Direct Synthesis of Unprotected 2-Azidoamines from Alkenes via an Iron-Catalyzed Difunctionalization Reaction

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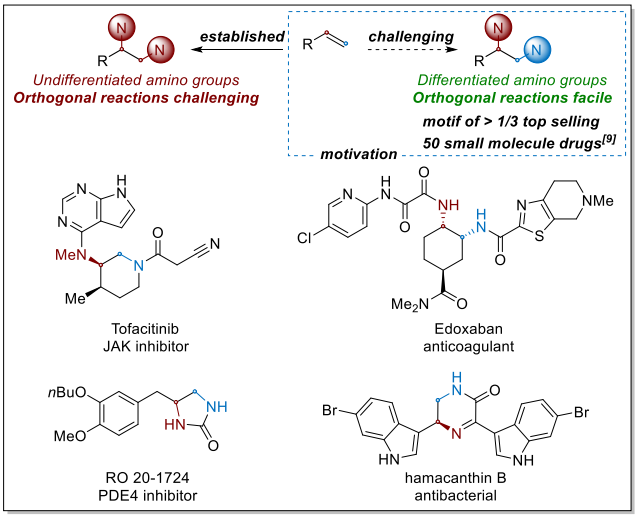
Supporting Information Placeholder

ABSTRACT: Unprotected, primary 2-azidoamines are versatile precursors to vicinal diamines, which are among the most common motifs in biologically active compounds. Herein, we report their operationally simple synthesis through an iron-catalyzed difunctionalization of alkenes. A wide array of alkene substrates are tolerated, including complex drug-like molecules and a tripeptide. Facile derivatizations of the azidoamine group demonstrate the versatility of this masked diamine motif in chemoselective, orthogonal transformations. Applications of the methodology in the concise synthesis of RO 20-1724 and in a formal total synthesis of (±)-hamacanthin B further demonstrate the broad synthetic potential of this highly functional group tolerant reaction.

Vicinal diamines are privileged structural motifs encountered across the molecular sciences, particularly in natural products, medicinal chemistry and catalysis.[1] Therefore, the rapid access to this ubiquitous functionality starting from simple hydrocarbon feedstocks, such as alkenes, can dramatically facilitate the synthesis and discovery of functional molecules. Several approaches have been explored to install two vicinal amino groups through the catalytic diamination of alkenes.[2] However, these reactions are still considerably limited when compared to well established methods for the synthesis of other important 1,2-difunctionalized alkanes, such as diols.[3] Besides the scope being often limited to activated alkenes, a more significant limitation is the lack of methods to access a diamine precursor which can be orthogonally transformed into synthetically relevant unsymmetrical diamine products (Scheme 1).

Scheme 1. Importance of unsymmetrical vicinal diamines



The azido group has recently emerged as a convenient amino group surrogate in formal catalytic diamination reactions (Scheme 2).[4] Most notably, Lin[5] and Xu[6] have described elegant electrochemical and iron-catalyzed processes, respectively, for the direct synthesis of diazides starting from a wide variety of alkenes (Scheme 2a). Whereas these reactions are powerful tools to access symmetrical vicinal diamines in two steps, they are less suitable in cases where two chemically distinct amino groups need to be orthogonally synthesized (e. g. through amide coupling), a scenario which is common in target-oriented synthesis.[7] Indeed, diazides suffer from poor regioselectivity upon monoreduction, making the direct synthesis of 2-azidoamines from alkenes highly challenging.[8]

Scheme 2. Synthesis of azido-containing, masked vicinal diamines from alkenes

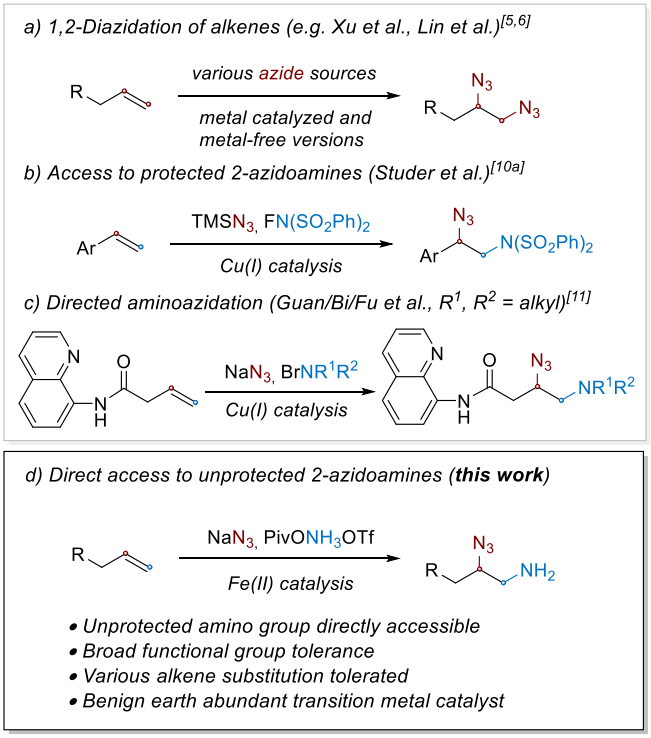
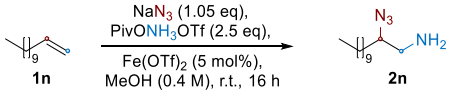


Table 1. Selected optimization results[a]



Entry	Deviation from standard conditions	Yield of 2[b]
1	None	68
2	Under inert atmosphere	65
3	$Fe(OAc)_2$	65
4	$Fe(OAc)_2$ trace metals basis (>99.99%)	66
5	No metal	<5
6	$AcONH_3OTf$ as reagent	43
7	1.5 eq $PivONH_3OTf$	43
8	Covalent azide source[c]	<5
9	MeCN as solvent	64
10	HFIP as solvent	<5

[a]See SI for detailed information. [b]H-NMR yields in % using trichloroethylene as an internal standard. [c]Such as trimethylsilyl azide, tosyl azide or diphenylphosphoryl azide.

Alternatively, some progress has been made to install both an azido group and a protected amino group. However, these reactions are synthetically limited because they either introduce a nearly unprotectable form of the amino group (e.g. $N(SO_2Ph)_2$, Scheme 2b)[10] or they rely on a suitably positioned directing group (Guan/Bi/Fu´s work, Scheme 2c).[11]

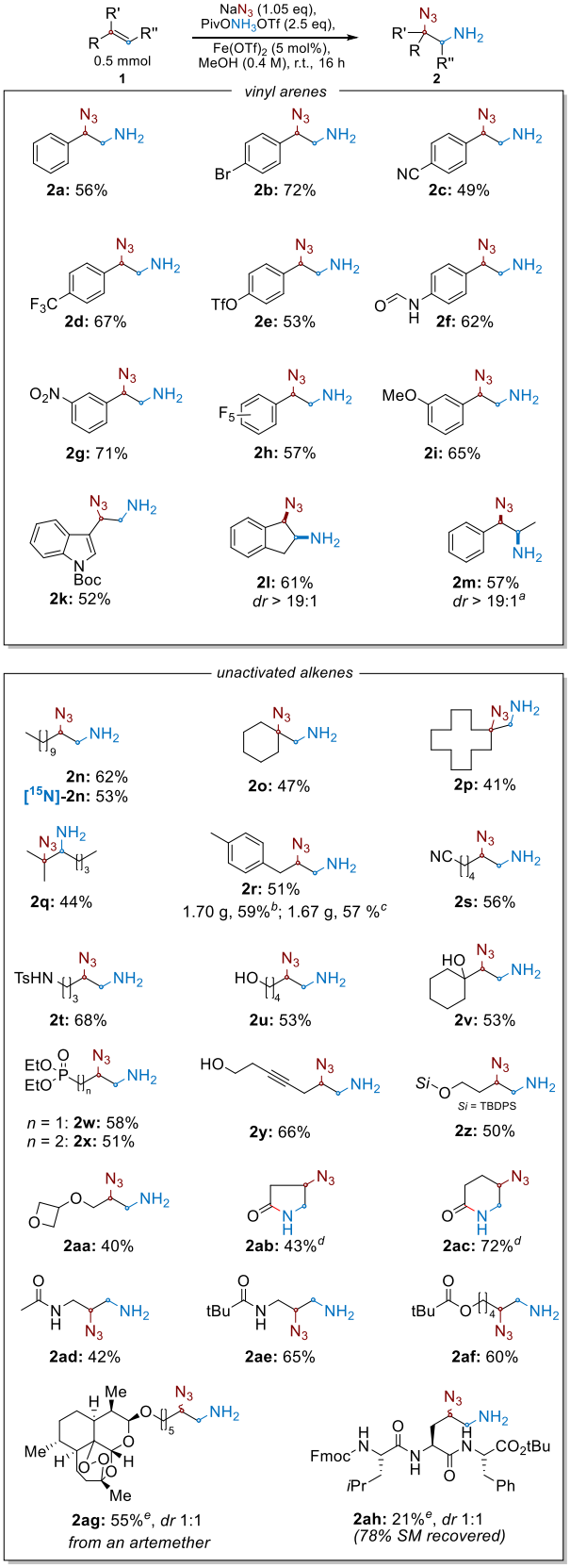
Thus, a simple, catalytic aminoazidation reaction exhibiting a broad substrate scope and allowing for the installation of, ideally, an unprotected amino group, would certainly allow for the step-economical and orthogonal synthesis of nearly any 1,2-diamine derivative, thereby accelerating the synthesis and discovery of bioactive molecules (Scheme 2d).[12–15]

Herein, we report an iron-catalyzed difunctionalization reaction of unactivated alkenes to directly access unprotected, primary 2-azidoamines. This process tolerates a broad substrate scope including unactivated mono-, di- and trisubstituted alkenes bearing unprotected polar functional groups commonly found in drug-like molecules.

Based on our recent research interest to access amino alcohols and 2-chloroamines under iron catalysis,[16] we set out to develop conditions for the aminoazidation of alkenes using a traditionally more challenging substrate, 1-dodecene (Table 1, for further details see SI). Evaluation of different azide salts in combination with different transition metal catalysts and hydroxylamine derivatives led us to identify suitable reaction conditions for the aminoazidation of 1-dodecene. Especially iron(II) acetate and triflate efficiently

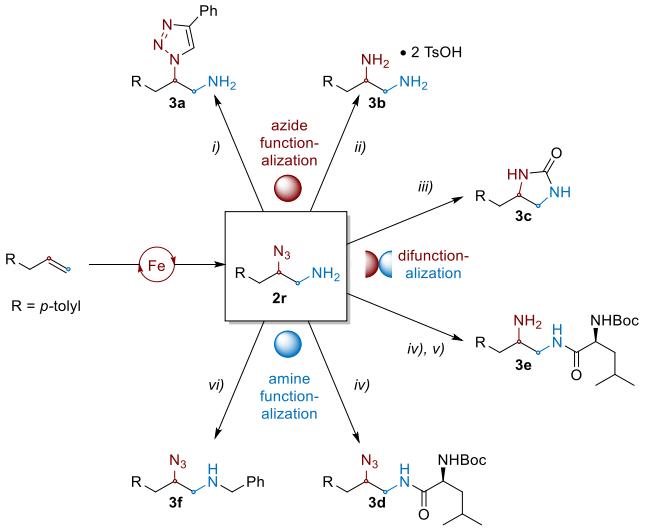
catalyzed the desired reaction in good yields using this usually unreactive substrate (Entries 1, 3, 4). The possible catalytic effect of impurities from the iron source was ruled out by a control experiment with a trace metals-based source which

Scheme 3. Scope of the aminoazidation reaction



Yields are of isolated products; *dr* determined by ^{1}H-NMR. [a](*E*)-alkene used. [b]Purified via column chromatography. [c]Purified via ammonium salt precipitation. [d]Starting from an ester bearing a terminal alkene. [e]See SI for detailed experimental information.

Scheme 4. Derivatization of azidoamine 2r



Conditions: i) Phenyl acetylene (1.2 eq), sodium ascorbate (0.4 eq), $CuSO_4$•5 H_2O (20%), tBuOH/H_2O, r.t., 62%; ii) PPh_3 (1.2 eq), THF/H_2O, 50 °C, then TsOH•H_2O (2.2 eq), Et_2O, r.t., 75%; iii) PMe_3 (1.1 eq), CO_2, MeCN, r.t., 67%; iv) *N*-Boc-Leu (1.2 eq), DIPEA (2.4 eq), HBTU (1.3 eq), THF, r.t., 70%; v) PMe_3 (3.4 eq), THF/H_2O, r.t., 79%; vi) benzaldehyde (1.2 eq), acetic acid (2.0 eq), $NaBH(OAc)_3$ (1.4 eq), DCE, r.t., 31%.

delivered the same outcome, confirming that the iron species plays a key role.[17] Covalent azide sources failed to afford any product while ionic azides were most suitable (Entry 8). Interestingly, this reaction can be performed open to air in technical grade methanol, a critical issue in the possible rapid adoption of this new reaction by synthetic practitioners.

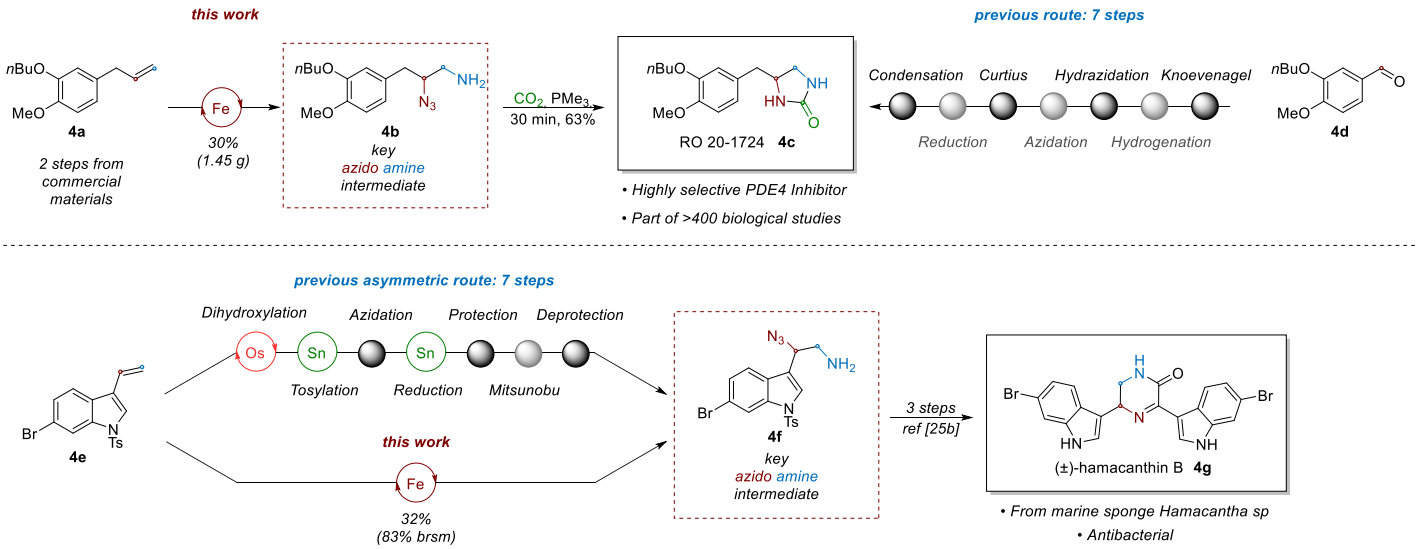
With the optimized conditions in hand, we then investigated the scope of the aminoazidation reaction (Scheme 3). Looking into aryl substituted alkenes, electron-poor (**2b**–**e, 2g**–**h**), as well as electron-rich (**2k**) systems were efficiently transformed into their corresponding azidoamines. Aryl substituted internal alkenes indene and *trans*-β-methyl styrene afforded *syn*-addition products **2l** and **2m** in excellent diastereoselectivity (*dr* > 19:1).

With regards to unactivated alkenes, mono-, 1,1-di- and trisubstituted alkenes performed well (**2n**–**q**). This is especially important, since the products bearing a tertiary azide offer the possibility to be transformed into an α-tertiary amine functionality, a common motif in natural products with only limited accessibility.[18]

Aside from various carbon scaffolds, several functional groups were found to be tolerated under the reaction conditions, such as aryl (pseudo)halides (**2b**, **2e**), multiple aryl substituents (**2b**–**l**), nitriles (**2c**, **2s**), protected amines (**2k**, **2t**, **2ah**), free alcohols (**2u**, **2v**, **2y**) and phosphonates (**2w**, **2x**). Remarkably, even alkynes in close proximity remained untouched (**2y**). Acid labile functionalities were also tolerated, e.g. free, tertiary alcohols (**2v**), silyl ethers (**2z**) and *N*-Boc protecting groups (**2k**, Boc = *tert*-butyloxycarbonyl). Furthermore, heterocycles (indole in **2k**, oxetane in **2aa**) further expanded the wide scope of this transformation. Synthetically relevant carboxylic acid derivatives, such as amides (**2ab**–**ae**), formamides (**2f**) and esters (**2af**), performed well under the reaction conditions. Interestingly, esters with a shorter alkenyl chain cyclized in the process to afford lactams **2ab** and **2ac** in a single step.

This excellent functional group tolerance encouraged us to tackle even more challenging substrates. An artemether derived substrate (**2ag**) was converted in moderate yield to the desired product, leaving the highly oxidized cage structure and the sensitive peroxo

Scheme 5. Synthetic applications of 2-azidoamines[23, 25]



group intact. Excitingly, an allyl glycine-based tripeptide reacted cleanly to form the corresponding azidoamine product **2ah** in an unoptimized 21% yield along with 78% of unreacted alkene starting material isolated, demonstrating the excellent chemoselectivity of this reaction. Another aspect worth mentioning here is the scalability of the presented methodology. On a gram scale, azidoamine **2r** was obtained in comparable yield and purity, regardless of the method of purification (see SI for further details). Collectively, these results clearly highlight the synthetic potential of this new methodology for early- and late-stage introduction of an azidoamine functionality.

Due to the high demand for the synthesis of isotopically labeled compounds, we synthesized a [^{15}N] labeled version of the reagent, starting from [^{15}N]-hydroxylamine.[19] This new reagent was used to generate the corresponding labeled product [^{15}N]-**2n** with excellent isotopic purity and in good yields, highlighting its potential for the rapid synthesis of [^{15}N]-compounds.

We next investigated the potential of azidoamines in subsequent synthetic transformations. Azides have found broad synthetic utility in copper-catalyzed azide-alkyne cycloaddition (CuAAC)[20] and Staudinger-bioconjugation.[21] Using the azidoamine as a starting material, a Click-type CuAAC reaction proceeded selectively at the azido group, leaving the unprotected amine untouched. The synthetic utility of the formed 2-azidoamines was further demonstrated through several orthogonal derivatization reactions (Scheme 4).

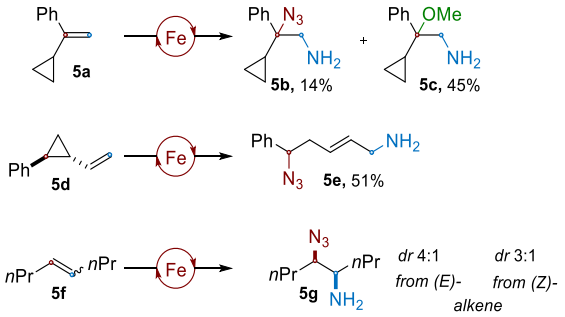
Subjecting **2r** to a phosphine mediated Staudinger reduction afforded diamine **3b** in good yield. Conventional reductive amination or amide coupling delivered secondary amine **3f** and amide 3**d**. The azide moiety of the latter could be further reduced in a subsequent step to obtain primary amine **3e**. This sequence clearly showcases the orthogonality of this simple masked diamine motif. Making combined use of both nitrogen moieties, a Staudinger/aza-Wittig (SAW) cyclization afforded directly imidazolidinone **3c** in one step.[22]

We next applied our methodology to the concise synthesis of biologically relevant molecules. RO 20-1724 (Scheme 5) is a highly specific inhibitor of cAMP-specific phosphodiesterase type IV (PDE 4, IC_{50} = 2 µM) commonly used in pharmaceutical research.[23] Starting from allyl aryl **4a**, we could access key intermediate **4b** on a 1.45 g scale through a direct iron-catalyzed aminoazidation reaction. Subjecting this intermediate to the adapted SAW conditions next afforded RO 20-1724 in 63% yield. This new route does not only decrease the step count significantly (previously reported: 7 steps), but, according to the report by the Audioso lab,[22] also bears the potential to introduce an isotopically labeled carbon atom through the use of labeled CO_2 in the last step.[24]

Furthermore, we utilized our methodology in the formal total synthesis of the antibacterial marine natural product hamacanthin B.[25] A previous enantioselective synthesis of (*S*)-**4g** relied on a 7-step sequence, which included several steps based on toxic compounds, such as an osmium catalyst and tin reagents, to access key intermediate **4f** which was next converted to the final natural product in three steps. Remarkably, our new aminoazidation reaction enabled us to completely bypass the 7-step sequence to access key intermediate **4f** in a single catalytic step, providing a new, shorter formal synthesis of the racemic form of this natural product.

Intrigued by the features of the presented methodology, we next conducted some control experiments to shed light on the reaction mechanism. Comparing the outcome of two different radical clocks, the cyclopropyl ring of the slower opening substrate **5a** was preserved, whereas the rapidly opening substrate **5d** readily underwent ring opening (Scheme 6).[26] Correlating it with rates reported in literature, the lifetime of the presumably formed radical could be tentatively stated as short-lived (**5a**$^{\bullet}$: k_r =4 x 10^5 s^{-1}, **5d**$^{\bullet}$: k_r =7 x 10^{10} s^{-1}).[26] Furthermore, unactivated, internal alkenes (*E*)- and (*Z*)-oct-4-ene resulted in a very similar ratio of *cis*- and *trans*- product, supporting a stepwise mechanism involving a carbon-centered radical. At this stage it is not clear whether the amino group is introduced via an aminium radical[27] or an iron-based aminating species.[28]

Scheme 6. Control experiments



Yields are of isolated products; *dr* determined by GC-FID. See SI for detailed experimental information.

In conclusion, we have reported the direct synthesis of unprotected primary 2-azidoamines from a wide range of different alkenes. This mild and highly selective transformation provides an operationally simple and robust access to versatile 2-azidoamines using a benign and inexpensive iron catalyst. The products obtained can further engage in various derivatizations where the azidoamine motif functions as an ideal masked 1,2-diamine, enabling a fast and orthogonal transformation to many useful building blocks. In a broader context, these features emphasize the value of the presented methodology for the versatile synthesis of diamine derivatives which are ubiquitously found in bioactive molecules.

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Notes

The authors declare no competing financial interest.

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