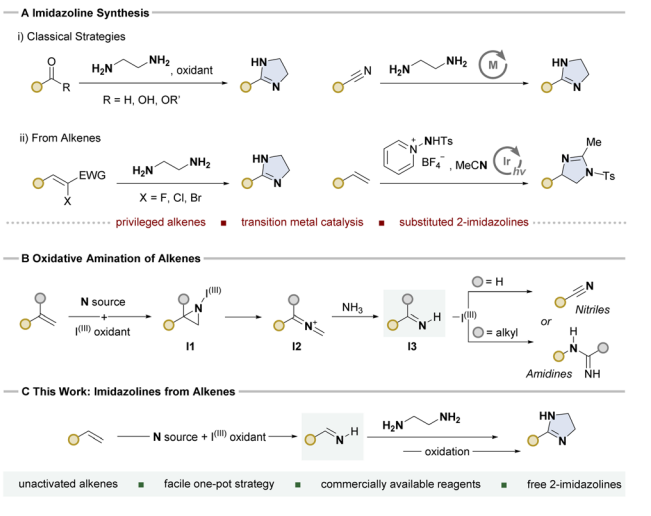

Fig. 1 (A) Literature precedents for the synthesis of 2-imidazolines. (B) Oxidative amination of alkenes, recently developed by our group. (C) The reaction design for the direct transformation of alkenes to 2-imidazolines.

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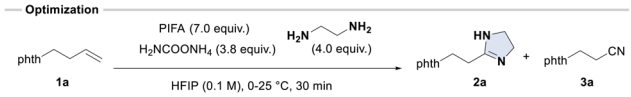
unactivated alkenes to 2-imidazolines to maximize the reaction's applicability. Our group recently reported an oxidative amination strategy *via* nitrogen atom insertion into unactivated carbon–carbon double bonds, yielding either nitriles or amidines, depending on the initial alkene substitution pattern (Fig. 1B).[24] Key to this reactivity is the combination of an ammonia source and a hypervalent iodine reagent, forming an electrophilic nitrogen species *in situ*,[25] which engages with unsaturated bonds to achieve various transformations, such as atom swaps or nitrogen atom insertions.[26–29] For the oxidative amination of alkenes, the electrophilic nitrogen reagent undergoes a formal [2 + 1]-cycloaddition with the alkene, furnishing an activated aziridine **I1**. This subsequently undergoes a concerted electrocyclic ring-opening, forming an aza-allenium species **I2**. Aminolysis by ammonia generates an imine **I3** after proton transfer and extrusion of formaldimine. Imine **I3** then undergoes rapid oxidation events to the final nitrile or amidine. We hypothesized that the imine intermediate **I3** might be intercepted by a suitable diamine nucleophile, followed by oxidation to the desired 2-imidazoline (Fig. 1C). However, challenges arise from the highly oxidative reaction conditions leading to compatibility issues with several oxidation-sensitive species, including the diamine reagent itself as well as the desired product of the reaction. Moreover, the proposed diamine attack onto the imine intermediate needs to outcompete the rapid oxidation to the nitrile.

Herein, we describe the successful realization of this concept in which unactivated alkenes are directly converted to unsubstituted 2-imidazolines *via* a carbon–carbon double bond cleavage using inexpensive, commercially available reagents. The high functional group compatibility was demonstrated on a wide range of alkenes and drug-like molecules, highlighting its potential use for immediate applications in late-stage diversification.

Results and discussion

We initially focused on the use of ammonium carbamate as the nitrogen source and (bis(trifluoroacetoxy)iodo) benzene (PIFA) as the hypervalent iodine reagent.[24] The primary challenge of the reaction development was to find conditions that favor the interception of the proposed imine intermediate **I3** by a diamine over its oxidation to the nitrile **3a**. We selected alkene **1a** and ethylenediamine as our model system. We were delighted to find that 2-imidazoline **2a** (Fig. 2, entry 1) was obtained in moderate yield with only small amounts of nitrile **3a** as byproduct. PIFA was generally demonstrated to be the most efficient oxidant for the targeted transformation, with other iodine(III) reagents such as (diacetoxyiodo)benzene (PIDA) providing significantly lower yields of the desired product **2a** (Fig. 2, entry 3). Moreover, the reaction was found to proceed only in the presence of fluorinated, protic solvents, among which hexafluoroisopropanol (HFIP) proved to be the most efficient for the formation of 2-imidazoline **2a** (Fig. 2, entries 4, 7, and 8). Achieving high yields of the desired product **2a** and favoring its formation over nitrile **3a** required 4 equivalents of ethylenediamine, likely due to the undesired oxidation of the



Entry	Deviation from above	Conv. of **1a**[a]	Yield of **2a**[a]	Yield of **3a**[a]
1	5.6 equiv. PIFA	72%	63%	4%
2	8.0 equiv. PIFA	100%	43%	9%
3	7.0 equiv PIDA	60%	39%	0%
4	**None**	**100%**	**99%**	**0%**
5	7.6 equiv. $H_2NCOONH_4$, 5.6 equiv. PIFA	64%	47%	10%
6	5.6 equiv. PIFA, 2.0 equiv. diamine	100%	38%	18%
7	ACN (0.1 M)	3%	0%	0%
8	TFE (0.1 M)	28%	15%	10%

Fig. 2 Selected optimization data for the transformation of alkenes to 2-imidazolines. [a]Refers to ^{1}H NMR yield determined with dibromomethane as internal standard.

diamine under the reaction conditions (Fig. 2, entries 1 and 6). After careful adjustments of the ratio of ammonium carbamate, PIFA, and ethylenediamine, we found reaction conditions that gave access to 2-imidazoline **2a** in high yield with, remarkably, no detected formation of nitrile **3a** (Fig. 2, entry 4).

With the optimized conditions in hand, we set out to explore the functional group tolerance and synthetic utility of this transformation (Fig. 3). Aliphatic, unactivated alkenes cleanly afforded 2-imidazolines **2a** to **2j** in good yields, while halogens, TBS-protected, as well as unprotected alcohols remained untouched. Esters, acetamides, and Boc-protected amines were well tolerated (**2g** to **2i**). Styrene derivatives (**2l** and **2n**) could be obtained in high yield. Electron-deficient heterocycles such as 4-vinylpyridine resulted in a decrease in yield (35% for **2m** *versus* 99% for **2l**). Next, we investigated internal alkenes. Symmetrical *trans*-4-octene furnished two equivalents of 2-imidazoline **2o** by cleavage of the carbon–carbon double bond, whereas cyclohexene underwent ring-opening to give bis-imidazoline **2p** in good yield. The conjugated diene, cinnamylideneacetophenone (**1q**), also reacted under our conditions to give both imidazoline fragments **2l** and **2q** in moderate yield. Moreover, we demonstrated the synthesis of tolazoline **2k**, an adrenoblocking drug,[30] in one step from allylbenzene in good yield by applying our reaction conditions. Next, we investigated whether our reaction was amenable to more complex substrates. Hexenyl esters from ambrisentan, ataluren, telmisartan, artesunate, and lumacaftor all afforded 2-imidazolines **2r** to **2v** in good to high yields, showcasing the potential of our method for late-stage diversification of drug-like molecules.

Next, different derivatizations of the obtained 2-imidazolines were tested. Simple oxidation with PIDA under basic conditions afforded imidazole **3l**, another valuable heterocycle. The oxidative ring-opening of 2-imidazoline **2l** to **4l** could be achieved under basic conditions and elevated temperatures (Fig. 4A). Interestingly, we found that exposing bromo-substituted 2-imidazoline **2d** to basic conditions led to a nucleophilic substitution reaction by the imidazoline's NH on the bromide, forming fused amidine **2w** (Fig. 4B). We then tested

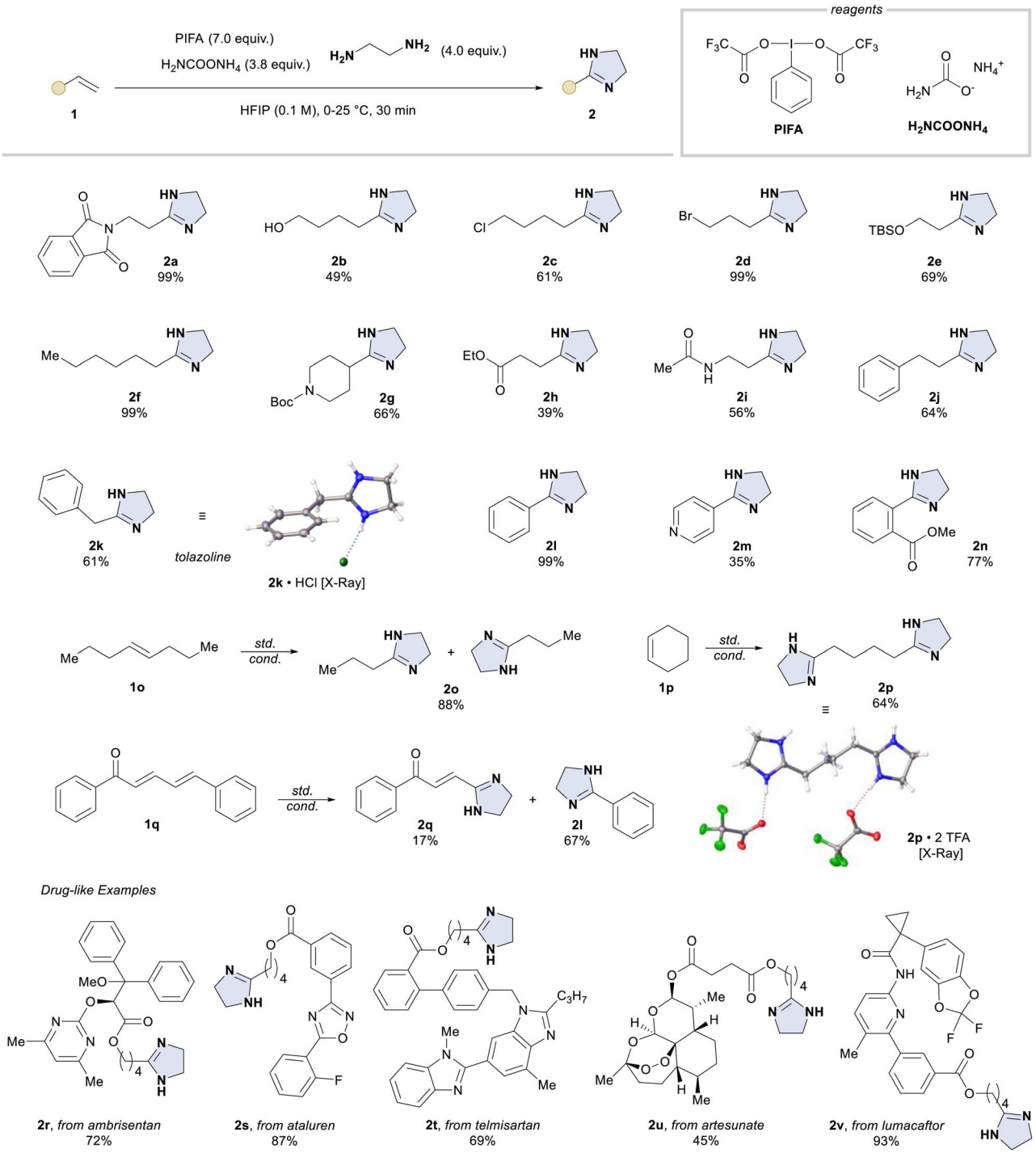


Fig. 3 Scope of the reaction of alkenes to 2-imidazolines. The yields are given as isolated yields on 0.5 mmol scale.

different leaving groups and chain lengths. Tosyl worked similarly to bromide (**2x**), as well as longer alkyl chains performed well, giving six- and seven-membered fused amidines (**2y** and **2z**).

To better understand the underlying mechanism (Fig. 4C) and gain evidence for imine **I3** being a possible intermediate in our reaction, we performed several control experiments (see SI for more details). Using $^{15}NH_4OAc$ in the presence of an equivalent amount of K_3PO_4 instead of ammonium carbamate as the ammonia source yielded the desired product without any ^{15}N incorporation. This suggests that both nitrogen atoms in the product arise from ethylendiamine, supporting a mechanism in which imine **I3** was intercepted by the diamine, consequently releasing any ^{15}N-labelled species. However, we cannot rule out that the imine first hydrolyzes to a short-lived aldehyde intermediate, given that an aldehyde was chemically competent when used as the substrate in the reaction. Finally,

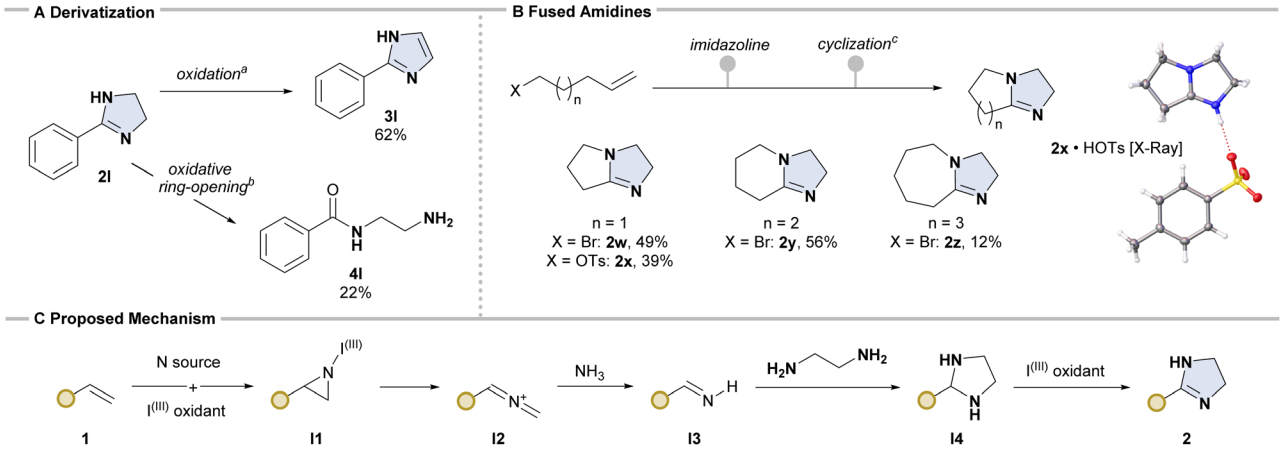


Fig. 4 (A) and (B) Scope diversification. The yields are given as isolated yields on 0.5 mmol scale. [a]Oxidation of 2-imidazoline **2l** to imidazole **3l**: K_2CO_3 (1.1 equiv.), PIDA (1.1 equiv.), DMSO (0.1 M), r.t., 48 h. [b]Oxidative ring-opening of 2-imidazoline **2l**: KOH (0.2 equiv.), *i*PrOH/H_2O (1/1, 0.25 M), 95 °C, 48 h. [c]Cyclization to fused amidines: aqueous 1 M NaOH (10 equiv.), DCM (0.1 M), r.t., 16 h. (C) Proposed mechanism of the reaction of alkenes to 2-imidazolines.

an alternative mechanism through attack of the diamine onto a nitrile intermediate could be ruled out, given the lack of reactivity of the latter under the reaction conditions, showing that it is not a chemically competent species.

Conclusions

In summary, we have developed a method for the direct conversion of unactivated alkenes into unsubstituted 2-imidazolines using commercially available reagents. The key to this reactivity is the successful trapping, by a diamine, of a short-lived imine species generated *in situ* from the reaction between an alkene and a combination of ammonia with a hypervalent iodine reagent. Given the operationally simple and rapid reaction, together with the broad functional group tolerance, we believe that this reaction will find immediate applicability in the synthesis of heterocyclic building blocks and the late-stage diversification of complex compounds.

Author contributions

S. S. and A.-S. K. P. conceived the project. S. S., A.-S. K. P., G. R. conducted the experimental work and analysed the data. B. M. supervised the research. S. S., A.-S. K. P., and B. M. wrote the manuscript with input from all authors.

Conflicts of interest

There are no conflicts to declare.

Data availability

CCDC 2529027–2529029 contain the supplementary crystallographic data for this paper.[31a–c]

Supplementary information (SI) is available. See DOI: https://doi.org/10.1039/d6sc03337g.

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