# Catalyst-Free Direct Olefin Halo-Hydroxylamination: Rapid Synthesis of Multifunctional Hydroxylamines (MFHAs) for Structurally Complex Amines and *N*-Heterocycles

Young-Do Kwon,[a] Daniel Joaquin,[a] Melany Carpio,[b] Muhammed Yousufuddin,[b] László Kürti*[a]

[a] Department of Chemistry, Rice University, Houston, Texas 77030, USA. [b] Department of Natural Sciences, University of North Texas at Dallas, Dallas, Texas 75241, USA.

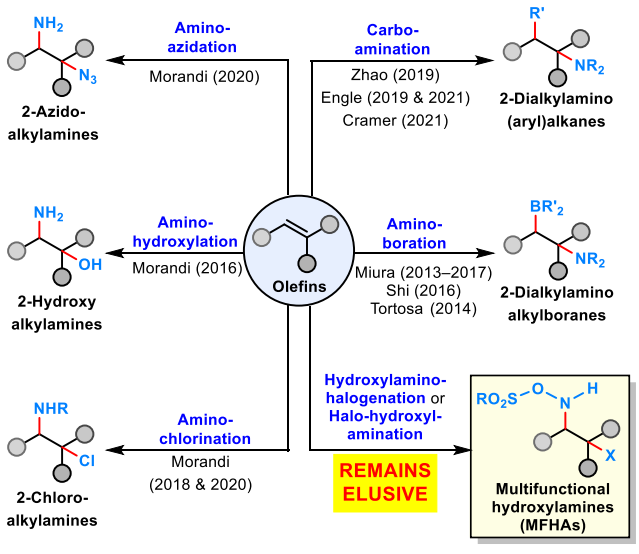
*Alkene 1,2-difunctionalization, olefin halo-hydroxylamination, N-haloalkyl O-activated hydroxylamines, multifunctional hydroxylamines, C–N bond formation, C(sp²)-H amination, olefin aziridination, N-unprotected amines, N-heterocycles.*

**ABSTRACT:** Herein, we introduce a novel and powerful alkene difunctionalization process where anomeric amides (e.g., *N*-halogenated *O*-activated hydroxylamines) react directly with olefins, without the use of catalysts or additives, to yield the corresponding *N*-haloalkyl *O*-activated hydroxylamines. These multifunctional hydroxylamines (MFHAs), containing both alkyl halide and *O*-activated hydroxylamine moieties, are convenient building blocks/electrophilic aminating reagents for the synthesis of structurally complex *N*-unprotected secondary amines and *N*-heterocycles. Both activated and unactivated alkenes (including cyclic and acyclic olefins, dienes, and enynes) are effectively converted to the corresponding difunctionalized hydroxylamine derivatives with excellent atom economy. The versatility of MFHAs was demonstrated through the synthesis of various nitrogen-containing molecules.

Amines and their derivatives are common in drug molecules and natural products, with cyclic amines often serving as key bioactive cores.[1] Designing new active pharmaceutical ingredients (APIs) requires balancing the desired biological activity with minimal toxicity (i.e., optimal drug-like properties), necessitating precise structural adjustments. *N*-Heterocycles are vital in this process, enhancing key drug-like properties. On average, the top 200 small molecule drugs contain 2.8 nitrogen atoms, with 80% including at least one *N*-heterocyclic fragment. About 60% of FDA-approved drugs feature at least one *N*-heterocycle, and 95% contain at least one nitrogen atom. Additionally, 45% of drug candidates have chiral amine moieties.[2] Consequently, organic chemists focus extensively on developing better strategies for synthesizing structurally complex amines, essential building blocks in biomedical research.[3]

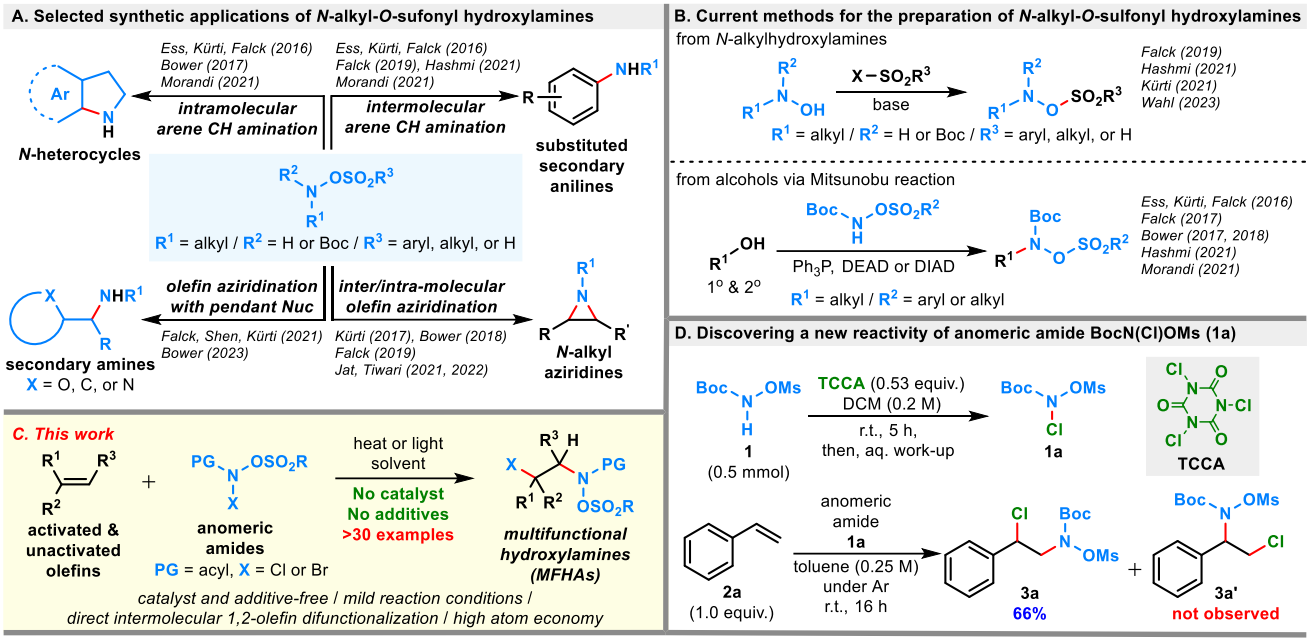
The vicinal difunctionalization of alkenes is a versatile tool for introducing up to two desired functional groups onto the C=C bond of target molecular scaffolds. The intermolecular aminative olefin difunctionalization is a key transformation for generating a C–N bond, while inserting additional functional groups of interest (e.g., halogens, hydroxyl groups, azido-, boron-, as well as alkyl/aryl moieties).[4] Significant efforts have been dedicated to aminohalogenation, which delivers a halogen atom and either protected or free amine groups onto an alkene.[5] However, *the catalyst-free direct intermolecular 1,2-halo-hydroxylamination (i.e., 1,2-hydroxylamino-halogenation) of alkenes remains elusive* (**Figure 1**). Such a direct 1,2-difunctionalization of olefins could produce structurally complex *multifunctional hydroxylamines (MFHAs)* in a single step using anomeric amides as reagents. Anomeric amides are *N,N*-di-activated amide derivatives, such as *N*-acyl-*N*-halo-*O*-sulfonyl hydroxylamines, where the nitrogen atom is doubly electrophilic due to the presence of two weak bonds (N–X and N–O). Along with incorporating the *O*-activated hydroxylamino moiety (i.e., *O*-sulfonyl hydroxylamine, which can be used for C–H aminations and/or olefin aziridinations[6]), a halogen atom would also be inserted onto the C=C π-bond of olefin substrates under mild and catalyst-free reaction conditions, providing an additional functional handle. The MFHAs could then be utilized in various transition metal-catalyzed cross-electrophile and cross-electrophile-nucleophile couplings,[7] followed by diverse cyclization reactions (i.e., arene C–H amination, Friedel–Crafts reaction and enolate α-amination) to access structurally complex *N*-heterocycles.

**Figure 1. Overview of key intermolecular aminative olefin difunctionalizations. The elusive 1,2-halo-hydroxylamination.**




*O*-Activated (i.e., *O*-acylated, *O*-sulfonylated and *O*-arylated) hydroxylamines are widely used both as electrophilic aminating reagents and building blocks to forge C–N bonds by exploiting their weak N–O bonds [i.e., C(sp³)–H or C(sp²)–H amination and olefin aziridination].[6,8]

**Figure 2. Synthetic routes to prepare *N*-alkyl-*N*-protected-*O*-sulfonyl hydroxylamines and their applications.**




For example, *N*-alkyl-*O*-sulfonyl hydroxylamines have been successfully employed for the synthesis of secondary anilines and arene-fused *N*-heterocycles via inter/intra-molecular arene C($sp^2$)–H amination reactions and for the preparation of *N*-alkyl aziridines via nitrenoid insertion into C=C bonds (**Figure 2A**).[6]

Currently, the preparation of *N*-protected-*N*-alkyl-*O*-sulfonyl hydroxylamines can be achieved via the *O*-sulfonylation of *N*-acylated-*N*-alkyl hydroxylamines (**Figure 2B**).[6] The required *N*-alkyl hydroxylamines can be primarily prepared by the partial reduction of oximes and aliphatic nitro compounds as well as via the careful oxidation of primary and secondary amines.[9] Alternatively, the *N*-alkylation of *N*-protected-*O*-sulfonyl hydroxylamines is possible using 1° and 2° alcohols via the Mitsunobu reaction (**Figure 2B**).[6]

Since transition metal complexes can readily cleave N–O bonds in *O*-activated hydroxylamines, it is crucial to avoid using even catalytic amounts of metal complexes during their preparation. Thus, our goal was to develop a catalyst-free direct intermolecular 1,2-olefin difunctionalization method that produces *multifunctional hydroxylamines (MFHAs)* in a single step, while preserving the N–O bond. We envisioned that readily available *O*-activated hydroxylamines (such as *N*-Boc-*O*-Ms hydroxylamine) could be further activated by replacing the N–H bond with an N–halogen (i.e., N–Cl or N–Br) bond. The resulting *N*-halogenated species, containing multiple weak bonds, was expected to react directly with the C=C π-bond of alkenes. This 1,2-addition process would then generate the corresponding *N*-haloalkyl-*O*-activated hydroxyl-amines (MFHAs; **Figure 2C**). To test our hypothesis, *N*-Boc-*O*-Ms hydroxylamine was reacted with trichloroisocyanuric acid (TCCA) at room temperature over a period of 5 hours (**Figure 2D**). After a quick aqueous work-up, the anticipated *N*-Cl-*N*-Boc-*O*-Ms hydroxylamine (**1a**) was isolated as an NMR-pure white solid. Next, anomeric amide **1a** was mixed with styrene **2a** and the reaction mixture was allowed to stir at room temperature overnight. Following a reductive aqueous workup with 10 wt% $Na_2SO_3$ in water, the crude material was purified by flash column chromatography, resulting in a 66% isolated yield of MFHA product **3a** as a single regioisomer.

We decided to comprehensively optimize the reaction conditions, including solvent, temperature, and concentration, to improve the isolated yield and shorten the overall reaction time. We observed that anomeric amide **1a** fully decomposes in solution over 24 hours at room temperature. To achieve the best olefin difunctionalization outcomes, we found that it was ideal to use **1a** within 1 hour of preparation.

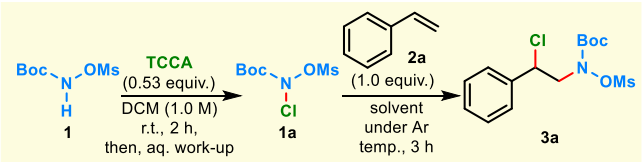
We determined that the *N*-chlorination of *O*-activated hydroxylamine **1** was complete in only 2 hours when the *N*-chlorination reaction was performed at a higher concentration (1.0 M vs 0.2 M). After workup and solvent removal, the NMR pure **1a** was dissolved in toluene ($c$ = 0.25 M), and styrene **2a** was added – next, the reaction mixture was heated to 50 °C and stirred at this temperature until the full consumption of **1a** (ca. 3 hours). After concentration and column chromatography, the pure MFHA (**3a**) was isolated in 76% isolated yield (Entry 1, **Table 1**). Over a dozen solvents were screened, while all other reaction parameters were kept unchanged (entries 2–6, **Table 1**, and **Table S1**, ESI). Halogenated solvents (i.e., 1,2-dichloroethane, chloroform, dichloromethane; entries 4–6, **Table 1**) led to high product isolated yields (up to 83%). Overall, dichloromethane provided the best outcome.

Next, we evaluated the effects of various reaction temperatures, concentrations, and atmospheres (argon and nitrogen versus air). Dichloromethane proved to be the most successful solvent, despite refluxing at a lower temperature than the standard 50 ºC used for testing other solvents. Surprisingly, MFHA **3a** was obtained with the high isolated yield of 79% even at room temperature compared

to reflux conditions (83% of **3a**; entries 6 & 7, **Table 1**). Higher reaction concentrations (0.5 M versus 0.25 M and 0.1 M) resulted in increased isolated yields of **3a** (entries 7–9, **Table 1**). Performing the reaction under air, as opposed to under argon or nitrogen atmospheres, significantly reduced product formation (84% to 30% of **3a**; entry 9 versus entry 10, **Table 1**).

When the anomeric amide **1a** was used for the difunctionalization of **2a** without an aqueous workup, MFHA **3a** was obtained with a poor isolated yield (84% to 22%; **Table S2**, ESI). Additionally, performing *N*-chlorination of **1** in the presence of **2a** resulted in a very low yield of MFHA **3a** (**Table S2**, ESI). In summary, the optimized reaction conditions involve using equimolar quantities of **2a** and freshly prepared anomeric amide [MsON(Cl)Boc, **1a**] in dichloromethane (c = 0.5 M) stirred at room temperature for 3 hours (referred to hereafter as ***General Procedure I.***).

**Table 1. Selected Optimization of Reaction Conditions for olefin difunctionalization using *N*-Cl-*N*-Boc-*O*-Ms hydroxylamine[a,b]**



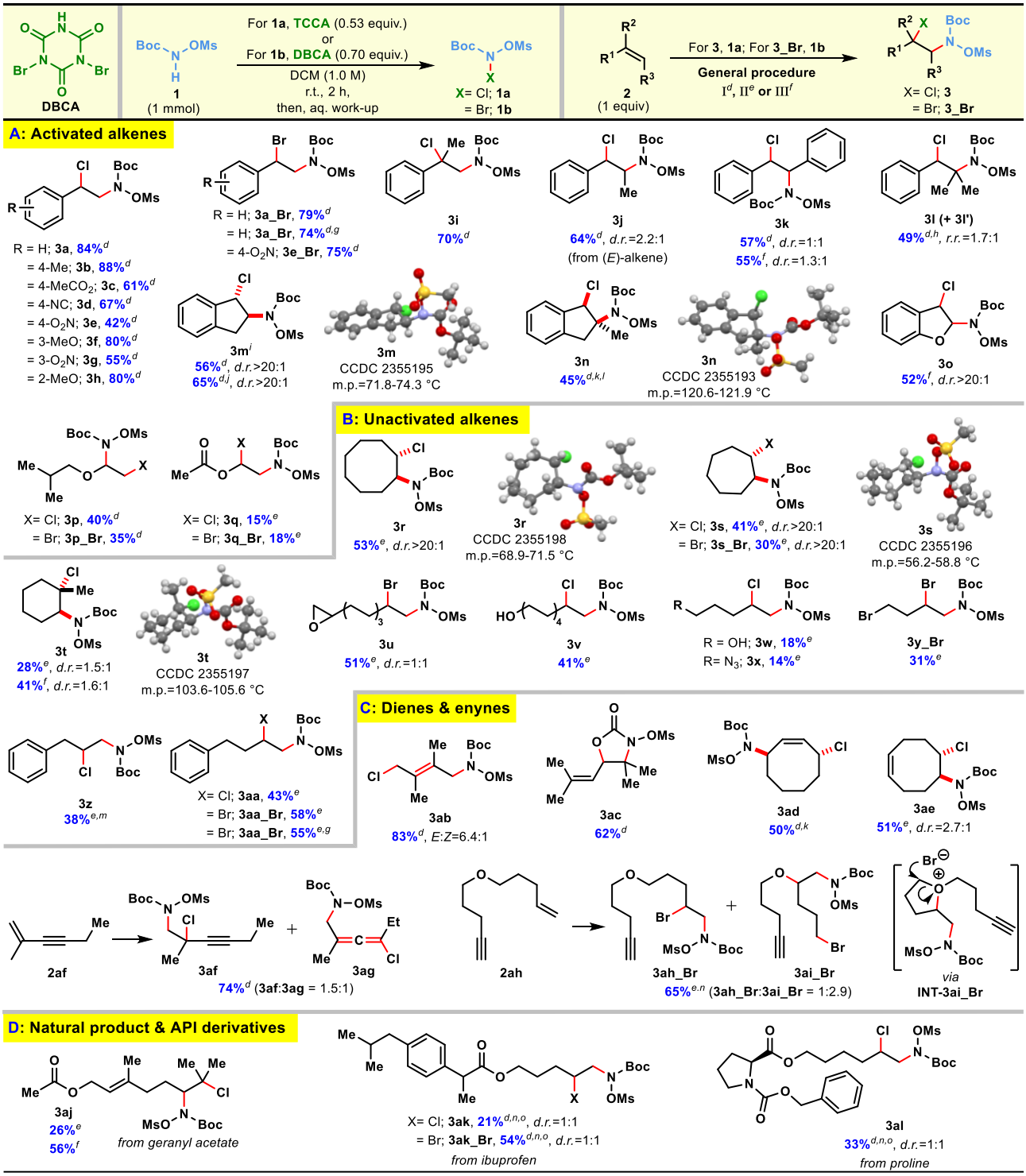

| Entry | Solvent[c] | Temperature (°C) | Yield (%)[d] 3a |
|---|---|---|---|
| 1 | Toluene (0.25 M) | 50 | 76 |
| 2 | DMF (0.25 M) | 50 | 51 |
| 3 | Acetonitrile (0.25 M) | 50 | 81 |
| 4 | 1,2-DCE (0.25 M) | 50 | 77 |
| 5 | Chloroform (0.25 M) | 50 | 80 |
| 6 | DCM (0.25 M) | reflux | 83 |
| 7 | DCM (0.25 M) | r.t. | 79 |
| 8[e] | DCM (0.10 M) | r.t. | 72 |
| **9[f]** | **DCM (0.5 M)** | **r.t.** | **84** |
| 10[g] | DCM (0.25 M; air) | r.t. | 30 |

[a]Reaction scale: 1.0 mmol. [b]*N*-Cl-*N*-Boc-*O*-Ms hydroxylamine was freshly prepared for each entry. [c]0.25 M reaction concentration. [d]Isolated yields after purification. [e]0.1 M reaction concentration instead of 0.25 M. [f]0.5 M reaction concentration instead of 0.25 M. [g]under air instead of argon.

With the optimized reaction conditions in hand (i.e., ***General Procedure I.***), the scope of substrates was explored (**Table 2**). Simple unsubstituted styrene **2a** and electron-rich styrenes (**2b**, **2f** & **2h**) furnished the corresponding MFHAs (**3a**, **3b**, **3f**, and **3h**) in 80–88% isolated yields (**Table 2A**). Styrenes containing electron-withdrawing groups (i.e., cyano **2d**, nitro **2e** & **2g**, ester **2c**) afforded the corresponding MFHAs (**3c**–**3e** and **3g**) in 42–67% isolated yields. α-Methylstyrene furnished a single MFHA regioisomer (**3i**) with a 70% isolated yield. However, trans-β-methylstyrene produced two separable MFHA diastereomers (**3j**) in a 2.2:1 ratio, resulting in a combined 64% isolated yield. Two regioisomers (**3l** & **3l'**) were isolated from β,β-dimethyl styrene **2l**. Indene **2m** afforded a single MFHA diastereomer (**3m**) as observed by the NMR of the crude reaction mixture (**Table 2A**). After column purification on silica gel, **3m** was isolated in 56% yield along with an unexpected cyclic product (**37**) that featured the *N*-methanesulfonylhydroxy-2-oxazolidone scaffold (**Table 2C**; See ESI for details). MFHA **3n** was produced from 2-methyl indene **2n** in a moderate yield, and its stereochemistry and regiochemistry were determined by SCXRD. It is important to note that vinyl ether **2p** produced MFHA **3p** with a 40% isolated yield, but with *opposite regioselectivity* compared to all other terminal olefins (**Table 2A**).

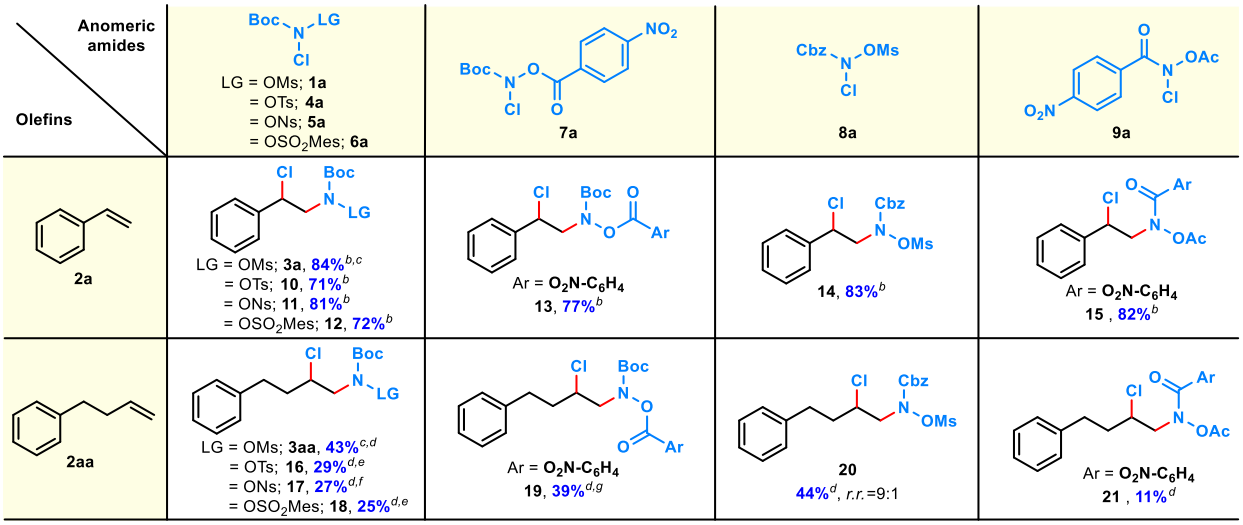
We also investigated both cyclic and acyclic unactivated alkenes as part of the scope of substrates (**Table 2B**). Under the optimized reaction conditions (i.e., ***General Procedure I.***), *cis*-cyclooctene **2r** gave a poor yield (23%) of the 1,2-difuntionalized product **3r**. Thus, further adjustment of the reaction conditions was performed on this substrate (See ESI for details). As a result, for unactivated alkenes, the brand new reaction conditions include equimolar quantities of the olefin substrate and freshly prepared anomeric amide (i.e., [MsON(Cl)Boc, **1a**]) at 60 °C (instead of room temperature) in chloroform (instead of dichloromethane; c = 0.5 M) over 3 hours (referred to hereafter as ***General Procedure II.***). Unlike the reaction of **1a** with isobutyl vinyl ether, vinyl acetate required a higher reaction temperature (60 °C versus room temperature) to produce MFHA **3q** in 15% isolated yield (**Table 2A**). The eight-membered cyclic hydroxylamine (**3r**) was synthesized with these newly optimized reaction conditions in 53% isolated yield (**Table 2B**). Other cyclic alkenes also participated in alkene 1,2-difunctionalization with anomeric amide reagent **1a**. For example, cycloheptene provided only product **3s** with a >20:1 d.r., while 1-methylcyclohexene **2t** afforded product **3t** in a 1.6:1 d.r. The relative stereochemistry of compounds **3r**, **3s** and **3t** was confirmed by SCXRD. The alkene bearing the unprotected primary alcohol moiety (**2v**) gave rise to the corresponding MFHA product (**3v**) in 41% isolated yield. When 5-penten-1-ol **2w**, capable of undergoing intramolecular etherification with its pendant primary alcohol group, was used as the substrate, only the linear alkene addition product **3w** was obtained. The azido group ($-N_3$) was compatible with the mild reaction conditions for synthesizing MFHA, resulting in the preparation of compound **3x** from 5-azido-1-pentene **2x** (**Table 2B**). MFHA products **3z** and **3aa** were obtained with moderate isolated yields (38% to 43%) from the corresponding unactivated terminal olefins (**Table 2B**). Several conjugated dienes were also difunctionalized with **1a**. 2,3-Dimethylbuta-1,3-diene **2ab** and 1,3-cyclooctadiene **2ad** afforded 1,4-addition products **3ab** and **3ad**, with isolated yields of 83% and 50%, respectively (**Table 2C**).

**Table 2. Substrate scope for alkene difunctionalization with *N*-chloro-*N*-Boc-*O*-(methanesulfonyl)hydroxylamine.**[a,b,c]




[a]Reaction scale: 1.0 mmol, unless otherwise noted. [b]All yields are isolated yields after column purification. [c]Anomeric amides **1a** and **1b** were prepared freshly for each reaction. [d]***General Procedure I***: **1a** or **1b**, alkene (1.0 equiv.), dichloromethane, r.t., 3 h, under argon. [e]***General Procedure II***: **1a** or **1b**, alkene (1.0 equiv.), chloroform, 60 °C, 3 h, under argon. [f]***General Procedure III***: **1a** or **1b**, alkene (1.0 equiv.), dichloromethane, r.t., 1 h, under argon and 365 nm light. [g]5.0 mmol scale. [h]14 hours of reaction time. [i]2-Oxazolidone-derived side product was isolated. See ESI for the details. [j]5.2 mmol scale. [k]2.0 mmol scale. [l]Two other products were observed. [m]3.0 equiv. of alkene. [n]0.5 mmol scale. [o]6 Hours of reaction time.

**Table 3. Studies on alkene difunctionalization with various *N*-Cl-*N*-protected-*O*-activated hydroxylamine.[a]**




[a]Reaction scale: 1.0 mmol; All yields are isolated yields after column purification; Anomeric amide reagents **1a** and **4a–9a** were prepared freshly for each reaction. [b]***General Procedure I***: anomeric amide reagent, alkene (1.0 equiv.), dichloromethane, r.t., 3 h, under argon. [c]The yield is from Table 2. [d]***General Procedure II***: anomeric amide reagent, alkene (1.0 equiv.), chloroform, 60 °C, 3 h, under argon. [e]9 hours of reaction time. [f]8 hours of reaction time. [g]18 hours of reaction time.

The reaction of 2,5-dimethylhexa-2,4-diene **2ac** with **1a** led to the formation of the corresponding *N*-methanesulfonylhydroxy-2-oxazolidone **3ac** in 62% isolated yield (**Table 2C**). Product **3ae** was synthesized from cycloocta-1,5-diene **2ae** in 51% isolated yield with a 2.7:1 d.r. The reaction of 2-methylhex-1-en-3-yne (**2af**, conjugated enyne) with reagent **1a** gave 1,2-addition product **3af** as well as a 1,4-addition product **3ag** containing an allene moiety.

Anomeric amide reagent **1a** was regioselectively incorporated into one of the C=C π-bonds of geranyl acetate **2aj** to afford MFHA product **3aj**. Two other olefins, an ibuprofen derivative **2ak** and a *N*-Cbz-protected proline derivative **2al** were also successfully difunctionalized with **1a,** affording MFHA products **3ak** and **3al** in 21% and 33% isolated yields, respectively. Neither *trans*-stilbene **2k** nor benzofuran **2o** reacted with **1a** under the reaction conditions of ***General Procedure I***. However, under the reaction conditions of ***General Procedure II*** (i.e., at 60 °C) **2k** was converted to MFHA **3k** in 57% isolated yield, while **2o** remained unreactive. At this juncture we decided to explore the 1,2-difunctionalization process under photochemical conditions (e.g., 365 nm blue light at room temperature in DCM solvent for 1 h, ***General Procedure III***) with olefins **2k** and **2o** that were both unreactive under ***General Procedure I.*** To our delight, the corresponding MFHAs, **3k** and **3o**, were successfully obtained using a Penn Photoreactor M2.

***General Procedure III*** significantly improved the efficiency of the 1,2-difunctionalization reaction for several olefins that previously yielded corresponding MFHAs poorly under the other two conditions. Notably, we observed an increase in the yields of products **3t** (from 28% to 41%) and **3aj** (from 26% to 56%) starting from 1-methylcyclohexene **2t** and geranyl acetate **2aj**, respectively.

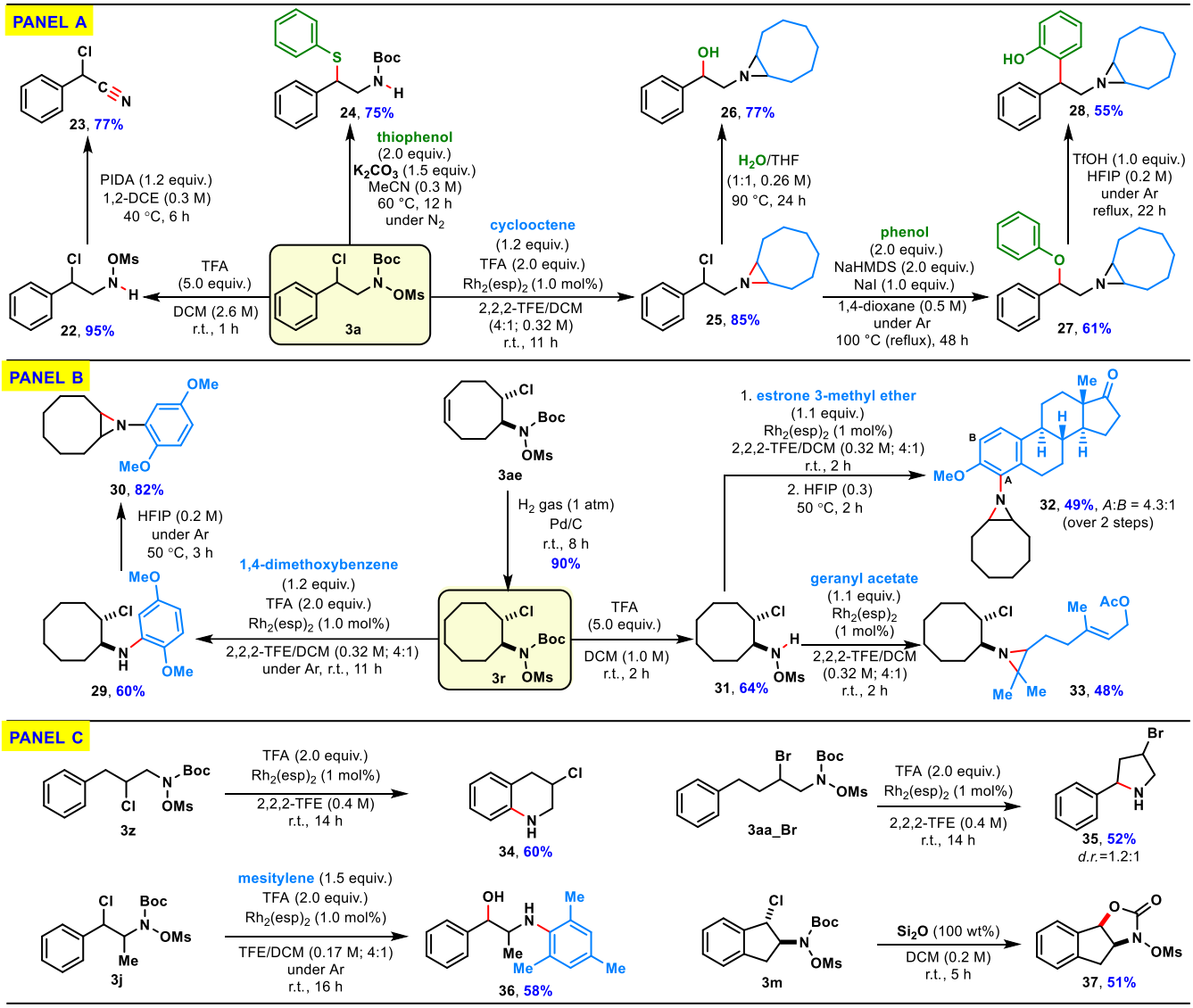
Another halogen, specifically bromine (Br) instead of chlorine (Cl), was also evaluated for the difunctionalization of alkenes (**Table 2**). Various alkenes, including styrenes, aliphatic cyclic and linear alkenes, and an enyne, were subjected to bromo-hydroxylamination using anomeric amide BocN(Br)OMs **1b**. This reagent was freshly prepared by reacting BocNHOMs **1** with dibromoisocyanuric acid (DBCA) in dichloromethane. The reaction of styrene **2a** with reagent **1b** under the conditions of ***General Procedure I*** resulted in the isolation of MFHA **3a_Br** with a 79% yield. When 4-nitrostyrene **2e** was reacted with **1b**, the corresponding bromo-hydroxylaminated product **3e_Br** was obtained in a 75% isolated yield. This represents a significant yield increase (from 42% with Cl to 75% with Br) compared to the reaction of **2e** with **1a**.

Interestingly, the reaction of **1b** with isopropyl vinyl ether **2p** using the conditions of *General Procedure I* yielded MFHA **3p_Br** with the same *reversed regiochemistry* observed in product **3p**.

We also found that a terminal olefin substrate with a pendent terminal epoxide functionality (**2u**) furnished the corresponding MFHA **3u_Br** in 51% isolated yield and demonstrated the functional group tolerance of an epoxide under the conditions of ***General Procedure II***. MFHAs **3y_Br** and **3aa_Br** were also prepared from the corresponding terminal alkenes **2y** & **2aa**, respectively.

The 1,2-difunctionalization of enyne **2ah** with **1b**, following *General Procedure II*, produced the expected MFHA product **3ah_Br**. Additionally, a skeletally rearranged product (**3ai_Br**) was formed, likely due to neighboring group participation via a cyclic oxonium ion intermediate, **INT-3ai_Br**. For the ibuprofen derivative **2ak**, the yield of the corresponding MFHA product was significantly higher when using anomeric amide reagent **1b** compared to reagent **1a**, with yields of 54% for **3ak_Br** versus 21% for **3ak**.

**Scheme 1. Synthetic application of MFHAs.**




When the difunctionalization reactions were scaled up from 1 mmol to 5 mmol for olefinic substrates **2a**, **2m**, and **2aa**, the isolated yields remained comparable. This observation demonstrates the robustness of the overall process, including the preparation of both anomeric amide reagents **1a** and **1b**.

We also aimed to broaden the scope of preparing MFHAs beyond *N*-haloalkyl-*N*-Boc-*O*-methanesulfonyl hydroxylamines (**Table 3**). First, various leaving groups other than methanesulfonate (OMs) were tested: *O*-activated hydroxylamines with different acyl groups (i.e., *O*-tosyl, *O*-nosyl, *O*-mesitylenesulfonyl, and *O*-(4-nitrobenzoyl)) were *N*-chlorinated with TCCA (*see* procedure outlined for **1a** in ESI). Subsequently, the freshly prepared anomeric amides (**4a** to **7a**) were reacted with styrene **2a** using the conditions of ***General Procedure I***. The corresponding MFHA products (**10**–**13**) were isolated in high yields (71–81%). Next, the Boc group was replaced with a Cbz group, while the original OMs leaving group was kept on the anomeric amide precursor (**Table 3**). The reaction of anomeric amide **8a** with styrene **2a** provided MFHA product **14** in 83% isolated yield. Recently, the Baran lab reported the anomeric amide (**9a**) as an efficient electrophilic halogenating reagent, especially for heteroarenes.[10]

Since the Baran lab's chlorinating reagent **9a** is structurally similar to our anomeric amide reagents (**1a** and **4a**–**7a**) which we prepared in this study, the reactivity of **9a** in alkene chloro-hydroxylaminations was investigated. For the preparation of **9a**, TCCA was used instead of *tert*-butyl hypochlorite (employed by the Baran lab for *N*-chlorination) to minimize deviations from the halo-hydroxylamination conditions used in our current study. Thus, the freshly prepared **9a** was reacted with styrene **2a**, and MFHA product **15** was obtained in 83% isolated yield.

Next, the reaction of six anomeric amide reagents (**4a**-**9a**, **Table 3**) with unactivated alkene **2aa** was evaluated under the conditions of ***General Procedure II***. Using reagents **4a**–**8a**, the corresponding MFHA products **16-20**

were obtained in modest to moderate isolated yields (25-44%), which are comparable to the yield obtained using BocN(Cl)OMs **1a** (43%). It is important to note that the 1,2-addition of N-Cbz anomeric amide reagent **8a** across the C=C double bond of olefin **2aa** led a regioisomeric product mixture (**20**; 9:1), while the same reaction using *N*-Boc anomeric amide **1a** only gave rise a single regioisomer (**3aa**; **Table 2**)

We also tested the reaction between Baran's anomeric amide **9a** and unactivated alkene **2aa** under the conditions of ***General Procedure II***. However, only 11% of the corresponding MFHA product (**21**) was isolated. This result suggests that **9a** might be better suited for the chloro-hydroxylamination of activated alkenes, such as styrene **2a**.

The MFHAs produced through our novel intermolecular olefin halo-hydroxylamination reaction feature two synthetic handles (C–X and N–O bonds) that can be leveraged in subsequent transformations to enhance molecular complexity. For example, the *O*-activated hydroxylamine moiety can be used for inter- or intramolecular C–H amination reactions.[6,8] This class of hydroxylamines can also be used for the direct and stereospecific synthesis of aziridines from olefins via transition-metal catalysis. The C-X bonds can either be substituted with nucleophiles or subjected to transition metal-catalyzed cross-coupling reactions.[7] Over a dozen complexity-building transformations were performed to evaluate the synthetic potential of MFHAs (**Scheme 1**). After the facile removal of the Boc group from **3a**, geminal chloro cyanide **23** was prepared via the oxidation of *O*-activated hydroxylamine **22**. The C-Cl bond in **3a** was substituted with thiophenol furnishing compound **24** in 75% isolated yield. Following the *in-situ* removal of the Boc group in **3a** with TFA, a highly efficient di-rhodium-catalyzed olefin aziridination took place with cyclooctene and the corresponding *N*-alkylaziridine (**25**) was isolated in 85% yield (**Scheme 1A**). Aziridine **25** was first converted to the corresponding benzylic alcohol **26** using water as the nucleophile. Next, the C-Cl bond was substituted with sodium phenoxide to afford aryl ether **27** in 61% isolated yield. An intriguing rearrangement occurred when phenyl ether **27** was heated to reflux with one equivalent of triflic acid, yielding the structurally complex *O*-alkylated phenol **28** (**Scheme 1A**).

The catalytic hydrogenation of the C=C double bond in MFHA **3ae** furnished the corresponding saturated cyclooctane derivative **3r** in 90% isolated yield without either C-Cl or N–O bond cleavage (**Scheme 1B**). A di-rhodium-catalyzed intermolecular C–H amination of 1,4-dimethoxybenzene with the *in-situ* Boc deprotected **3r** afforded secondary *N*-alkylaniline **29**. Next, an elusive electron-rich *N*-aryl aziridine **30** was readily prepared from aniline **29**, in 82% isolated yield, simply by warming it at 50 $^{o}$C in HFIP over 3 hours. The intermolecular arene C($sp^2$)–H amination of *O*-Me estrone with Boc-deprotected MFHA **31** was followed by an HFIP-promoted *N*-arylaziridine formation to afford **32** in 49% isolated yield over 2 steps. Geranyl acetate was regioselectively *N*-alkyl aziridinated at the 6,7 C=C double bond to afford structurally complex aziridine **33** in 48% isolated yield.

Tetrahydroquinoline **34** and pyrrolidine **35** were obtained from MFHAs **3z** and **3aa_Br** via intramolecular C($sp^2$)–H and C($sp^3$)–H amination, respectively (**Scheme 1C**). Importantly, the C-Cl and C-Br moieties remained intact. When MFHA **3j** was treated with mesitylene in the presence of catalytic amounts of a di-rhodium complex, *N*-aryl-1,2-aminoalcohol **36** was obtained in 58% isolated yield. Finally, after stirring the solution of MFHA **3m** with silica gel in DCM, we observed an intramolecular nucleophilic substitution of the C-Cl bond to furnish the corresponding *N*-methanesulfonylhydroxy-2-oxazolidone derivative (**37**) in 51% isolated yield.

In conclusion, we have successfully demonstrated that several anomeric amides (i.e., N-protected-N-halogenated O-activated hydroxylamines) react directly with olefins without the need for catalysts or additives, producing the corresponding multifunctional hydroxylamines (MFHAs). This transformation achieves 1,2-halo-hydroxylamination of the olefin C=C double bond. Both activated and unactivated alkenes, including cyclic and acyclic olefins, dienes, and enynes, are efficiently converted to the corresponding difunctionalized hydroxylamine derivatives with excellent atom economy.

The resulting MFHAs, containing both an alkyl halide and an *O*-activated hydroxylamine moiety, serve as convenient building blocks/reagents for synthesizing structurally complex *N*-unprotected secondary amines and *N*-heterocycles. The relatively mild reaction conditions allow for the tolerance of various functional groups, such as free alcohol, epoxide, azide, ester, and ether. The synthetic versatility of these MFHAs, which are excellent N-electrophilic aminating agents, has been demonstrated through the preparation of various nitrogen-containing molecules.

We achieved the direct synthesis of *N*-alkyl and *N*-arylaziridines from unactivated olefins and *N*-alkylanilines from arenes via Rh-catalyzed inter- and intramolecular arene C($sp^2$)-H amination. Additionally, the synthesis of 2-phenyl-4-bromopyrrolidine was accomplished through an intramolecular Rh-catalyzed C($sp^3$)-H amination. To understand the mechanistic underpinnings of these intriguing olefin halo-hydroxylamination reactions, mechanistic studies using both DFT calculations and experiments are currently underway and will be reported in due course.

## ASSOCIATED CONTENT

**Supporting Information**.
Experimental details, optimization study, compound characterization, SCXRD data, NMR spectra (PDF).

## AUTHOR INFORMATION

### Corresponding Authors

**László Kürti** – Department of Chemistry, Rice University, Houston, TX 77030, USA; E-mail: Kürti.laszlo@rice.edu

### Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

### Notes

The authors declare no competing financial interest.

## ACKNOWLEDGMENTS

This work was supported by Rice University, National Institutes of Health (R35 GM-136373) and the Robert A. Welch Foundation (Grant C-1764).

## REFERENCES

1. (a) Gomtsyan, A. Heterocycles in drugs and drug discovery. *Chemistry of Heterocyclic Compounds (New York, NY, United States)* **2012**, *48* (1), 7-10; (b) Dua, R.; Shrivastava, S.; Sonwane, S. K.; Srivastava, S. K. Pharmacological significance of synthetic heterocycles scaffold: a review. *Adv. Biol. Res.* **2011**, *5* (3), 120-144; (c) Poulie, C. B. M.; Bunch, L. Heterocycles as Nonclassical Bioisosteres of α-Amino Acids. *ChemMedChem* **2013**, *8* (2), 205-215; (d) Saini, M. S.; Kumar, A.; Dwivedi, J.; Singh, R. A review: biological significances of heterocyclic compounds. *Int. J. Pharma Sci. Res.* **2013**, *4* (3), 66-77; (e) St. Jean, D. J.; Fotsch, C. Mitigating Heterocycle Metabolism in Drug Discovery. *J. Med. Chem.* **2012**, *55* (13), 6002-6020.
2. (a) Ghislieri, D.; Green, A. P.; Pontini, M.; Willies, S. C.; Rowles, I.; Frank, A.; Grogan, G.; Turner, N. J. Engineering an Enantioselective Amine Oxidase for the Synthesis of Pharmaceutical Building Blocks and Alkaloid Natural Products. *J. Am. Chem. Soc.* **2013**, *135* (29), 10863-10869; (b) Masand, V. H.; Al-Hussain, S.; Alzahrani, A. Y.; El-Sayed, N. N. E.; Yeo, C. I.; Tan, Y. S.; Zaki, M. E. A. Leveraging nitrogen occurrence in approved drugs to identify structural patterns. *Expert Opin. Drug Discovery* **2024**, *19* (1), 111-124.
3. Kürti, L. Streamlining amine synthesis. *Science* **2015**, *348*, 863-864.
4. (a) Hemric, B. N.; Garcia, T. A.; Barni, A. E. Strategies for Direct, Transition Metal-Free Addition of Nitrogen Synthons to Alkenes. *Helv. Chim. Acta* **2024**, *107* (1), e202300160; (b) Chen, X.; Xiao, F.; He, W.-M. Recent developments in the difunctionalization of alkenes with C-N bond formation. *Org. Chem. Front.* **2021**, *8* (18), 5206-5228; (c) Huang, N.; Luo, J.; Liao, L.; Zhao, X. Catalytic Enantioselective Aminative Difunctionalization of Alkenes. *J. Am. Chem. Soc.* **2024**, *146* (10), 7029-7038; (d) Hirano, K.; Miura, M. Hydroamination, Aminoboration, and Carboamination with Electrophilic Amination Reagents: Umpolung-Enabled Regio- and Stereoselective Synthesis of N-Containing Molecules from Alkenes and Alkynes. *J. Am. Chem. Soc.* **2022**, *144* (2), 648-661; (e) Wu, Z.; Hu, M.; Li, J.; Wu, W.; Jiang, H., Recent advances in aminative difunctionalization of alkenes. *Org. Biomol. Chem.* **2021**, *19* (14), 3036-3054; (f) Xie, L.; Wang, S.; Zhang, L.; Zhao, L.; Luo, C.; Mu, L.; Wang, X.; Wang, C., Directed nickel-catalyzed regio- and diastereoselective arylamination of unactivated alkenes. *Nat Commun*. **2021**, *12* (1), 6280; (g) van der Puyl, V. A.; Derosa, J.; Engle, K. M. Directed, Nickel-Catalyzed Umpolung 1,2-Carboamination of Alkenyl Carbonyl Compounds. *ACS Catal.* **2019**, *9*, 224−229; (h) Kang, T.; Kim, N.; Cheng, P. T.; Zhang, H.; Foo, K.; Engle, K. M. Nickel-Catalyzed 1,2-Carboamination of Alkenyl Alcohols. *J. Am. Chem. Soc.* **2021**, *143*, 13962−13970; (i) Ozols, K.; Onodera, S.; Woźniak, Ł.; Cramer, N. Cobalt(III)-Catalyzed Enantioselective Intermolecular Carboamination by C−H Functionalization. *Angew. Chem. Int. Ed.* **2021**, *60*, 655−659; (j) Li, Z.; Zhang, M.; Zhang, Y.; Liu, S.; Zhao, J.; Zhang, Q. Multicomponent Cyclopropane Synthesis Enabled by Cu-Catalyzed Cyclopropene Carbometalation with Organoboron Reagent: Enantioselective Modular Access to Polysubstituted 2-Arylcyclopropylamines. *Org. Lett.* **2019**, *21*, 5432−5437; (k) Matsuda, N.; Hirano, K.; Miura, M. Regioselective and Stereospecific Copper-Catalyzed Aminoboration of Styrenes with Bis(pinacolato)diboron and O-Benzoyl-N,N-dialkylhydroxylamines. *J.Am. Chem. Soc.* **2013**, *135*, 4934−4937; (l) Sakae, R.; Matsuda, N.; Hirano, K.; Satoh, T.; Miura, M. Highly Stereoselective Synthesis of (Borylmethyl)cyclopropylamines by Copper-Catalyzed Aminoboration of Methylenecyclopropanes. *Org.Lett.* **2014**, *16*, 1228−1231; (m) Sakae, R.; Hirano, K.; Satoh, T.; Miura, M. Copper-Catalyzed Stereoselective Aminoboration of Bicyclic Alkenes. *Angew. Chem. Int. Ed.* **2014**, *54*, 613−617; (n) Nishikawa, D.; Hirano, K.; Miura, M. Copper-Catalyzed Regio and Stereoselective Aminoboration of Alkenylboronates. *Org. Lett.* **2016**, *18*, 4856−4859; (o) Sakae, R.; Hirano, K.; Miura, M. Ligand-Controlled Regiodivergent Cu-Catalyzed Aminoboration of Unactivated Terminal Alkenes. *J. Am. Chem. Soc.* **2015**, *137*, 6460−6463; (p) Kato, K.; Hirano, K.; Miura, M. Copper-Catalyzed Regio- and Enantioselective Aminoboration of Unactivated Terminal Alkenes. *Chem.–Eur. J.* **2018**, *24*, 5775−5778.; (q) Jiang, H.-C.; Tang, X.-Y.; Shi, M. Copper-catalyzed regio- and enantioselective aminoboration of alkylidenecyclopropanes: the synthesis of cyclopropane-containing β-aminoalkylboranes. *Chem. Commun.* **2016**, *52*, 5273−5276; (r) Parra, A.; Amenós, L.; Guisán-Ceinos, M.; López, A.; Ruano, J. L. G.; Tortosa, M. Copper-Catalyzed Diastereo- and Enantioselective Desymmetrization of Cyclopropenes: Synthesis of Cyclopropylboronates. *J. Am. Chem. Soc.* **2014**, *136*, 15833−15836. (s) Makai, S.; Falk, E.; Morandi, B., Direct Synthesis of Unprotected 2-Azidoamines from Alkenes via an Iron-Catalyzed Difunctionalization Reaction. *J. Am. Chem. Soc.* **2020**, *142* (51), 21548-21555; (t) Legnani, L.; Morandi, B., Direct Catalytic Synthesis of Unprotected 2-Amino-1-Phenylethanols from Alkenes by Using Iron(II) Phthalocyanine. *Angew. Chem. Int. Ed.* **2016**, *55*, 2248-2251.
5. (a) Falk, E.; Makai, S.; Delcaillau, T.; Gurtler, L.; Morandi, B., Design and Scalable Synthesis of N-Alkylhydroxylamine Reagents for the Direct Iron-Catalyzed Installation of Medicinally Relevant Amines. *Angew. Chem. Int. Ed.* **2020**, *59*, 21064-21071; (b) Legnani, L.; Prina-Cerai, G.; Delcaillau, T.; Willems, S.; Morandi, B., Efficient access to unprotected primary amines by iron-catalyzed aminochlorination of alkenes. *Science* **2018**, *362*, 434-439; (c) Chemler, S. R.; Bovino, M. T., Catalytic Aminohalogenation of Alkenes and Alkynes. *ACS Catal.* **2013**, *3* (6), 1076-1091; (d) Li, G.; Saibau Kotti, S. R. S.; Timmons, C. Recent development of regio- and stereoselective aminohalogenation reaction of alkenes. *Eur. J. Org. Chem.* **2007**, (17), 2745-2758; (e) Engl, S.; Reiser, O., Catalyst-Free Visible-Light-Mediated Iodoamination of Olefins and Synthetic Applications. *Org. Lett.* **2021**, *23* (14), 5581-5586; (f) Feng, G.; Ku, C. K.; Zhao, J.; Wang, Q., Copper-Catalyzed Three-Component Aminofluorination of Alkenes and 1,3-Dienes: Direct Entry to Diverse beta-Fluoroalkylamines. *J. Am. Chem. Soc.* **2022**, *144* (44), 20463-20471; (g) Li, Y.; Liang, Y.; Dong, J.; Deng, Y.; Zhao, C.; Su, Z.; Guan, W.; Bi, X.; Liu, Q.; Fu, J., Directed Copper-Catalyzed Intermolecular Aminative Difunctionalization of Unactivated Alkenes. *J. Am. Chem. Soc.* **2019**, *141* (46), 18475-18485; (h) Martínez, C.; Muñiz, K., A Versatile Metal-Free Intermolecular Aminochlorination of Alkenes. *Adv. Synth. Catal.* **2014**, *356* (1), 205-211; (i) Rajbongshi, K. K.; Saikia, I.; Chanu, L. D.; Roy, S.; Phukan, P., A Metal-Free Protocol for Aminofunctionalization of Olefins Using TsNBr2. *J. Org. Chem.* **2016**, *81* (13), 5423-5432; (j) Yu, W. Z.; Chen, F.; Cheng, Y. A.; Yeung, Y. Y., Catalyst-free and metal-free electrophilic bromoamidation of unactivated olefins using the N-bromosuccinimide/sulfonamide protocol. J. Org. Chem. **2015**, *80* (5), 2815-2821; (k) Yu, W. Z.; Cheng, Y. A.; Wong, M. W.; Yeung, Y. Y., Atmosphere- and Temperature-Controlled Regioselective Aminobromination of Olefins. *Adv. Synth. Catal.* **2017**, *359* (2), 234-239.
6. (a) Ma, Z.; Zhou, Z.; Kürti, L., Direct and Stereospecific Synthesis of N-H and N-Alkyl Aziridines from Unactivated Olefins Using Hydroxylamine-O-Sulfonic Acids. *Angew. Chem. Int. Ed.* **2017**, *56* (33), 9886-9890; (b) Zhu, Y.; Smith, M. J. S.; Tu, W.; Bower, J. F., A Stereospecific Alkene 1,2-Aminofunctionalization Platform for the Assembly of Complex Nitrogen-Containing Ring Systems. *Angew. Chem. Int. Ed.* **2023**, *62* (16),

e202301262; (c) Chandra, D.; Yadav, A. K.; Singh, V.; Tiwari, B.; Jat, J. L., Fe(II)-Catalyzed Synthesis of Unactivated Aziridines (N-H/N-Me) from Olefins Using O-Arylsulfonyl Hydroxylamines. *ChemistrySelect* **2021**, *6* (39), 10524-10526; (d) Farndon, J. J.; Ma, X.; Bower, J. F., Transition Metal Free C-N Bond Forming Dearomatizations and Aryl C-H Aminations by in Situ Release of a Hydroxylamine-Based Aminating Agent. *J. Am. Chem. Soc.* **2017**, *139* (40), 14005-14008; (e) Wang, T.; Hoffmann, M.; Dreuw, A.; Hasagić, E.; Hu, C.; Stein, P. M.; Witzel, S.; Shi, H.; Yang, Y.; Rudolph, M.; Stuck, F.; Rominger, F.; Kerscher, M.; Comba, P.; Hashmi, A. S. K., A Metal-Free Direct Arene C–H Amination. *Adv. Synth. Catal.* **2021**, *363* (11), 2783-2795; (f) Farndon, J. J.; Young, T. A.; Bower, J. F., Stereospecific Alkene Aziridination Using a Bifunctional Amino-Reagent: An Aza-Prilezhaev Reaction. *J. Am. Chem. Soc.* **2018**, *140* (51), 17846-17850; (g) Jat, J. L.; Yadav, A. K.; Pandey, C. B.; Chandra, D.; Tiwari, B., Direct N-Me Aziridination of Enones. *J. Org. Chem.* **2022**, *87* (5), 3751-3757; (h) Paudyal, M. P.; Wang, M.; Siitonen, J. H.; Hu, Y.; Yousufuddin, M.; Shen, H. C.; Falck, J. R.; Kürti, L., Intramolecular N-Me and N-H aminoetherification for the synthesis of N-unprotected 3-amino-O-heterocycles. *Org. Biomol. Chem.* **2021**, *19* (3), 557-560; (i) Munnuri, S.; Anugu, R. R.; Falck, J. R., Cu(II)-Mediated N-H and N-Alkyl Aryl Amination and Olefin Aziridination. *Org. Lett.* **2019**, *21* (6), 1926-1929; (j) Falk, E.; Gasser, V. C. M.; Morandi, B., Synthesis of N-Alkyl Anilines from Arenes via Iron-Promoted Aromatic C-H Amination. *Org. Lett.* **2021**, 23 (4), 1422-1426; (k) Paudyal, M. P.; Adebesin, A. M.; Burt, S. R.; Ess, D. H.; Ma, Z.; Kürti, L.; Falck, J. R. Dirhodium-catalyzed C-H arene amination using hydroxylamines. *Science* **2016**, *353*, 1144-1147; (l) Tiwari, B.; Jat, J. L.; Chandra, D.; Kumar, P.; Singh, V., Metal- and Additive-Free Intermolecular Aziridination of Olefins Using N-Boc-O-tosylhydroxylamine. *Synthesis* **2022**, *54* (20), 4513-4520; (m) Behnke, N. E.; Kwon, Y. D.; Davenport, M. T.; Ess, D. H.; Kürti, L., Directing-Group-Free Arene C(sp(2))-H Amination Using Bulky Aminium Radicals and DFT Analysis of Regioselectivity. *J. Org. Chem.* **2023**, *88* (16), 11847-11854.

7. (a) Mathieu, G.; Azek, E.; Lai, C.; Lebel, H., Hydroxylamine Umpolung in Copper-Catalyzed Cross-Coupling Reactions to Synthesize N-Arylhydroxylamine Derivatives. *ACS Catal.* **2024**, *14* (7), 4675-4682; (b) Berman, A. M.; Johnson, J. S. Copper-Catalyzed Electrophilic Amination of Organozinc Nucleophiles: Documentation of O-Benzoyl Hydroxylamines as Broadly Useful $R_2N(+)$ and RHN(+) Synthons. *J. Org. Chem.* **2006**, *71*, 219-224. (c) Yeung, Y. W.; Chan, C. M.; Chen, Y. T.; Chan, M.; Luo, M.; Gao, X.; Du, B.; Yu, W. Y., Cu-Catalyzed Cross-Electrophilic Coupling of alpha-Diazoesters with O-Benzoyl Hydroxylamines for the Synthesis of Unnatural N-Alkyl alpha-Amino Acid Derivatives. *Org. Lett.* **2023**, *25* (4), 619-623; (d) Campeau, L. C.; Hazari, N., Cross-Coupling and Related Reactions: Connecting Past Success to the Development of New Reactions for the Future. *Organometallics* **2019**, *38* (1), 3-35; (e) Choi, J.; Fu, G. C., Transition metal-catalyzed alkyl-alkyl bond formation: Another dimension in cross-coupling chemistry. *Science* **2017**, *356*, eaaf7230; (f) Kambe, N.; Iwasaki, T.; Terao, J., Pd-catalyzed cross-coupling reactions of alkyl halides. *Chem. Soc. Rev.* **2011**, *40* (10), 4937-4947; (g) Weix, D. J., Methods and Mechanisms for Cross-Electrophile Coupling of $C(sp^2)$ Halides with Alkyl Electrophiles. *Acc. Chem. Res.* **2015**, *48* (6), 1767-1775.
8. (a) Chu, D.; Ellman, J. A., Stereospecific Synthesis of Unprotected, alpha,beta-Disubstituted Tryptamines and Phenethylamines from 1,2-Disubstituted Alkenes via a One-Pot Reaction Sequence. *Org. Lett.* **2023**, *25* (20), 3654-3658; (b) Legnani, L.; Prina Cerai, G.; Morandi, B., Direct and Practical Synthesis of Primary Anilines through Iron-Catalyzed C–H Bond Amination. *ACS Catal.* **2016**, *6* (12), 8162-8165; (c) Ma, X.; Farndon, J. J.; Young, T. A.; Fey, N.; Bower, J. F. A Simple and Broadly Applicable C-N Bond Forming Dearomatization Protocol Enabled by Bifunctional Amino Reagents. *Angew. Chem. Int. Ed.* **2017**, *56* (46), 14531-14535; (d) Svejstrup, T. D.; Ruffoni, A.; Julia, F.; Aubert, V. M.; Leonori, D., Synthesis of Arylamines via Aminium Radicals. *Angew. Chem. Int. Ed.* **2017**, *56* (47), 14948-14952; (e) Smith, M. J. S.; Tu, W.; Robertson, C. M.; Bower, J. F., Stereospecific Aminative Cyclizations Triggered by Intermolecular Aza-Prilezhaev Alkene Aziridination. *Angew. Chem. Int. Ed.* **2023**, *62* (48), e202312797; (f) Cheng, Q.-Q.; Zhou, Z.; Jiang, H.; Siitonen, J. H.; Ess, D. H.; Zhang, X.; Kürti, L., Organocatalytic nitrogen transfer to unactivated olefins via transient oxaziridines. *Nature. Catal.* **2020**, *3* (4), 386-392; (g) Jinan, D.; Mondal, P. P.; Nair, A. V.; Sahoo, B., O-Protected NH-free hydroxylamines: emerging electrophilic aminating reagents for organic synthesis. *Chem Commun.* **2021**, *57* (99), 13495-13505; (h) Gasser, V. C. M.; Makai, S.; Morandi, B., The advent of electrophilic hydroxylamine-derived reagents for the direct preparation of unprotected amines. *Chem. Commun.* **2022**, *58* (72), 9991-10003; (i) D'Amato, E. M.; Borgel, J.; Ritter, T., Aromatic C-H amination in hexafluoroisopropanol. *Chem. Sci.* **2019**, *10* (8), 2424-2428; (j) Zhou, Z.; Ma, Z.; Behnke, N. E.; Gao, H.; Kürti, L., Non-Deprotonative Primary and Secondary Amination of (Hetero)Arylmetals. *J. Am. Chem. Soc.* **2017**, *139* (1), 115-118; (k) Munnuri, S.; Adebesin, A. M.; Paudyal, M. P.; Yousufuddin, M.; Dalipe, A.; Falck, J. R., Catalyst-Controlled Diastereoselective Synthesis of Cyclic Amines via C-H Functionalization. *J. Am. Chem. Soc.* **2017**, *139* (50), 18288-18294; (l) Zhou, Z.; Cheng, Q. Q.; Kürti, L., Aza-Rubottom Oxidation: Synthetic Access to Primary alpha-Aminoketones. *J. Am. Chem. Soc.* **2019**, *141* (6), 2242-2246; (m) Jones, B. T.; Garcia-Carceles, J.; Caiger, L.; Hazelden, I. R.; Lewis, R. J.; Langer, T.; Bower, J. F., Complex Polyheterocycles and the Stereochemical Reassignment of Pileamartine A via Aza-Heck Triggered Aryl C-H Functionalization Cascades. *J. Am. Chem. Soc.* **2021**, *143* (38), 15593-15598; (p) Jat, J. L.; Paudyal, M. P.; Gao, H.; Xu, Q.-L.; Yousufuddin, M.; Devarajan, D.; Ess, D. H.; Kürti, L.; Falck, J. R. Direct Stereospecific Synthesis of Unprotected N-H and N-Me Aziridines from Olefins. *Science* **2014**, *343* (6166), 61-65, DOI: 10.1126/science.1245727; (q) Zhou, Z.; Kürti, L., Electrophilic Amination: An Update. *Synlett* **2019**, *30* (13), 1525-1535.
9. (a) Rahaim, Jr., R. J.; Maleczka, Jr., R. E. Pd-Catalyzed Silicon Hydride Reductions of Aromatic and Aliphatic Nitro Groups. *Org. Lett.* **2005**, *7*, 5087-5090; (b) Heydari, A.; Banan, A.; Valizadeh, H.; Moghimi, A. Selective Oxidation of Secondary Amines to N,N-Disubstituted Hydroxylamines by Choline Peroxydisulfate. *Synlett* **2017**, *28* (17), 2315-2319; (c) Hill, J.; Hettikankanamalage, A. A.; Crich, D. Diversity-Oriented Synthesis of N,N,O-Trisubstituted Hydroxylamines from Alcohols and Amines by N-O Bond Formation. *J. Am. Chem. Soc.* **2020**, *142* (35), 14820-14825; (d) Li, D.; Zhang, C.; Yue, Q.; Xiao, Z.; Wang, X.; Zhang, Q., Synthesis of O-Aroyl-N,N-dimethylhydroxylamines through Hypervalent Iodine-Mediated Amination of Carboxylic Acids with N,N-Dimethylformamide. *Synthesis* **2017**, *49* (18), 4303-4308; (e) Lu, B.; Yu, J.; Zhang, X.; Chen, G.-Q., Recent advances on catalytic asymmetric hydrogenation of oximes and oxime ethers. *Tetrahedron Lett.* **2024**, *136*, 154914; (f) Mas-Rosello, J.; Cramer, N., Catalytic Reduction of Oximes to Hydroxylamines: Current Methods, Challenges and Opportunities. *Chem. Eur. J.* **2022**, *28* (10), e202103683; (g) Penning, T. M.; Su, A. L.; El-Bayoumy, K., Nitroreduction: A Critical Metabolic Pathway for Drugs, Environmental Pollutants, and Explosives. *Chem. Res. Toxicol.* **2022**, *35* (10), 1747-1765; (h) Tan, F.; Zheng, P.; Zou, Y.-Q., Highly Selective Asymmetric Hydrogenation of Oximes to Hydroxylamine Derivatives. *Chem.* **2020**, *6* (7), 1517-1519; (i) Wang, G.; Chen, T.; Jia, K.; Ma, W.; Tung, C. H.; Liu, L., Catalytic Asymmetric Oxidation of Amines to Hydroxylamines. *J. Am. Chem. Soc.* **2023**, *145* (40), 22276-22283.
10. Wang, Y.; Bi, C.; Kawamata, Y.; Grant, L. N.; Samp, L.; Richardson, P. F.; Zhang, S.; Harper, K. C.; Palkowitz, M. D.;

Vasilopoulos, A.; Collins, M. R.; Oderinde, M. S.; Tyrol, C. C.; Chen, D.; LaChapelle, E. A.; Bailey, J. B.; Qiao, J. X.; Baran, P. S. Discovery of N-X anomeric amides as electrophilic halogenation reagents. *Nat Chem.* 2024. https://doi.org/10.1038/s41557-024-01539-4