

Iron-catalysed radical Markovnikov hydroamidation of complex alkenes

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Nitrogen atoms are integral components of various chemical functional groups, including amines, amides and N-heterocycles, among others. Consequently, they play an important role in pharmaceuticals, agrochemicals, natural products, materials and commodity chemicals. The formation of C–N bonds is reliably achieved through methods, such as reductive amination, N-alkylation and cross-coupling. Hydroamination, starting with alkenes, presents a valuable alternative for accessing organic compounds containing nitrogen, as alkenes are highly abundant. Here we present a method for the iron-catalysed radical hydroamidation of alkenes. To this end, we developed a radical amidation reagent that can be readily prepared on a large scale, facilitating the efficient transfer of the synthetically valuable cyanamide functionality across both activated and unactivated double bonds. The scope of the reaction is remarkably broad, demonstrating its applicability to the diastereoselective hydroamidation of complex terpene natural products. Importantly, the synthesis of ¹⁵N-labelled amines is possible using this strategy. Subsequent chemistry, converting the distinctive cyanamide functionality into other useful groups, further validates the value of the developed methodology.

Nitrogen atoms play a ubiquitous role across pharmaceuticals, agrochemicals, natural products, materials and various commodity chemicals. Moreover, at the core of life itself lies the simplest amine, ammonia, whose function as a fertilizer sustains the world's food production. Accordingly, biological systems utilize ammonia as a fundamental building block for synthesizing complex molecules. In organic compounds, nitrogen atoms appear in various important functional groups, including amines, amides and N-heterocycles, among others. Consequently, the development of synthetic methodologies for forming carbon–nitrogen (C–N) bonds is paramount¹. Practical approaches to forge these sigma bonds involve amine alkylation, reductive amination of carbonyl groups with amines, and transition-metal-catalysed C–N cross coupling of N-nucleophiles with alkyl or aryl halides^{2–7}. Alternatively, alkenes have proven effective substrates in hydroamination reactions using transition-metal catalysis^{8–11}. For terminal alkenes, this can yield two regioisomeric products: the anti-Markovnikov or the branched Markovnikov product, depending on the method chosen (Fig. 1a).

In addition to transition-metal-catalysed hydroaminations, effective radical processes have emerged over the past two decades. Considering N-centred radicals, the anti-Markovnikov products are obtained with high regioselectivity as a result of N-radical addition at the terminal position of the alkene functionality^{12–16}. Conversely, regioisomeric hydroamination products are formed through metal-hydride hydrogen atom transfer reactions (MHAT)¹⁷, followed by radical C–N bond formation. Silanes are commonly used as stoichiometric hydride sources in these reactions. Cobalt catalysis, in combination with azodicarboxylates¹⁸ or α -azoesters¹⁹ as C-radical trapping reagents, has proven to be efficient. Notable, nitric oxide²⁰, alkyl nitrite²¹ and phenylsulfonyl azide^{22,23} have been also successfully used as radical amination reagents in Co-catalysed processes. Probably even more valuable are the corresponding hydroamination processes catalysed or mediated by iron salts, as iron is highly abundant and cost efficient. Arylazo sulfones²⁴, nitroarenes²⁵, diazo compounds²⁶ and other amine sources^{27,28} have been used as the radical amination reagents in these processes. Despite these advancements, a universally applicable

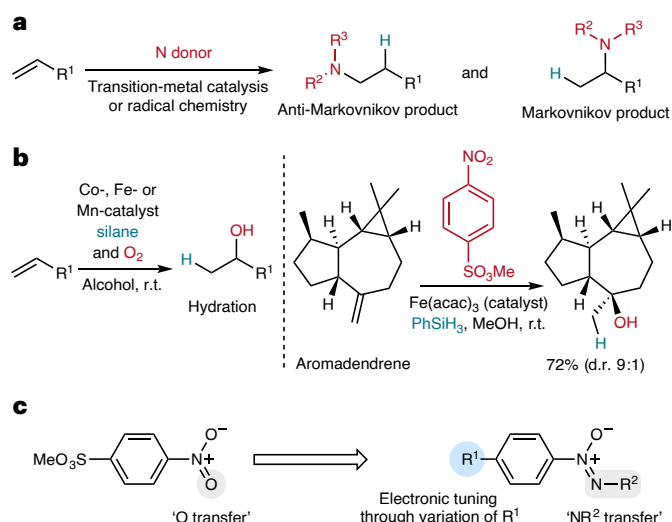


Fig. 1 | Hydroamination and hydration of alkenes. **a**, Hydroamination of terminal alkenes using transition-metal catalysis or radical methods provides either the Markovnikov or the anti-Markovnikov product. **b**, Mukaiyama-type hydration with O_2 as the radical trapping reagent and improved variant that uses a nitroarene as the C-radical oxygenation reagent, exemplified by the hydration of a complex natural product, aromadendrene. **c**, The design of a radical amination reagent based on the structure of the successful nitroarene oxygen atom donor. r.t., room temperature; $Fe(acac)_3$, iron acetylacetonate.

method for the Fe-catalysed hydroamination of complex alkenes remains to be reported.

The most prominent reaction across all MHAT transformations is the hydration, often called Mukaiyama hydration²⁹, where the C-radical generated after initial hydrogen atom transfer to an alkene is oxidized by air (Fig. 1b). This reaction has demonstrated its importance through numerous applications in the synthesis of complex natural products, effectively showcasing its utility¹⁷. However, achieving control over diastereoselectivity in these transformations has often posed challenges, primarily due to the near diffusion-controlled nature of C-radical trapping with O_2 . To address this critical issue, we recently introduced electron-poor nitroarenes as the oxygenation reagents in iron-catalysed alkene hydrations³⁰. The scope of this reaction was remarkably broad, leading to its successful application in complex natural product synthesis^{31–35}. Moreover, the diastereoselectivity observed was consistently superior to that of classical Mukaiyama-type hydrations.

Encouraged by these findings, we decided to develop a broadly applicable radical amination reagent for the stereoselective Fe-catalysed hydroamination of complex alkenes on the basis of the molecular structure of the highly efficient nitroarene oxygen atom donor. As an initial step in our reagent design process, we opted to replace the nitro functionality with an azoxy functionality, while keeping the central arene moiety that can be readily substituted at the *para*-position to additionally tune the electronic properties of the targeted amination reagent (Fig. 1c). This structure-based design led us to first propose azoxyarenes that are known and easily accessible compounds³⁶.

Studies were commenced by preparing a series of azoxyarenes **2a–2d** with the goal to add an aniline moiety across a double bond (please refer to Supplementary Fig. 3 for the synthesis of these reagents). The unactivated alkene **1a** was selected as the model substrate. Initial screening of the conditions with the ester-substituted reagent **2a** revealed that the desired hydroamination can be achieved with $Fe(dibm)_3$ as the catalyst (Supplementary Table 1). Thus, reaction of **1a** with the reagent **2a** (1.2 equiv.), $PhSiH_3$ (3.0 equiv.) and $Fe(dibm)_3$

(10 mol%) in an ethanol–dichloromethane (DCM) mixture (1:1) at room temperature provided the desired product **4a**, albeit in 11% yield only (Fig. 2). The nitrile congener **2b** gave the same yield, while the corresponding CF_3 derivative (**2c**) and the nitro derivative (**2d**) afforded worse results. Contrary to our expectation, an electron-withdrawing *para*-substituent seems to be detrimental to the reaction outcome. We therefore installed electron-donating substituents at the aryl moiety (see **2e–2h**) and identified the *para*-dimethylamino-azoxybenzene **2h** as an improved reagent in this series. The amine **4a** was formed in 18% yield with exclusive Markovnikov selectivity.

Investigations were continued by varying the R^2 substituent in the reagent. As electron-donating groups at the arene moiety improved the C-radical trapping efficiency, we decided to install π -acceptors as N substituents to increase the polarity of the $N=N$ double bond. The N-benzoyl system **2i** did not afford any of the targeted hydroamination product, probably for steric reasons. An improved yield was noted with the N-ethoxycarbonyl reagent **2j** to afford the hydrazide **5a** in 57% yield. Thus, the addition reaction worked more efficiently; however, final N–N-bond cleavage did not occur for this transformation. Realizing the importance of steric effects, we then tested the reagent **2k** carrying the small cyano group and obtained the hydrocyanamidation product **3a** in 30% yield. Surprisingly, the major product in this reaction was the secondary alcohol **6a** through a Mukaiyama-type hydration. Thus, reagent **2k** can obviously act as an O donor as well as an NCN donor. Reaction efficiency further improved with the CF_3 -substituted congener **2l** with the desired hydroamination product **3a** and **6a** being formed in roughly equal amounts (81% overall yield). The best result in this cyanamide series was obtained with the *para*-dimethylamino-substituted radical trapping reagent **2m** that provided the targeted **3a** in 58% yield along with alcohol **6a** (36%). We intensively tried to improve the ratio of hydroamination versus hydration product by further optimizing reaction conditions. However, all our attempts failed. Of note, by carefully excluding O_2 , we could show that the alcohol **6a** is fully derived from reagent **2m** and not through air-mediated radical oxygenation. A logical progression in the optimization campaign, therefore, was to remove the oxygen atom from the reagent, hoping that the resulting cyanoazo compound would retain sufficient reactivity as a C-radical acceptor. The cyanated azo compounds **2n** and **2o** can be readily prepared on a larger scale³⁷ (see ‘General procedure 3’ in the Supplementary Information, page 6). Under standard conditions, reagent **2n** delivered the desired cyanamide **3a** in 55% yield. As a side product, *n*-butylbenzene resulting from hydrogenation¹⁷ of **1a** was formed in 40% yield. We were pleased to find that the dimethylamino-reagent **2o** performed very well affording the targeted cyanamide **3a** in 83% yield and formation of the hydrogenation product was fully suppressed. It is noteworthy that the cyanamide functionality easily introduced via our methodology possesses distinct properties both as a highly valuable building block in organic synthesis and as a ligand for various metals³⁸. In addition, cyanamides have recently gained attention as privileged reactive functionalities in bioactive compounds, for example, serving as covalent inhibitors of deubiquitinating enzymes³⁹.

With the optimized conditions in hand, various activated and unactivated alkenes bearing different functionalities could be efficiently hydroamidated (Fig. 3). Considering monosubstituted alkenes, both simple aliphatic and aromatic systems worked well, with isolated yields ranging from 67% to 82% (**3a–3d** and **3f**). Notably, an aryl iodide moiety that can be used in subsequent cross-coupling reactions was tolerated. Styrenes (**3c** and **3d**) and an internal aryl-substituted activated alkene (**3e**) underwent highly regioselective Markovnikov hydroamination in good yields (67–87%). The reaction also worked well on 1,1-disubstituted alkenes (**3k**, **3n** and **3o**). Furthermore, internal cyclic alkenes engaged in the hydrofunctionalization to give the corresponding cyanamidation products (**3l** and **3m**). For unsymmetrical 1,2-disubstituted internal alkenes, low regioselectivity was observed for 4-methyl-2-pentene (**3p**) and the even more sterically biased

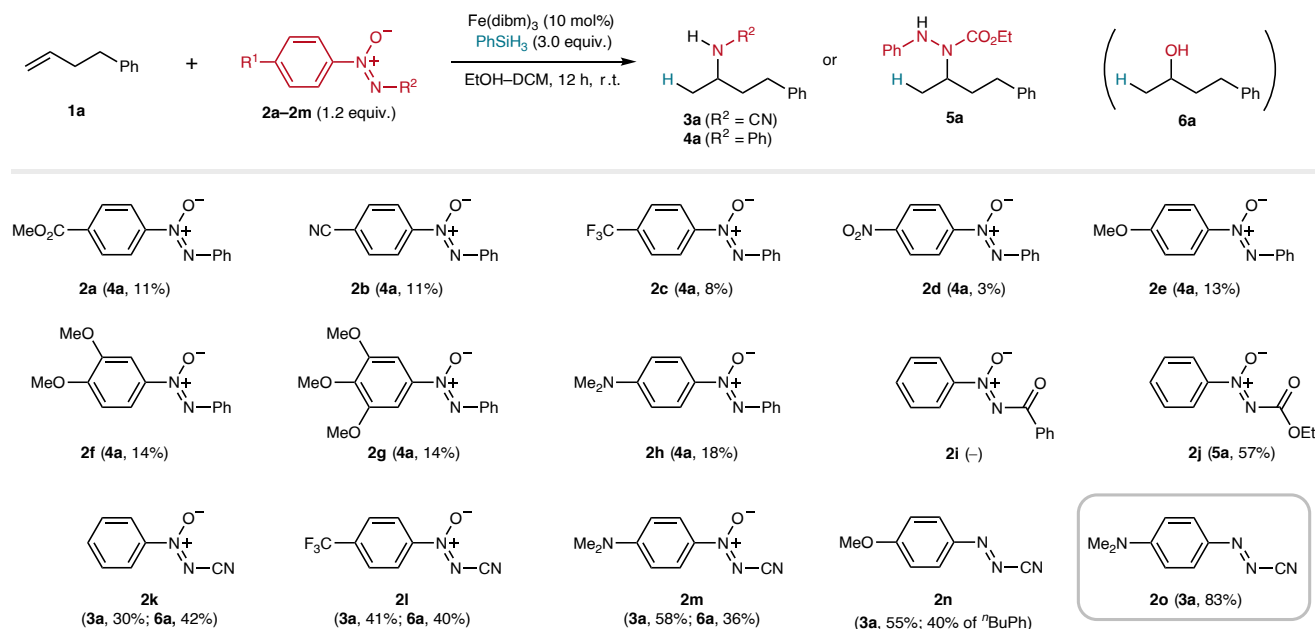


Fig. 2 | Evolution of the radical amination/amidation reagent using alkene **1a as the model substrate.** Conditions: **1a** (0.2 mmol) in ethanol (EtOH)–DCM (1:1, 2 ml). $\text{Fe}(\text{dibm})_3$, iron tris(diisobutylmethane). The grey box highlights the best hydroamidation reagent.

4,4-dimethyl-2-pentene (**3q**) also reacted with moderate selectivity. O-benzoylated crotyl alcohol also provided a low regioselectivity (**3r**), while complete regiocontrol was achieved in the hydroamidation of a vinyl amide to give the *N,N*-acetal **3s**. The regioselectivity of the latter aligns with MHAT-type reactions on vinyl amides¹⁷. However, hydroamidation did not work for the electron-poor double bond in methyl crotonate and crotononitrile. The radical hydroamidation was compatible with commonly used functional groups, including halogen (**3d**, **3g** and **3h**), silane (**3h**), boronic acid pinacol ester (**3i**), phthalimide (**3j**), ester (**3n**, **3k**, **3ag**, **3aj**, **3ak** and **3al**), nitrile (**3o**), acetal (**3ak**), ketone (**3u**, **3ab** and **3ah**) and free alcohols (**3aa** and **3af**).

To illustrate the potential of the developed radical hydroamidation strategy, we applied the reaction to late-stage modification of natural products and drug derivatives. For example, the chemical modification of bicyclic monoterpenes is readily achieved, as exemplified by the hydroamidation of (+)- α -pinene and (–)- β -pinene to afford the tertiary cyanamides **3w** and *ent*-**3w** in very good yields (79% and 82%, respectively) and excellent diastereoselectivity (>20:1 for both pinene isomers). Products derived from ring opening of the strained four-membered rings in these systems were not identified, indicating a highly efficient trapping of the tertiary C-radical by reagent **2o**. (+)-3-Carene could be hydroamidated to provide **3v** (62%) with moderate selectivity (diastereomeric ratio (d.r.) 2:1). Epoxides are tolerated, as documented by the successful hydroamidation of natural (–)-caryophyllene oxide to afford **3y** in 88% yield and excellent diastereoselectivity (>20:1). The relative configuration of **3y** was unambiguously assigned by X-ray structure analysis. More complex (+)-aromadendrene gave the tertiary cyanamide **3z** with a good stereoselectivity (d.r. 7:1) in high yield (81%). (–)- α -Cedrene was an eligible substrate to afford the tertiary cyanamide **3x** as a single diastereoisomer in 73% yield. The hydroamidation of the terminal double bond in 1-(–)-carvone could be achieved; however, the enone moiety was also hydrogenated under the applied conditions to give **3u**. As mentioned above, the free alcohol moiety in β -citronellol was well tolerated (**3aa**, 86%). Notably, this successful transformation further showed that 1,1,2-trisubstituted alkenes are eligible substrates for our Fe-catalysed radical hydroamidation. For jasmone and (*Z*)-9-tricosene, the products **3ab** and **3ac** could be isolated in 69% and 83% yields as regioisomeric

mixtures. Considering jasmone, hydroamidation of the enone moiety does not occur for electronic reasons, while its hydrogenation is probably suppressed for steric reasons. The relative electron-rich coumarin ring in osthole (**3ad**) was retained, and its terminal double bond was chemoselectively cyanamidated. Other heterocycles are also tolerated, and, for example, hydroamidation of pentoxifylline occurred in good yield (**3ae**, 86%). Pentacyclic triterpenoid derivatives could be transformed, as documented by the hydroamidation of acyl-protected betulinol, which gave the desired tertiary cyanamide **3ag** in excellent 97% yield. The steroidal compound lanosterol reacted with complete chemoselectivity, and the tetrasubstituted alkene moiety in the ring remained unreacted (**3af**). Likewise, electron-rich arenes and naphthalene rings were also compatible (**3ai** and **3aj**). The structures of **3ag**, **3ah** and **3ai** were further confirmed through X-ray analysis. It is important to note that many of the presented products are difficult to construct through de novo synthesis. Furthermore, various styrene derivatives derived from estrone (**3ah**), diacetone-D-glucose (**3ak**) and fenofibrate (**3al**) could be hydroamidated in moderate-to-excellent yields.

The highly valuable cyanamide functionality in these products can undergo various transformations to afford diverse compound classes (Fig. 4a). The hydrolysis of cyanamide **3a** with potassium hydroxide in ethanol/ H_2O in the presence of a crown ether gave the free amine **7** in good yield (81%). Aminolysis of the cyanamide moiety in **3a** with acetaldoxime and InCl_3 afforded the urea **8** with excellent yield (95%)⁴⁰. The latter can be further hydrolysed to the free amine **7** using diethylenetriamine (DETA, 93%)⁴¹. N-benzoylation of **3a** with benzoyl chloride using sodium hydride as the base afforded the N-benzoyl-protected amide **9** (98%). The product cyanamides also serve as hub structures for the preparation of tetrazoles, as shown by the successful transformation of **3a** through nitrile/azide cycloaddition to give **10**. A ZnCl_2 -catalysed formal (3 + 2) cycloaddition between compound **3a** and an amidoxime reagent provided the 1,2,4-oxadiazole **12** (92%), which represents a key structural motif in a number of bioactive compounds. Moreover, under acidic conditions, cyanamide **3a** reacted with *ortho*-aminothiophenol to the aminated benzothiazole **11**. Recently, a methodology using adaptive dynamic homogeneous catalysis with nickel under visible-light-driven redox reaction conditions to realize

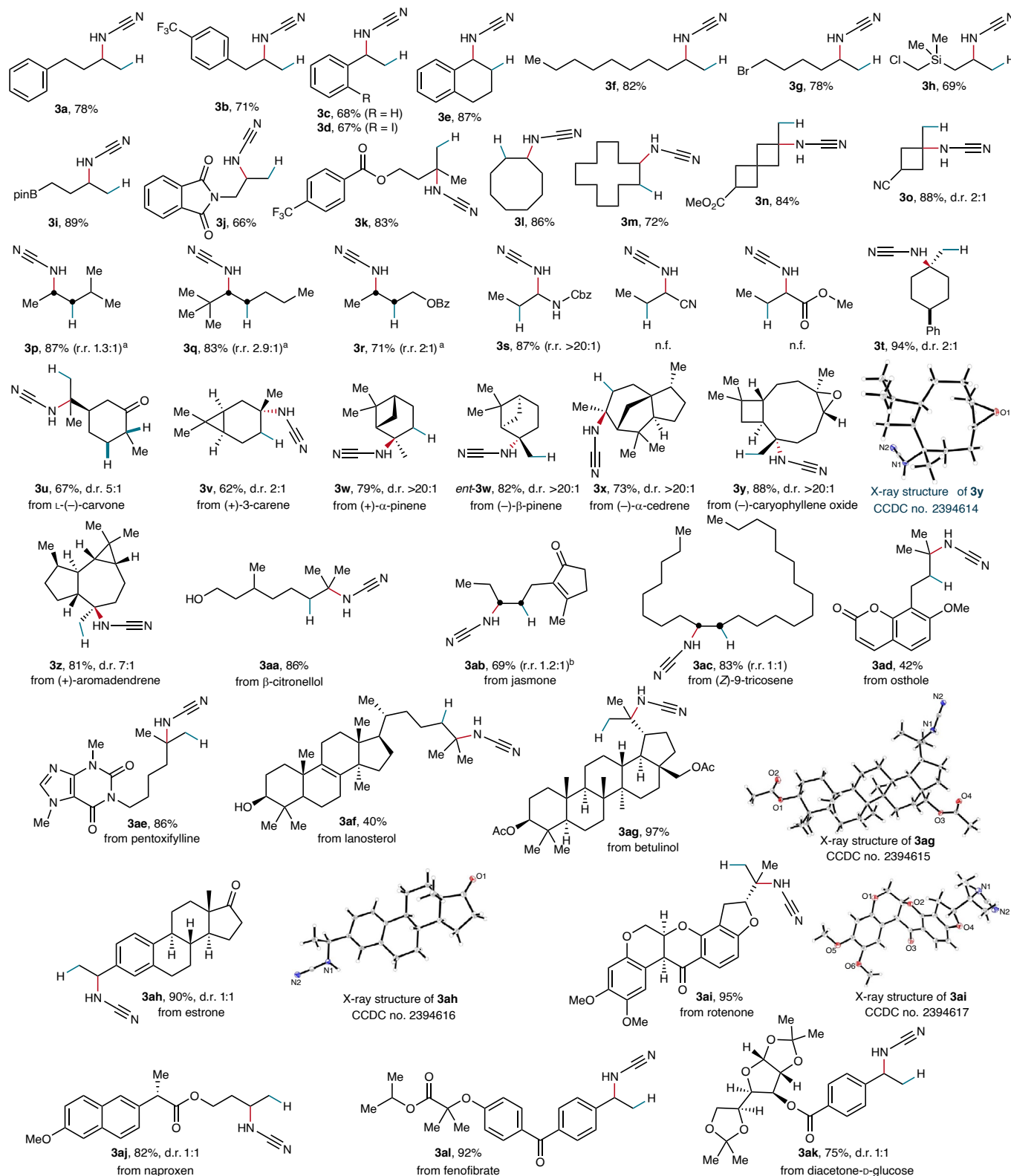


Fig. 3 | Scope of the Fe-catalysed hydroamidation of complex alkenes including natural products. Conditions: alkene (0.2 mmol) in EtOH-DCM (1:1, 2 ml). Fe(dibm)₃ (10 mmol%); iron tris(diisobutylmethane). Phenylsilane (0.6 mmol). Reagent 2o (0.24 mmol). n.f., no functionalization; Bpin, pinacolborane. X-ray structure of compounds 3y, 3ag, 3ah and 3ai. Reactions were carried out on 0.1 mmol scale, and all yields provided refer to isolated yields. Diastereoselectivity (if applicable) was determined by gas chromatography

or NMR spectroscopy analysis, and the relative configuration was assigned by X-ray analysis of single crystals or in analogy to a known related compound. r.r., regioselectivity ratio; Cbz, benzyloxycarbonyl. ^aMajor isomer of the two inseparable regioisomers drawn. ^bRegioisomers could not be unambiguously assigned. In products 3p, 3q, 3r, 3ab and 3ac, the two black dots indicate the sites where the N atom is attached to the carbon backbone in the two regioisomers. However, only one regioisomer is depicted in the figure.

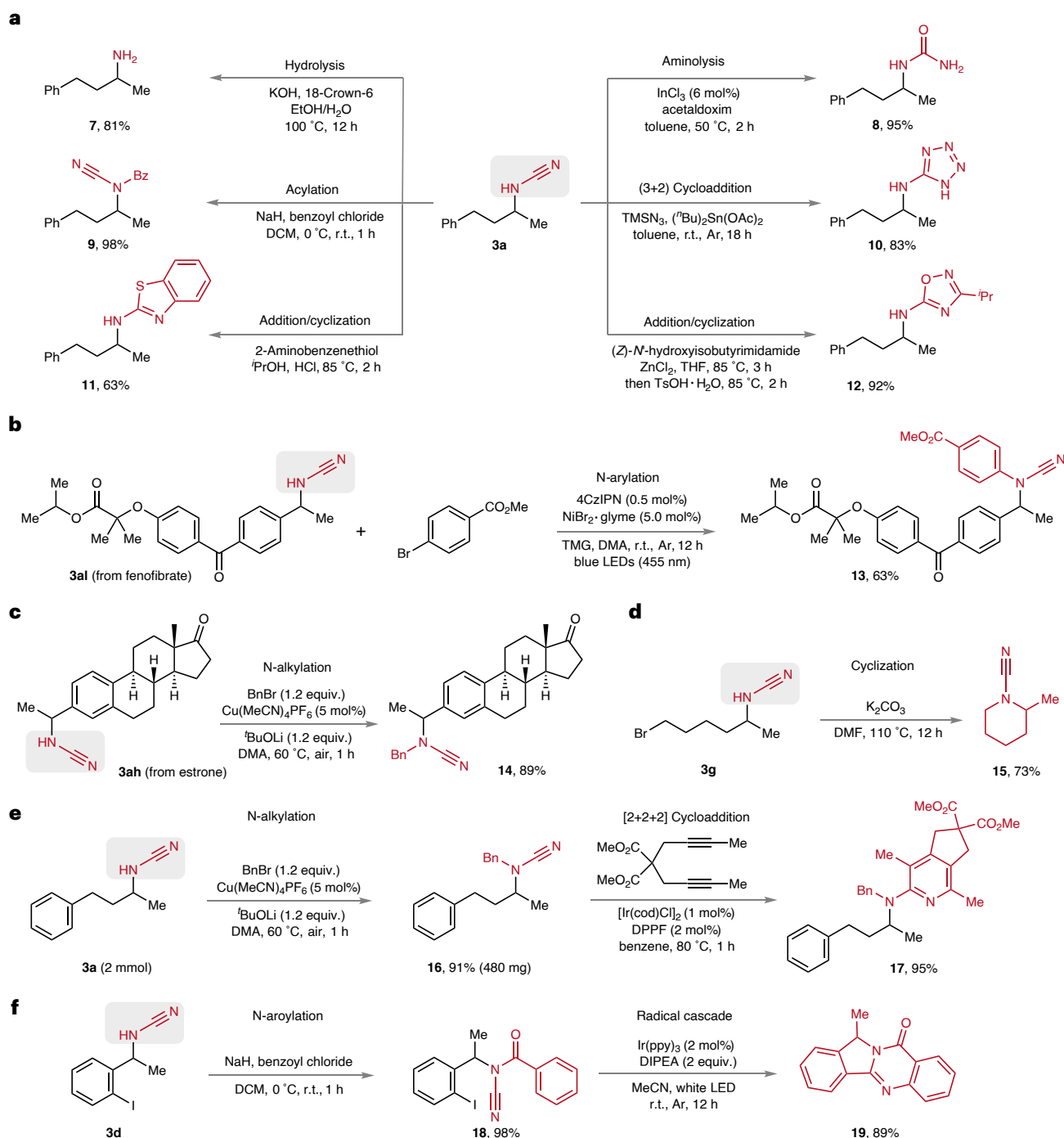


Fig. 4 | Chemical transformation of the cyanamide functionality. **a**, Different reactions of the cyanamide functionality either at the NH moiety or at the nitrile group. The free amine **7** can also be obtained through hydrolysis of the urea **8** with DETA at 140 °C for 12 h (93% yield). **b**, N-arylation through cooperative photoredox/nickel catalysis. **c**, Cu-catalysed N-benzylation. **d**, Intramolecular N-alkylation at elevated temperature under basic conditions. **e**, N-benzylation followed by Ir-catalysed cycloaddition for pyridine

construction. **f**, N-arylation and subsequent radical cascade cyclization. Reactions were carried out on 0.1 mmol scale, and all yields provided refer to isolated yields. TMS, trimethylsilyl; Bz, benzoyl; THF, tetrahydrofuran; 4CzIPN, 1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene; TMG, tetramethylguanidine; DMA, dimethylacetamide; LED, light-emitting diode; DMF, dimethylformamide; cod, 1,5-cyclooctadiene; DPPF, 1,1'-bis(diphenylphosphino)ferrocene; ppy, 2-phenylpyridine; DIPEA, diisopropylethylamine.

C(sp²)-(hetero)atom coupling was reported⁴². Applying this method, the C–N coupling of cyanamide **3a** with an aryl iodide was achieved (see **13**, Fig. 4b). Benzyl bromide can be used as N-alkylation reagent for cyanamides applying copper catalysis to afford the corresponding N-benzylated amides, as documented by the successful preparation of **14** (89%; Fig. 4c). Importantly, N-cyanated piperidines can be readily accessed through intramolecular N-alkylation under basic conditions,

as shown by the transformation of **3g** to **15** (73%; Fig. 4d). Cyanamides after N-benzylation are eligible substrates for Ir-catalysed [2 + 2 + 2] cycloaddition with α,ω-diynes (Fig. 4e). This atom-economic route was successfully used for the construction of a 2-aminopyridine (**17**, 95%)⁴³. Finally, starting from cyanamide **3d**, the synthesis of a tetracyclic pyrroloquinazoline was achieved in two steps using a photoredox radical cascade strategy (**19**, 89%; Fig. 4f)⁴⁴.

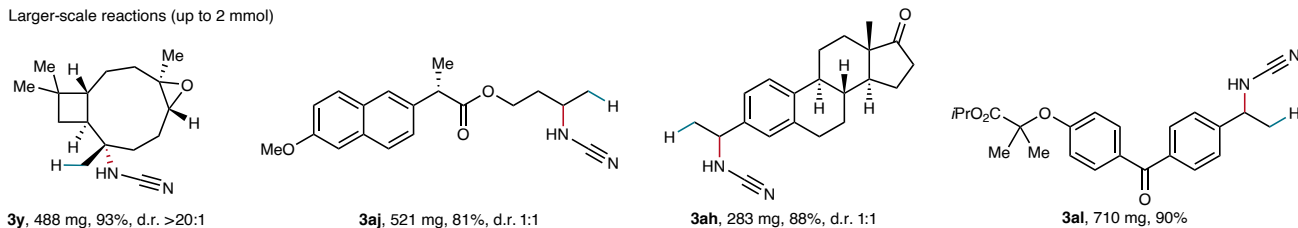
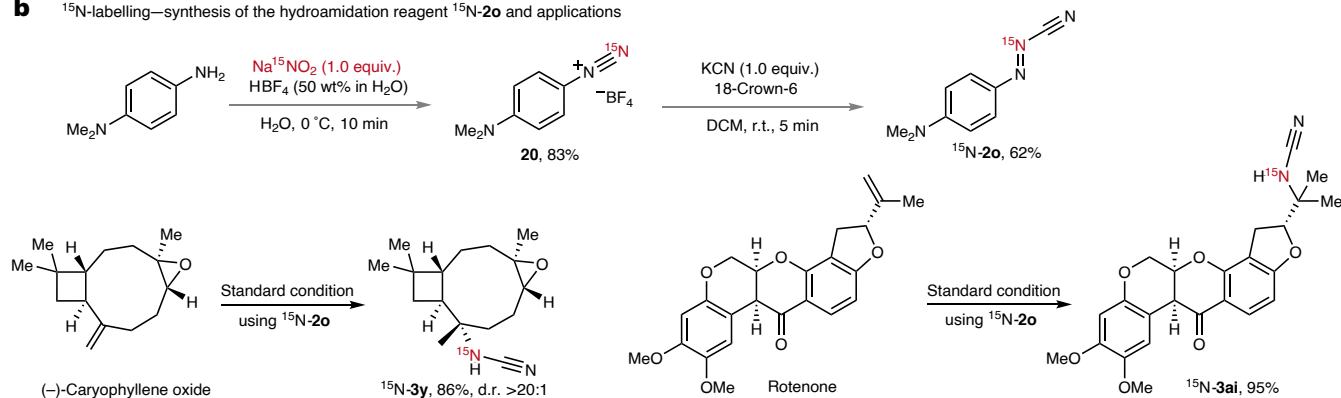
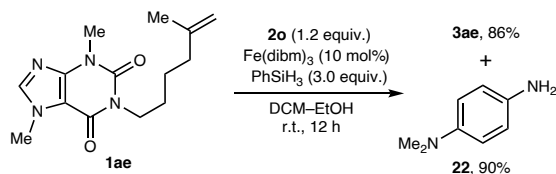
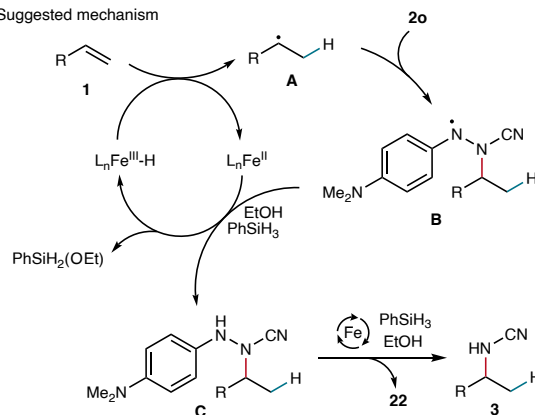
a Larger-scale reactions (up to 2 mmol)**b** ^{15}N -labelling—synthesis of the hydroamidation reagent ^{15}N -**2o** and applications**c** Radical probe experiment**d** Transformation of **2o** under optimized conditions**e** Suggested mechanism

Fig. 5 | Scale-up synthesis, ^{15}N -labelling, mechanistic studies and proposed mechanism. a, Larger-scale experiments using reagent **2o**. **b**, The ^{15}N -labelled hydroamidation reagent ^{15}N -**2o** is readily prepared from commercial $\text{Na}^{15}\text{NO}_2$. This reagent can be used for the synthesis of complex ^{15}N -marked amine

derivatives. **c**, A 5-*exo*-cyclization experiment showing the radical nature of the process. **d**, Analysis of the remainder of reagent **2o** after a successful hydroamidation under optimized conditions. **e**, The proposed mechanism for the Fe-catalysed alkene hydroamidation.

To demonstrate the practicality and robustness of the method in both medicinal and process chemistry, we ran the radical alkene hydrofunctionalization at a larger scale using $(-)$ -caryophyllene oxide as well as a naproxen, an estrone and a fenofibrate derivative as starting materials (Fig. 5a). Hydroamidation of $(-)$ -caryophyllene oxide on a 2 mmol scale gave 93% isolated yield of **3y** without compromising the high diastereoselectivity (>20:1). Likewise, the other three test compounds could be hydroamidated at a larger scale in very good yields (**3aj**, **3ah** and **3al**, 81–90%).

More excitingly, we were able to prepare the selectively ^{15}N -isotopically labelled hydroamidation reagent ^{15}N -**2o** in a two-step procedure using commercial $\text{Na}^{15}\text{NO}_2$ (52%), which was then successfully used for the ^{15}N -labelling of complex natural compounds through Fe-catalysed hydroamidation (Fig. 5b). Thus, $(-)$ -caryophyllene oxide was readily transformed to the isotopically labelled amide ^{15}N -**3y**, which was isolated 86% yield with excellent diastereoselectivity and an excellent ^{15}N -incorporation ratio (>95%). In analogy, rotenone was successfully converted to its ^{15}N -labelled cyanamide ^{15}N -**3ai** (95%). This strategy highlights the synthetic versatility and potential for precise

isotopic labelling within complex molecular frameworks, offering valuable tools for advanced applications in natural product synthesis.

To shed light on the mechanism of the hydroamidation, additional experiments were conducted. The radical nature of the hydroamidation was additionally supported by a hydrofunctionalization comprising a radical 5-*exo*-cyclization (Fig. 5c). α,α -Diallyl-malonic acid diethyl ester was reacted under the standard conditions with reagent **2o**, and the cyclization product **21** was isolated in good yield and *cis*-diastereoselectivity (71%, d.r. 10:1). We further investigated the fate of the remainder of reagent **2o** after successful hydroamidation. Radical hydrofunctionalization of **1ae** under the optimized conditions gave the desired product **3ae** in 86% along with 90% the aminoaniline **22** (Fig. 5d). It is important to note that aniline **22** serves as the starting material for the preparation of the reagent **2o**, demonstrating that the portion of the hydroamidation reagent not transferred to the alkene moiety is reusable, further enhancing the atom economy of our iron-catalysed hydroamidation process.

Based on these findings and previous reports on Fe-catalysed hydrofunctionalization reactions^{30,45,46}, we propose the following

mechanism (Fig. 5e). In-situ-generated iron(III) hydride first reacts regioselectively with the alkene via MHAT to give the corresponding adduct radical **A**. This C-radical **A** then adds regioselectively to reagent **2o** to give the hydrazinoyl radical **B**. The regioselectivity of this reaction is governed by steric and electronic effects. The N-radical **B** is then probably reduced by the immediately generated iron(II) species in the presence of ethanol to give the intermediate **C**. The concomitantly formed iron(III)OEt species can subsequently be reduced with the silane to reform the iron(III) hydride, completing the catalytic cycle. As a stoichiometric byproduct PhSiH₂OEt is formed. Further reduction of the N–N bond in the N-cyanated hydrazine **C** with phenylsilane through iron catalysis eventually provides the cyanamide product **3**. As a byproduct of the final reductive N–N bond cleavage step, the aniline **22** is formed.

Taken together, we have developed a general method for radical Markovnikov-type hydroamidation of various complex alkenes using a catalyst derived from earth-abundant iron. This was achieved through careful design of an alkyl radical amidation reagent. Tuning of steric and electronic effects of the radical acceptor showed that the readily prepared azo compound **2o** is an ideal radical amidation reagent. The alkene hydrofunctionalization reactions can be conducted under mild conditions, which is well reflected by the broad functional group tolerance and the broad scope. These practical transformations generally occur with high yields and high selectivity, and also late-stage hydroamidation of complex alkene-containing natural products is feasible. Importantly, we could show that the corresponding ¹⁵N-labelled hydroamidation reagent is easy to prepare from commercial Na¹⁵NO₂, allowing the late-stage ¹⁵N-labelling of complex alkenes through iron-catalysed radical hydroamidation. The product amides obtained through the hydroamidation process contain the highly valuable cyanamide functionality that can be chemically further transformed into diverse other important structural entities, as convincingly documented by a series of interesting follow-up reactions. We are confident that the strategy presented here will have broad applicability in pharmaceutical and synthetic research fields.

Methods

The general procedure for hydroamidation of alkenes was as follows. Under an argon flow, Fe(dibm)₃ (5.2 mg, 0.01 mmol, 10 mol%) was placed in an oven-dried Schlenk tube equipped with a magnetic stirring bar and dissolved in dry ethanol (0.5 ml) and dry dichloromethane (DCM, 0.5 ml). The alkene (0.10 mmol, 1.0 equiv.) and the radical amination/amidation reagent (0.12 mmol, 1.2 equiv.) were added, followed by dropwise addition of phenylsilane (0.300 mmol, 37.5 μl, 3.0 equiv.). The reaction was stirred for 12 h at room temperature. Afterwards, the solvent was evaporated and the residue was purified using flash chromatography to obtain the pure product.

Data availability

Details on the procedures and the corresponding datasets generated during and analysed during the current study are available within the article and its Supplementary Information. Crystallographic data for the structures reported in this article have been deposited at the Cambridge Crystallographic Data Centre, under deposition numbers CCDC 2394614 (**3y**), 2394615 (**3ag**), 2394616 (**3ah**) and 2394617 (**3ai**). Copies of the data can be obtained free of charge at <https://www.ccdc.cam.ac.uk/structures/>.

References

1. Ricci, A. *Amino Group Chemistry* (Wiley, 2008).
2. Roughley, S. D. & Jordan, A. M. The medicinal chemist's toolbox: an analysis of reactions used in the pursuit of drug candidates. *J. Med. Chem.* **54**, 3451–3479 (2011).
3. Guillena, G., Ramon, D. J. & Yus, M. Hydrogen autotransfer in the N-alkylation of amines and related compounds using alcohols and amines as electrophiles. *Chem. Rev.* **110**, 1611–1641 (2010).
4. Tripathi, R. P., Verma, S. S., Pandey, J. & Tiwari, V. K. Recent development on catalytic reductive amination and applications. *Current Org. Chem.* **12**, 1093–1115 (2008).
5. Surry, D. S. & Buchwald, S. L. Biaryl phosphane ligands in palladium-catalyzed amination. *Angew. Chem. Int. Ed.* **47**, 6338–6361 (2008).
6. Hartwig, J. F. Evolution of a fourth generation catalyst for the amination and thioetherification of aryl halides. *Acc. Chem. Res.* **41**, 1534–1544 (2008).
7. Górski, B., Barthelemy, A., Douglas, J., Juliá, F. & Leonori, D. Copper-catalysed amination of alkyl iodides enabled by halogen-atom transfer. *Nat. Catal.* **4**, 623–630 (2021).
8. Huang, L., Arndt, M., Gooßen, K., Heydt, H. & Gooßen, L. J. Late transition metal-catalyzed hydroamination and hydroamidation. *Chem. Rev.* **115**, 2596–2697 (2015).
9. Liu, R. Y. & Buchwald, S. L. CuH-catalyzed olefin functionalization: from hydroamination to carbonyl addition. *Acc. Chem. Res.* **53**, 1229–1243 (2020).
10. Streiff, S. & Jérôme, F. Hydroamination of non-activated alkenes with ammonia: a holy grail in catalysis. *Chem. Soc. Rev.* **50**, 1512–1521 (2021).
11. Lee, C., Kang, H.-J. & Hong, S. NiH-catalyzed C–N bond formation: insights and advancements in hydroamination of unsaturated hydrocarbons. *Chem. Sci.* **15**, 442–457 (2024).
12. Guin, J., Fröhlich, R. & Studer, A. Thiol-catalyzed stereoselective transfer hydroamination of olefins with N-aminated dihydropyridines. *Angew. Chem. Int. Ed.* **47**, 779–782 (2008).
13. Musacchio, A. J. et al. Catalytic intermolecular hydroaminations of unactivated olefins with secondary alkyl amines. *Science* **355**, 727–730 (2017).
14. Miller, D. C. et al. Anti-Markovnikov hydroamination of unactivated alkenes with primary alkyl amines. *J. Am. Chem. Soc.* **141**, 16590–16594 (2019).
15. Lardy, S. W. & Schmidt, V. A. Intermolecular radical mediated anti-Markovnikov hydroamination using N-hydroxyphthalimide. *J. Am. Chem. Soc.* **140**, 12318–12322 (2018).
16. Nguyen, T. M. & Nicewicz, D. A. Anti-Markovnikov hydroamination of alkenes catalyzed by an organic photoredox system. *J. Am. Chem. Soc.* **135**, 9588–9591 (2013).
17. Crossley, S. W. M., Obradors, C., Martinez, R. M. & Shenvi, R. A. Mn-, Fe-, and Co-catalyzed radical hydrofunctionalizations of olefins. *Chem. Rev.* **116**, 8912–9000 (2016).
18. Wasert, J. & Carreira, E. M. Convenient synthesis of alkylhydrazides by the cobalt-catalyzed hydrohydrazination reaction of olefins and azodicarboxylates. *J. Am. Chem. Soc.* **126**, 5676–5677 (2004).
19. Shen, X. et al. Ligand-promoted cobalt-catalyzed radical hydroamination of alkenes. *Nat. Commun.* **11**, 783 (2020).
20. Okamoto, T., Kobayashi, K., Oka, S. & Tanimoto, S. Cobalt-catalyzed reaction of nitric oxide with aryl-substituted olefins in the presence of tetrahydroborate ion. *J. Org. Chem.* **52**, 5089–5092 (1987).
21. Okamoto, T., Kobayashi, K., Oka, S. & Tanimoto, S. A high-yield regioselective synthesis of keto oximes from aryl-conjugated ethylenes and ethyl nitrite in the presence of cobalt complex and BH₄⁻ ion. *J. Org. Chem.* **53**, 4897–4901 (1988).
22. Waser, J., Nambu, H. & Carreira, E. M. Cobalt-catalyzed hydroazidation of olefins: convenient access to alkyl azides. *J. Am. Chem. Soc.* **127**, 8294–8295 (2005).
23. Gaspar, B., Waser, J. & Carreira, E. M. Cobalt-catalyzed synthesis of tertiary azides from α,α-disubstituted olefins under mild conditions using commercially available reagents. *Synthesis* **24**, 3839–3845 (2007).

24. Zhang, Y. et al. Modular synthesis of alkylarylazo compounds via iron(III)-catalyzed olefin hydroamination. *Org. Lett.* **21**, 2261–2264 (2019).
25. Gui, J. et al. Practical olefin hydroamination with nitroarenes. *Science* **348**, 886–891 (2015).
26. Zheng, J., Qi, J. & Cui, S. Fe-catalyzed olefin hydroamination with diazo compounds for hydrazone synthesis. *Org. Lett.* **18**, 128–131 (2016).
27. Leggans, E. K., Barker, T. J., Duncan, K. K. & Boger, D. L. Iron(III)/NaBH₄-mediated additions to unactivated alkenes: synthesis of novel 20'-vinblastine analogues. *Org. Lett.* **14**, 1428–1431 (2012).
28. Ishikawa, H. et al. Total synthesis of vinblastine, vincristine, related natural products, and key structural analogues. *J. Am. Chem. Soc.* **131**, 4904–4916 (2009).
29. Isayama, S. & Mukaiyama, T. A new method for preparation of alcohols from olefins with molecular oxygen and phenylsilane by the use of bis(acetylacetonato)cobalt(II). *Chem. Lett.* **18**, 1071–1074 (1989).
30. Bhunia, A., Bergander, K., Daniliuc, C. G. & Studer, A. Fe-catalyzed anaerobic Mukaiyama-type hydration of alkenes using nitroarenes. *Angew. Chem. Int. Ed.* **60**, 8313–8320 (2021).
31. Chesnokov, G. A. & Gademann, K. Concise total synthesis of peyssonoside A. *J. Am. Chem. Soc.* **143**, 14083–14088 (2021).
32. Xu, B., Liu, C. & Dai, M. Catalysis-enabled 13-step total synthesis of (–)-peyssonoside A. *J. Am. Chem. Soc.* **144**, 19700–19703 (2022).
33. Gan, X.-C. et al. Iron-catalyzed hydrobenzylation: stereoselective synthesis of (–)-eugenial C. *J. Am. Chem. Soc.* **145**, 15714–15720 (2023).
34. Gong, X., Huang, J., Sun, X., Chen, Z. & Yang, M. Total synthesis of illisimonin A and merrilactone A. *Angew. Chem. Int. Ed.* **62**, e202306367 (2023).
35. Zheng, X., Guo, X., Wang, H., Zhou, P.-P. & Chen, X. Total synthesis of (±)-rubrifloridilactone A. *J. Am. Chem. Soc.* **146**, 7198–7203 (2024).
36. Cai, B.-G., Empel, C., Yao, W., Koenigs, R. & Xuan, J. Azoxy compounds—from synthesis to reagents for azoxy group transfer reactions. *Angew. Chem. Int. Ed.* **62**, e202312031 (2023).
37. Ahern, M., Leopold, A., Beadle, J. & Gokel, G. Phase-transfer synthesis of arenediazocyanides and synthesis of arenediazosulfones from arenediazonium cations and the formation of reduced pyridazines by [2+4] cycloaddition reactions. *J. Am. Chem. Soc.* **104**, 548–554 (1982).
38. Larraufie, M.-H. et al. The cyanamide moiety, synthesis and reactivity. *Synthesis* **44**, 1279–1292 (2012).
39. Schmidt, M. et al. N-cyanopiperazines as specific covalent inhibitors of the deubiquitinating enzyme UCHL1. *Angew. Chem. Int. Ed.* **63**, e202318849 (2024).
40. Zhang, J. et al. Palladium(0)-catalyzed enantioselective construction of multifunctional piperidine derivatives from 1,3-dienes, N-cyano imines, and beyond. *Org. Lett.* **25**, 8133–8138 (2023).
41. Noshita, M., Shimizu, Y., Morimoto, H. & Ohshima, T. Diethylenetriamine-mediated direct cleavage of unactivated carbamates and ureas. *Org. Lett.* **18**, 6062–6065 (2016).
42. Ghosh, I. et al. General cross-coupling reactions with adaptive dynamic homogeneous catalysis. *Nature* **619**, 87–93 (2023).
43. Hashimoto, T. et al. Iridium-catalyzed [2+2+2] cycloaddition of α,ω-dienes with cyanamides. *Adv. Synth. Catal.* **357**, 3901–3916 (2015).
44. Han, Y., Jiang, H., Wang, R. & Yu, S. Synthesis of tetracyclic quinazolinones using a visible-light-promoted radical cascade approach. *J. Org. Chem.* **81**, 7276–7281 (2016).
45. Elfert, J., Bhunia, A., Daniliuc, C. & Studer, A. Intramolecular radical oxygen-transfer reactions using nitroarenes. *ACS Catal.* **13**, 6704–6709 (2023).
46. Elfert, J., Bhunia, A., Daniliuc, C. & Studer, A. Iron-catalyzed radical Markovnikov hydrohalogenation and hydroazidation of alkenes. *Nat. Commun.* **15**, 7230 (2024).

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Author contributions

M.H. and A.S. conceptualized the work. M.H. and A.S. conceived and designed the experiments. M.H. performed the experiments and analysed the data. C.G.D. conducted the X-ray crystal structure analysis. M.H. and A.S. wrote the paper.

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Competing interests

The authors declare no competing interests.

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