Oxidative amination of unactivated alkenes via nitrogen atom insertion into carbon-carbon double bonds

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Abstract: The synthesis of nitrogen-containing molecules through C–N bond formation is critical for the discovery and preparation of medicines, agrochemicals and materials. Traditional synthetic methods using alkenes as ubiquitous substrates leverage the reactivity of the C(sp^2)–C(sp^2) π bond for C–N bond formation. In contrast, methods that can form C–N bonds through complete cleavage of the double bond are scarce, despite the considerable synthetic potential of such a strategy. Here, we report the direct insertion of a nitrogen atom into unactivated carbon-carbon double bonds to access aza-allenium intermediates which can be converted either into nitriles or amidine products, depending on the initial alkene substitution pattern. This operationally simple and highly functional group tolerant reaction works on a wide range of unactivated alkenes. Our mechanistic proposal is supported by chemical trapping experiments, which concomitantly demonstrate the utility of our method to access valuable *N*-heterocycles. Overall, this study demonstrates the possibility to access reactive nitrogen-containing intermediates (i.e. aza-alleniums), which have ample potential for downstream diversification, from unactivated alkenes, opening new avenues for the discovery and preparation of important products.

One-Sentence Summary: Development of an oxidative amination reaction of unactivated alkenes *via* nitrogen atom insertion to access nitriles and amidines.

Main Text:

Nitrogen-containing molecules constitute one of the most important classes of compounds in the pharmaceutical, agrochemical and materials industries, with e.g. over 80% of recent top-selling drugs featuring at least one nitrogen atom.[1] Consequently, the construction of carbon–nitrogen bonds is a central research area in synthetic organic chemistry. Alkenes are key precursors to nitrogen-containing compounds, owing to their abundance in petrochemical feedstocks and naturally occurring terpenes,[2-5] as well as their ubiquity as synthetic intermediates. By leveraging the reactivity of the C(sp^2)–C(sp^2) π bond of alkenes, a plethora of synthetically useful reactions for the efficient introduction of nitrogen functional groups, including aziridination,[6,7] hydroamination,[8-14] or aminofunctionalization,[15,16] have been developed. In contrast, approaches to C–N bond construction that proceed through complete cleavage of the strong C(sp^2)–C(sp^2) double bond remain rare, despite the broad potential of such approaches to unlock new synthetic strategies (Fig. 1A). The synthetic appeal of such cleavage reactions is further highlighted by the synthetic utility of ozonolysis, one of the most important methods to cleave C(sp^2)–C(sp^2) double bonds in both industrial and academic settings (Fig. 1B).[17,18] Recent advancements in this area and related oxidative cleavage reactions, e.g. using photoexcited nitroarenes as active oxidants[19] as well as oxidative dealkenylation processes enabled by intermediate ozonolides,[20-22] have further advanced this field. Given the synthetic utility of these reactions and the synthetic relevance of nitrogen-containing compounds, the development of an alkene cleavage reaction directly leading to the formation of C–N bonds would likely become an invaluable tool for organic synthesis. However, the scarce previous reports of this reactivity are generally limited to the use of privileged alkenes, such as styrenes, leading to benzonitriles[23-25] and anilines,[26,27] or conjugate dienes, leading to cinnamonitriles[28] that are all readily accessible by other methods, thereby limiting the overall synthetic utility of these methods. Very recently, Gandelman and co-workers reported an aza-variant of the ozonolysis reaction that proceeds through an analogous mechanism involving a [3+2]-cycloaddition between an *in-situ* generated nitrenium species (from oxidation of a diaryltriazene) and an alkene.[29] While elegant in its design, this methodology is still limited in alkene scope and accessible nitrogen substituents. The limitations of current methods for oxidative amination of alkenes through C–C cleavage thus call for the design of mechanistically distinct manifolds that allow for the direct formation of useful nitrogen containing products, ideally under user-friendly reaction conditions.

A conceptually distinct strategy could involve the generation of an aziridine intermediate which, upon further oxidation, could undergo an electrocyclic rearrangement to generate an aza-allenium intermediate, leading to the insertion of a single nitrogen atom into a carbon-carbon double bond. Brown and Levin showed that aza-allenium osmium complexes can be accessed through nitrogen atom insertion of an osmium nitride complex into activated alkenes.[30-32] In contrast, free aza-alleniums could be synthesized and characterized by Würthwein.[33] More relevant to our design are the reports from Gassman proposing free aza-alleniums as intermediates in the solvolysis of *N*–Cl aziridine species[34] (Fig. 1C) and in the anodic oxidative ring opening of *N*–H aziridines.[35] Furthermore, an analogous carbon insertion has been successfully developed by Suero and coworkers by leveraging a hypervalent iodine diazoacetate as a carbyne equivalent to trigger a cyclopropanation-electrocyclic opening sequence to access a wide range of insertion products.[36] Inspired by these literature precedents, we envisaged that a strategy involving the *in-situ* formation of a *N*–LG aziridine (LG = leaving group), followed by ring-opening, would likely trigger the formation of a transient aza-allenium intermediate that could subsequently be intercepted by a suitable nucleophile, such as ammonia (Fig. 1D).

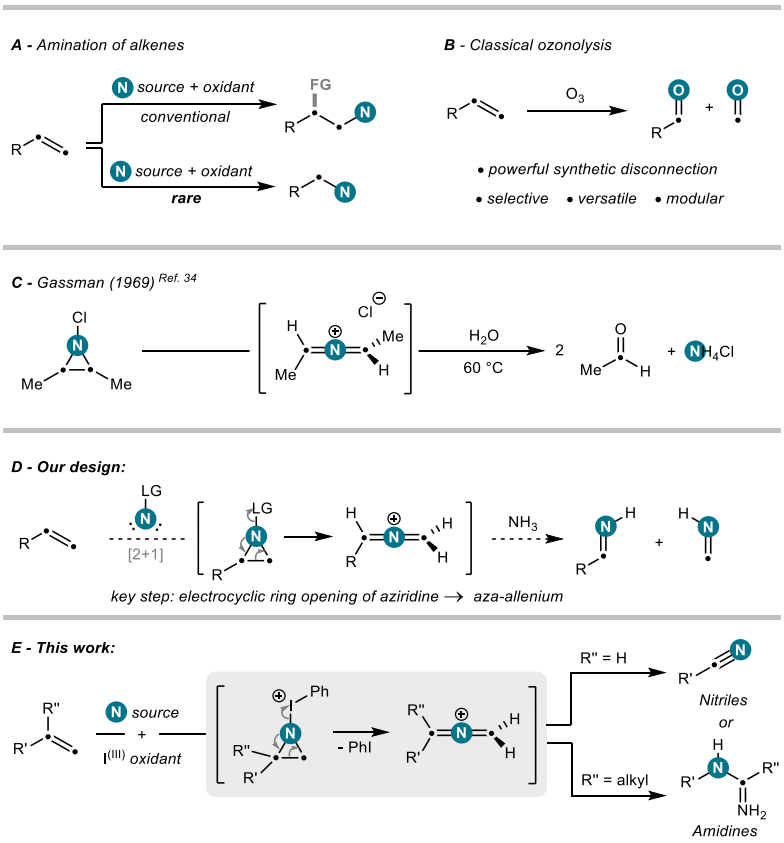

Figure 1: Context of this work. (**A**) Classical *versus* rare approaches to C–N bond construction using alkenes. (**B**) Ozonolysis of unactivated alkenes. (**C**) *N*-Chloro aziridines as precursors for transient aza-allenium salt generation. (**D**) Design of a nitrene synthon for nitrogen atom insertion into unactivated alkenes. **(E)** Development of an oxidative amination analogous to ozonolysis *via* transient aza-allenium formation.

Cleavage of the resulting hemi-aminal and further oxidation would then lead to the formation of nitriles, constituting overall a direct oxidative amination of alkenes. Such a transformation would be an important addition to the toolbox of organic chemists, enabling novel synthetic routes that previously relied on multi-step protocols.[37-39]

Here we report the successful development and application of this strategy. A wide range of terminal and internal alkenes, including cyclic substrates, formed the corresponding nitriles in high yields with excellent functional group tolerance. Additionally, we serendipitously discovered that 1,1-disubstituted alkenes undergo an additional aza-Beckmann rearrangement with exclusive regioselectivity and excellent stereoretention, resulting in a rare dealkenylative amination process delivering amidine products. Finally, preliminary chemical trapping experiments support the proposed mechanism and allowed us to access a diverse range of *N*-heterocycles.

At the outset of this project, we identified several key challenges associated with our reaction design: 1) low inherent reactivity of unactivated alkenes; 2) premature quenching of the proposed aza-alleniums with the solvent; 3) challenge to orchestrate and control a complex multistep sequence. We focused our attention on the generation of synthetic equivalents to iodonitrene species, which have previously been proposed as intermediates in nitrogen insertion chemistry,

using mixtures of ammonia and hypervalent iodine reagents.[40-43] A benefit of this approach is that the ratio of ammonia to hypervalent iodine reagent can be varied, offering a handle to tune the rate of the different elementary steps of our proposed mechanism. However, a major challenge to overcome is the lack of reactivity of these reactants towards unactivated alkenes, as these were unreactive and even served as spectator functional groups in previous reports.[40,41] Consistent with this hypothesis, a mixture of PIFA, a commercially available hypervalent iodine source, with ammonium carbamate as the source of nitrogen, did not lead to any observable reaction with 1-decene as a model substrate in methanol. Inspired by a literature precedent, highlighting the increased reactivity of hypervalent iodine reagents in fluorinated and hydrogen bond donating solvents[44] as well as the expected increased stability of aza-allenium (E = -3.7 on Mayr scale)[45] in poorly nucleophilic solvents, we next explored trifluoroethanol (TFE) and hexafluoroisopropanol (HFIP) (N_{TFE} = 1.1, N_{HFIP} = -1.9 on Mayr scale).[46] Gratifyingly, these solvents enabled the full conversion of the starting material to the expected nitrile product. With further optimization of the reaction conditions, we found that reducing the reaction time to 30 min alongside using an excess of the hypervalent iodine oxidant and ammonium carbamate gave almost quantitative yield of the desired nonanitrile product (**1a**). With these optimized reaction conditions in hand, we sought to explore the functional group tolerance of this transformation (see Figure 2 for the scope of linear alkenes).

We found that symmetric internal alkenes **2** and **3** quantitatively furnished two equivalents of the oxidative cleavage product, regardless of the stereochemistry of the alkene. When we subjected alkynes **4** and **5** to these reaction conditions, we also found the corresponding nitrile products, although in low yield. This result is worth highlighting since the oxidative cleavage of alkynes to nitriles under metal-free conditions has thus far only been accomplished for activated, conjugate alkynes.[47,48] Next, we investigated ester **6** and alcohol **7**, both of which cleanly afforded the nitrile product. Subsequently, we examined halogenated alkenes **8**-**10**, since for such substrates cyanation using nucleophilic substitution strategies is more challenging. Under our conditions, they readily reacted to the corresponding nitriles. We found that unprotected amines are not tolerated under our conditions, however Boc-protected amines **11** and **12** reacted smoothly. We also found that sufficiently electron-deficient heterocycles are tolerated, as **13** gave the product in high yield. We were also pleased to see that substrate **14**, constituting a more sterically hindered alkene, reacted in close to quantitative yield to the corresponding nitrile. Furthermore, substrates containing an oxetane ring (**15**), phthalimide (**16**), acetamide (**18**) and epoxide ring (**19**) as well as citronellol (**17**) all reacted smoothly. Next, we investigated whether our reaction was amenable to more complex molecules. Alkenyl ester **20** derived from cholic acid gave quantitative yield and so did (-)-methyl jasmonate (**21**) with full retention of stereochemical information. Methyl oleate (**22**), a common and inexpensive renewable feedstock, as well as piperine (**23**), a naturally occurring conjugated diene, also reacted under our conditions to give both oxidative cleavage fragments in moderate yield, respectively. Cyclohexene (**24**) yielded industrially relevant adiponitrile in quantitative yield. We further demonstrated a Thorpe-Ziegler reaction using stoichiometric amounts of KO^{t}Bu as a base, allowing for the aminative ring contraction of cyclohexene in two steps.

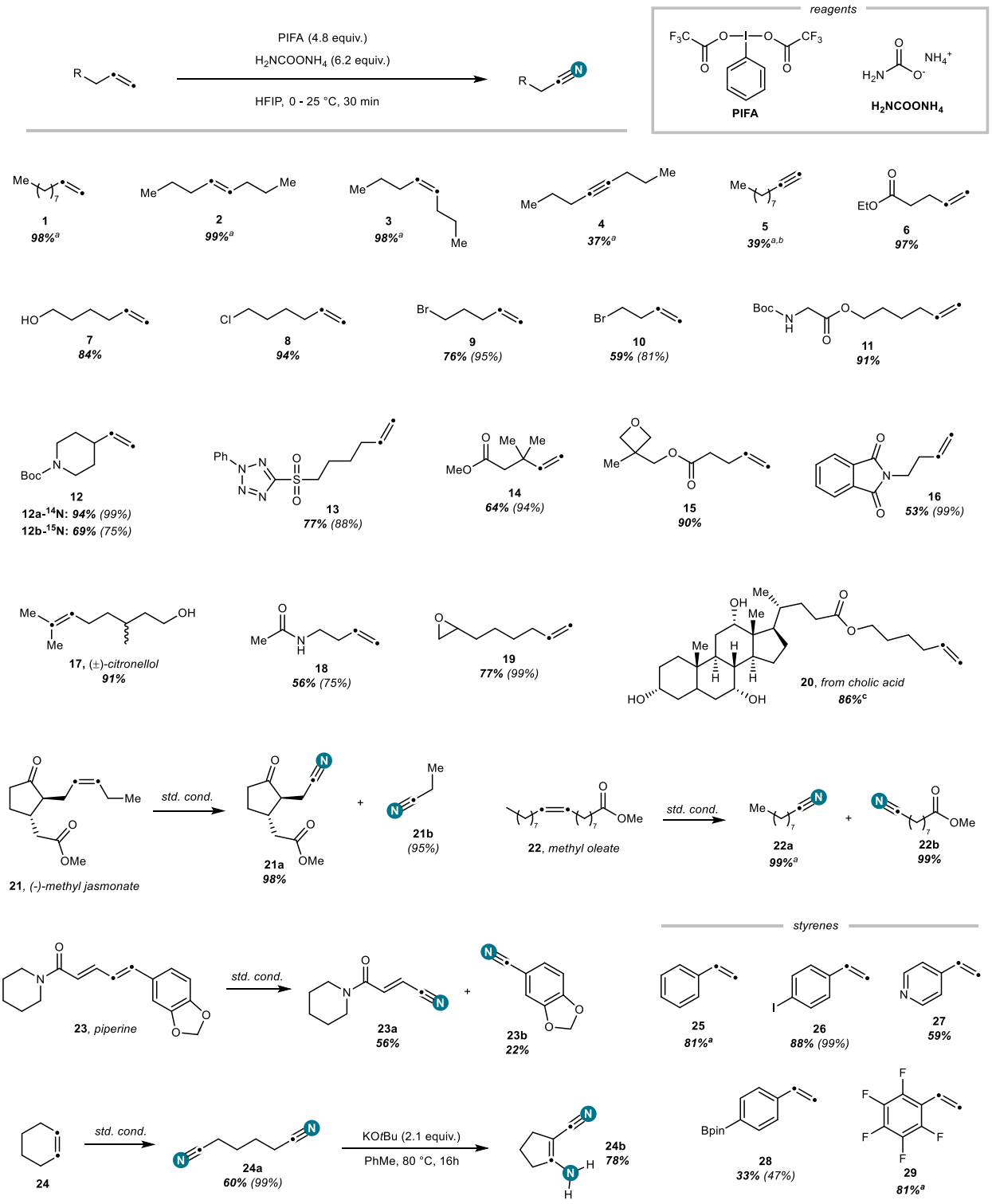

Figure 2: Scope of the oxidative cleavage of linear alkenes. All reactions were performed without exclusion of air or moisture. The yields are given as isolated yields on 1.0 mmol scale (In brackets: NMR yield on 0.1 mmol scale, using dibromomethane as internal standard). [a]GC yield (0.1 mmol scale; using *n*-dodecane as internal standard). [b]3.8 equiv. of PIFA and 5.2 equiv. of $H_2NCOONH_4$ were used. [c]Reaction was performed on 0.5 mmol scale.

Finally, selected styrene derivatives, including styrene (**25**), 4-iodostyrene (**26**), 4-vinylpyridine (**27**), 4-vinylpinacol boronic ester (**28**) and a perfluorinated styrene derivative (**29**), were successfully transformed under the optimized reaction conditions.

Next, the reactivity of branched alkenes was investigated (see Figure 3 for the scope of 1,1-disubstituted alkenes). Interestingly, when 2-methylundec-1-ene (**32**) was subjected to our reaction conditions, we observed complete conversion of the starting material to *N*-nonylacetimidamide as the sole product in 88% NMR yield (0.10 mmol scale). No constitutional isomers were detected, indicating an exclusively regioselective C–N bond formation process. The direct conversion of branched alkenes to acetimidamides involves a net C(sp^3)–C(sp^2) σ bond activation and therefore constitutes a rare example of an aminodealkenylation reaction.[20] Subjecting methylene cyclohexane (**30**) to our conditions, NMR analysis of a reaction aliquot revealed full conversion to the cyclic amidine species **30a**. Yet, after aqueous work-up and flash column chromatography, caprolactam was found as the only product in 98% isolated yield. We therefore hypothesize that the cyclic amidine is fully hydrolyzed in the work-up and during column chromatography (stationary phase: SiO_2) to the corresponding lactam. It was found that this could be partially prevented by using different purification conditions (stationary phase: neutral Al_2O_3), yielding a mixture of cyclic amidine and lactam after purification. We were thus able to react methylene cyclopentane (**31**) in the same manner, yielding a mixture of 2-iminopiperidine and valerolactam in the process. This finding represents an aza-analogue to the classical Beckmann rearrangement[49] which is used on megaton scale annually by the chemical industry for the synthesis of caprolactam.[50] Next, the reactivity of α-methylstyrene (**34**), a by-product of the cumene process and therefore a widely available and inexpensive feedstock chemical, was investigated under the reaction conditions. The use of trifluoroethanol (TFE) as the solvent was key to prevent undesired polymerization in this case, furnishing the desired *N*-phenylacetimidamide product in high yield. This is an interesting example of feedstock valorization, as the corresponding *N*-phenylamidine products are important heterocycle precursors for the synthesis of indoles, imidazoles and pyrimidines.[51]

We next subjected inexpensive naturally occurring terpenes to our reaction conditions. To our delight, we observed dealkenylative amidine formation for a wide range of branched alkene containing terpenes. The C(sp^3)–C(sp^2) σ bond activation operates with exclusive regioselectivity and with excellent stereoretention for all chiral scope entries. While Kwon's three-step aminodealkenylation reaction provides excellent yields across various substrates, it often leads to epimerization at the carbon center involved in C–N bond formation, particularly in monocyclic terpenoids.[20] In contrast, our method consistently occurs with no detectable epimerization observed in all cases, indicating an efficient and stereoselective C–N bond formation process.

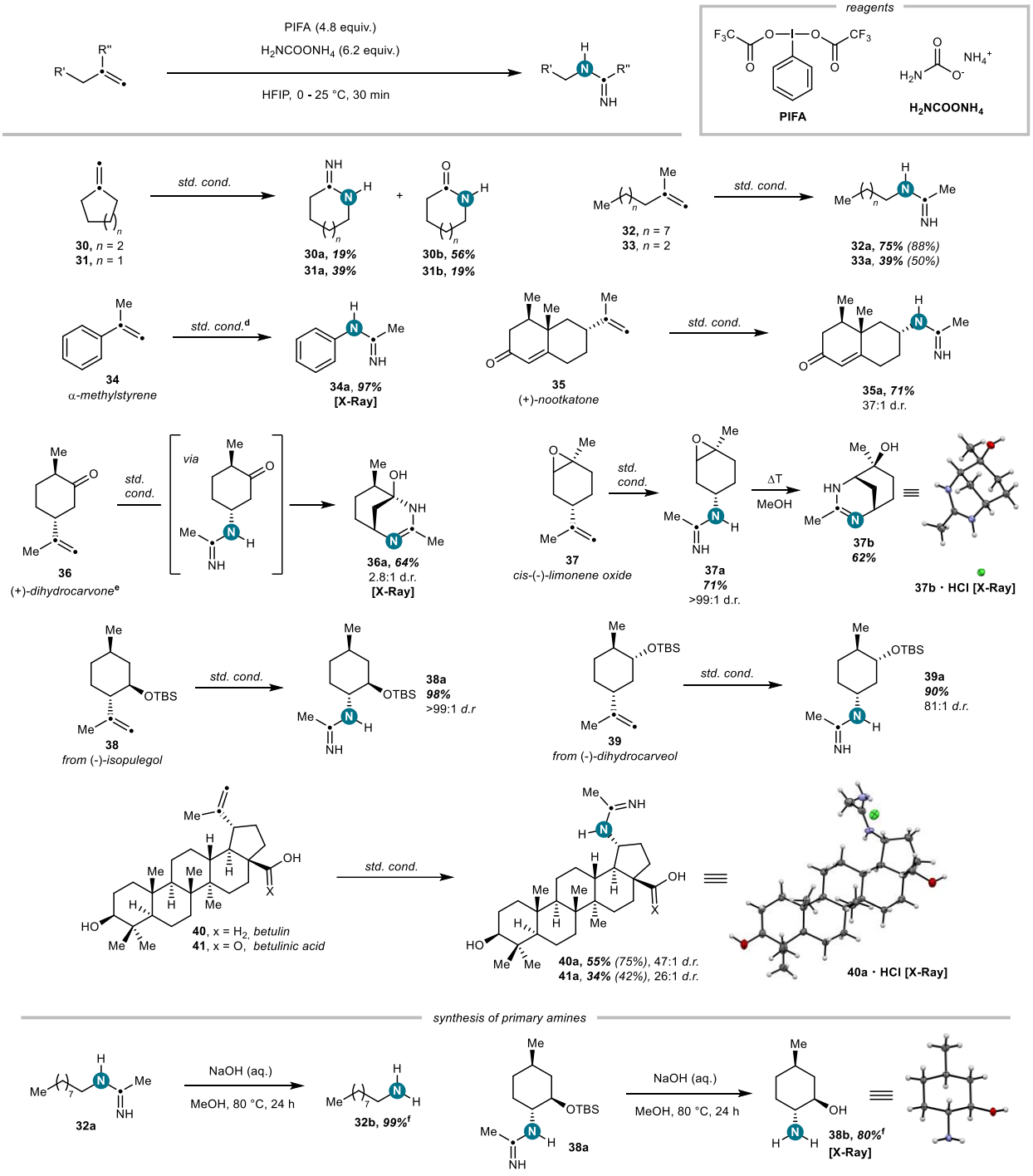

Figure 3: Scope of the oxidative cleavage of branched alkenes. All reactions were performed without exclusion of air or moisture. The yields are given as isolated yields on 1.0 mmol scale (In brackets: NMR yield on 0.1 mmol scale, using dibromomethane as internal standard). [d]TFE (0.1 M) was used instead of HFIP. [e]Commercial (+)-dihydrocarvone was used (mixture of 77% *n*-(+)-dihydrocarvone + 20% *iso*-(+)-dihydrocarvone). [f]NMR yield on 0.1 mmol scale, using mesitylene as internal standard. Single crystal X-Ray structures are depicted with ellipsoids at 50% probability (**37b, 38b**) and 30% probability (**40a·HCl**), respectively.

Examples include (+)-nootkatone (**35**), (+)-dihydrocarvone (**36**) and *cis*-(-)-limonene oxide (**37**), mirroring the functional group tolerance of the previous scope. (+)-Nootkatone is worth highlighting, since the formation of the corresponding amidine occurs with good selectivity over the more electron-deficient alkene. In addition, it was discovered that (+)-dihydrocarvone-derived amidine spontaneously cyclizes to **36a** and *cis*-(-)-limonene oxide-derived amidine was similarly found to undergo cyclization, but only at elevated temperatures. We then explored the reaction of TBS-protected (-)-isopulegol (**38**) and (-)-dihydrocarveol (**39**), both of which formed the corresponding amidines in excellent isolated yield. Subsequently, we demonstrated the utility of our methodology by reacting structurally complex betulin (**40**) and betulinic acid (**41**), both of which cleanly and exclusively reacted to the corresponding amidine products. Interestingly, contrary to cyclic amidines, hydrolysis of the terpene-derived amidine products was never observed. Lastly, the corresponding free amines can also readily be obtained using dilute aqueous NaOH solution under mild conditions. Our reaction conditions therefore enable the direct synthesis of unprotected amines from naturally occurring terpenes in a mild two-step reaction with excellent stereoretention, offering a rapid entry into highly valuable aminated building blocks.

In Figure 4, a preliminary mechanistic hypothesis for the reaction is presented. In accordance with previous literature,[40-43] we propose the *in-situ* formation of an electrophilic nitrogen species which engages in formal [2+1]-cycloaddition with the unactivated alkene **a**, furnishing activated aziridine species **b**. This species could then undergo a concerted electrocyclic ring-opening and dissociation of iodobenzene, forming aza-allenium salt **c** after the formal, direct insertion of a nitrogen atom into the C(sp^2)–C(sp^2) double bond of the starting material. The mass of intermediate **c** was detected *via* HRMS (see SI for details), supporting that this species could be an intermediate in the reaction. The intermediacy of aza-allenium was further supported by a trapping experiment using (-)-isopulegol (**42**) furnishing labile imine species **42a**, which we observed in the crude reaction mixture by NMR spectroscopy. This unstable species could successfully be hydrolyzed to **42b** or reduced to **42c** as a single diastereomer that was characterized by single crystal X-ray crystallography.

Following the formation of aza-allenium salt **c**, aminolysis by ammonia generates hemiaminal **d**, which can form imine species **e** after proton transfer and extrusion of methanimine. Imine **e** is proposed to coordinate to another equivalent of $I^{(III)}$ which causes an oxidation event to the corresponding nitrile **h** in the case of an aldimine. The intermediacy of an *N*-electrophilic imine intermediate **f** was supported by isolating the corresponding dihydropyrazole (**43a**) as a major product from reacting *N*-Boc protected aminobut-3-ene (**43**). When reacting 4-phenylbutene (**44**) under our conditions, we obtained nitrile product **44b** in 60% NMR yield, while also observing quinoline (**44a**) as the minor product in 20% NMR yield, formally following an intramolecular electrophilic aromatic substitution and oxidation sequence.[52] When reacting the α-methylated analogue (**45**), we observed exclusive formation of 2-methylquinoline (**45a**) in high yield. These combined results indicate that *N*-electrophilic imine species are likely key intermediates in the reaction.

In the case of a ketimine, the oxidation event is proposed to occur *via* a Beckmann rearrangement to nitrilium cation **i**. The nitrilium ion is trapped by excess ammonia, thus furnishing an amidine **j**.

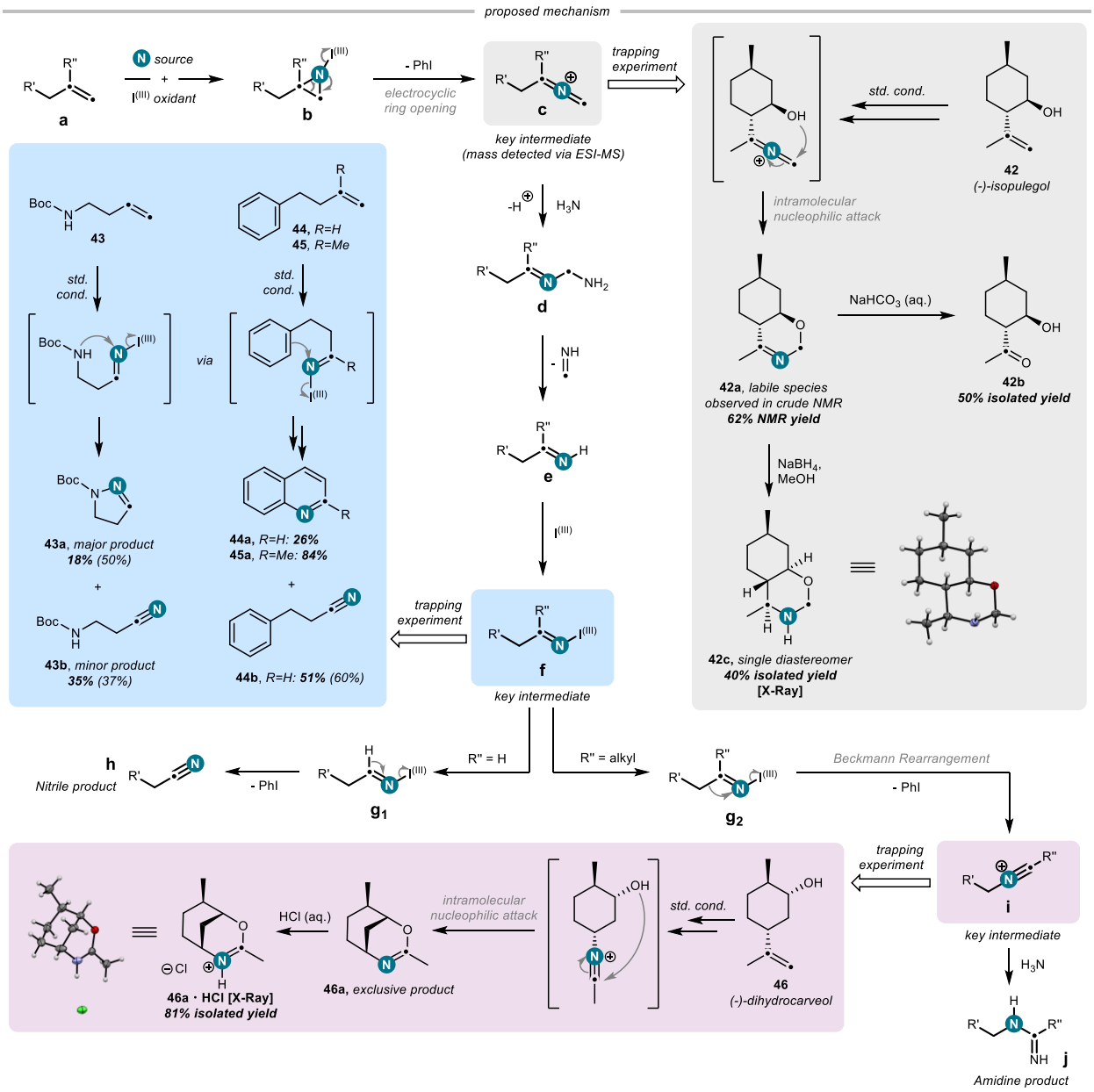

Figure 4: Preliminary mechanistic proposal for the oxidative amination of unactivated alkenes. All reactions were performed without exclusion of air or moisture. The yields are given as isolated yields on 1.0 mmol scale (In brackets: NMR yield on 0.1 mmol scale, using dibromomethane as internal standard). Single crystal X-Ray structures are depicted with ellipsoids at 50% probability.

When we subjected (-)-dihydrocarveol (**46**) to our reaction, which contains a branched alkene group adjacent to a secondary alcohol, we observed full conversion to an imidate product (**46a**) following an intramolecular trapping event of the nitrilium cation after the Beckmann rearrangement. Protonation using dilute aqueous acid allowed us to crystallize and characterize the hydrochloride salt.

Overall, the Beckmann rearrangement occurs with excellent retention of the stereochemical information and complete regioselectivity.

Besides their mechanistic value, the trapping experiments collectively demonstrate that our methodology can also be used for the direct synthesis of synthetically relevant *N*-heterocycles, such as 1,3-oxazinanes, *N*-substituted 4,5-dihydro-1*H*-pyrazoles or quinolines.

In summary, we have developed an oxidative amination reaction, in which linear alkenes are cleaved to nitriles and branched alkenes are transformed into amidines. We were able to support a mechanism involving nitrogen atom insertion into the C(sp^2)–C(sp^2) bond of unactivated alkenes, for the first time taking advantage of transient aza-allenium intermediates in a synthetically useful application. The reaction setup is operationally simple, requiring no exclusion of air or moisture and is tolerant of many functionalities. We demonstrated the utility of our reaction by valorizing several inexpensive naturally occurring terpenes and showed its applicability in the oxidative amination of complex targets. To probe our mechanistic proposal, we subjected several substrates to our reaction conditions, that contain various nucleophiles in proximity to the alkene in order to trap highly electrophilic intermediates intramolecularly. These experiments further demonstrate that this method can be used for the synthesis of various heterocycles *via* direct nitrogen atom incorporation. In a broader context, this study demonstrates that nitrogen insertion into alkenes can enable the formation of aza-allenium species as reactive nitrogen-containing intermediates with diverse synthetic utility and outstanding potential for downstream diversification, opening new avenues for the discovery and preparation of important nitrogen-containing products.

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Author contributions:

Y. B. conceived the project. Y. B., A.-S. K. P., N. N., B. B. B., F. F. conducted the experimental work and analyzed the data. B. M. supervised the research. Y. B. and B. M. wrote the manuscript with input from all authors.

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Supplementary Materials

Materials and Methods

Supplementary Text

Figs. 1 to 7