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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 is 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, as well as in the formal total syntheses of both (±)-hamacanthin B and (±)-quinagolide, further demonstrate the broad synthetic potential of this highly functional group tolerant reaction.

Introduction

Vicinal diamines are privileged structural motifs encountered across the molecular sciences, particularly in natural product synthesis, 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 amination 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 a scope often limited to activated alkenes and a reliance on protecting groups, 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 amination reactions (Scheme 2).⁴

Most notably, Lin⁵ and Xu⁶ 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

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 ₃ OTf as reagent	43
7	1.5 eq PivONH ₃ OTf	43
8	Covalent azide source ^c	<5
9	Technical grade MeOH	66
10	MeCN as solvent	64
11	HFIP as solvent	<5
12	Anhydrous LiN ₃ (2.5 eq)	75

^aSee SI for detailed information. ^b¹H-NMR yields in % using trichloroethylene as an internal standard. ^cSuch as trimethylsilyl azide, tosyl azide or diphenylphosphoryl azide.

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 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 the amino group in a form which is difficult to deprotect (e.g. N(SO₂Ph)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).^{12–16}

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.

Results and discussion

Based on our recent research interest to access amino alcohols and 2-chloroamines under iron catalysis,¹⁷ 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 delivered the same outcome, confirming that the iron species plays a key role.¹⁸ Evaluating different *O*-acylhydroxylamine reagents suggested that steric encumbrance around the carbonyl functionality was essential for efficient reactivity (Entry 6 and SI Table S2). 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

Scheme 3. Scope of the aminoazidation reaction

Yields are of isolated products; *dr* determined by ¹H-NMR. ^a(*E*)-alkene used, (*Z*)-alkene gave the same major diastereoisomer, albeit

in 5:1 *dr*. ^b*dr* determined by GC-FID. ^cPurified via column chromatography. ^dPurified via ammonium salt precipitation. ^eStarting from an ester bearing a terminal alkene. ^fSee SI for detailed experimental information.

Scheme 4. Derivatization of azidoamine **2t**

Conditions: i) Phenyl acetylene (1.2 eq), sodium ascorbate (0.4 eq), CuSO₄•5 H₂O (20%), tBuOH/H₂O, r.t., 62%; ii) PPh₃ (1.2 eq), THF/H₂O, 50 °C, then TsOH•H₂O (2.2 eq), Et₂O, r.t., 75%; iii) PMe₃ (1.1 eq), CO₂, MeCN, r.t., 67%; iv) *N*-Boc-Leu (1.2 eq), DIPEA (2.4 eq), HBTU (1.3 eq), THF, r.t., 70%; v) PMe₃ (3.4 eq), THF/H₂O, r.t., 79%; vi) benzaldehyde (1.2 eq), acetic acid (2.0 eq), NaBH(OAc)₃ (1.4 eq), DCE, r.t., 31%.

methanol, a critical issue in the possible rapid adoption of this new reaction by synthetic practitioners. During our optimization we found that excess anhydrous lithium azide gave an increase in yield (75% NMR yield), however, sodium azide was chosen for further experiments due to its commercial availability (Entry 12).

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-, di- and trisubstituted alkenes performed well (**2n–s**). 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.¹⁹ Remarkably, a triene derived from α -ionol reacted exclusively at the mono-substituted alkene, demonstrating a high sterically-controlled site-selectivity (**2r**). In all cases only one regioisomer was observed, making the reaction fully regioselective.

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**, **2u**), protected amines (**2k**, **2v**, **2ak**), free alcohols (**2w**, **2x**, **2aa**) and phosphonates (**2y**, **2z**). Remarkably, even alkynes in close proximity remained untouched (**2aa**). Acid labile functionalities were also tolerated, e.g. free, tertiary alcohols (**2x**), silyl ethers (**2ab**) and

N-Boc protecting groups (**2k**, Boc = *tert*-butoxycarbonyl). Furthermore, heterocycles (indole in **2k**, oxetane in **2ac**) further expanded the wide scope of this transformation. Synthetically relevant carboxylic acid derivatives, such as amides (**2ad–ag**), formamides (**2f**) and esters (**2ah**), performed well under the reaction conditions. Interestingly, esters with a shorter alkenyl chain cyclized in the process to afford lactams **2ad** and **2ae** in a single step.

This excellent functional group tolerance encouraged us to tackle even more challenging substrates. An artemether derived substrate (**2ai**) was converted in moderate yield to the desired product, leaving the highly oxidized cage structure and the sensitive peroxy group intact. Excitingly, an allyl glycine-based tripeptide reacted cleanly to form the corresponding azidoamine product **2ak** 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 **2t** was obtained in comparable yield and purity. To our delight, the product could be isolated in clean form through precipitation of the ammonium salt followed by liberation of the amine upon basic workup, avoiding purification by column chromatography completely. (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 [¹⁵N] labeled version of the reagent, starting from [¹⁵N]-hydroxylamine.²⁰ This new reagent was used to generate the corresponding labeled product [¹⁵N]-**2n** with excellent isotopic purity and in good yields, highlighting its potential for the rapid synthesis of [¹⁵N]-compounds. (see SI for detailed information)

We next investigated the potential of azidoamines in subsequent synthetic transformations. Azides have found broad synthetic utility in copper-catalyzed azide-alkyne cycloaddition (CuAAC)²¹ and Staudinger-bioconjugation.²² Using the azidoamine **2t** 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 **2t** to a phosphine mediated Staudinger reduction afforded diamine **3b** in good yield. Conventional reductive amination or amide coupling delivered secondary amine **3f** and amide **3d**. 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.²³

We next applied our methodology to the concise synthesis of biologically relevant molecules. RO 20-1724 (**4c**, Scheme 5) is a highly specific inhibitor of cAMP-specific phosphodiesterase type IV (PDE 4, IC₅₀ = 2 μM) commonly used in pharmaceutical research.²⁴ Starting from allyl aryl **4a**, we could access key intermediate **4b** on a 1.45 g scale with an unoptimized yield of 30% 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 Audisio lab,²³ also bears the potential to introduce short-lived isotopes through the use of labeled CO₂ in the last step.²⁵

Furthermore, we utilized our methodology in the formal total synthesis of the antibacterial marine natural product hamacanthin B

Scheme 5. Synthetic applications of 2-azidoamines^{24, 26, 27}

Yields are of isolated products; *dr* determined by NMR analysis. See supporting information for detailed experimental details.

4g.²⁶ A previously reported synthesis relied on an azidoamine intermediate for a key SAW-cyclization step to construct the diaza heterocycle of the final product. Remarkably, our new aminoazidation reaction enabled us to access key intermediate **4f** in a single catalytic step, providing a new and rapid formal synthesis of the racemic form of this natural product in a single step.

We next turned our attention toward applying our reaction to the synthesis of 3-azidopiperidines which are important precursors for a wide range of pharmaceutically active 3-aminopiperidines.^{13f} A representative thereof is the specific D₂ receptor agonist quinagolide, a drug prescribed against hyperprolactinemia and commercialized as its racemate.^{27a-c} Recently, Chavan and co-workers have shown alternative routes to construct the molecule, one featuring a 3-azidopiperidine intermediate (**4n**).^{27d-f} In this synthesis, the azido intermediate could be easily transformed into the desired sulfamide, however, the preparation of the masked diamine required a lengthy synthesis. We therefore targeted the synthesis of this 3-azidopiperidine core using our methodology. Starting from literature-known allyl β -tetralone **4i**, diastereoselective reduction gave rise to the desired *cis*-alcohol **4k** which was subsequently mesylated (see SI for further information, Ms = mesyl). Having set an appropriate leaving group, we applied our methodology to obtain azidoamine **4m** in a *dr* of 1:1 and 39% yield. Cyclization to form the piperidine ring, followed by alkylation led to the desired key intermediate **4n** in 8 steps from commercially available starting materials.

Collectively, these synthetic applications clearly show the method's potential for the synthesis of bioactive compounds.

Intrigued by the features of the presented methodology, we next conducted some control experiments to shed light on the reaction mechanism (Scheme 6). We first compared the behavior of two radical clocks with different rates of opening. The cyclopropyl substrate **5a**, which has a relative slow rate of opening, did not open, whereas the rapidly opening cyclopropyl substrate **5d** readily underwent ring opening (Scheme 6, a).²⁸ Correlating it with rates reported in literature, the lifetime of the putative formed radical can be tentatively Scheme 6. Control experiments

stated as short-lived (**5a**: $k_t = 4 \times 10^5 \text{ s}^{-1}$, **5d**: $k_t = 7 \times 10^{10} \text{ s}^{-1}$).²⁸ Subjecting radical clock **5a** to the standard conditions also gave methoxylated side-product **5c**, the formation of which could indicate the intermediacy of a benzylic cation which is then trapped by the methanol solvent. However, non-benzylic positions do not lead to any detectable formation of methoxylated product, suggesting the absence of a carbocation intermediate in these cases. Despite its short-lived nature, we next attempted to trap the radical intermediate. When (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) was added to the reaction, no adduct could be detected, albeit the yield of the azidoamine **5g** dropped significantly. Additional support for a step-wise mechanism is provided by the lack of stereoretention when using either (*E*)- and (*Z*)-oct-4-ene **5h**, which both led to a similar ratio of (*R**, *R**)- and (*R**, *S**)-product **5i**. Interestingly, a closer look into this experiment revealed, that isomerized alkene (*E*)-**5h** was detected in small amounts under standard reaction conditions. A similar observation was reported in a previously disclosed aminohalogenation reaction and was explained by a possible reversible addition of an amino radical onto a double bond.^{29,30}

To delve deeper into the electronic dependence of the aminoazidation reaction, a Hammett-study was next performed using intermolecular competition experiments. We obtained a slope of $\rho = -0.51$ (Scheme 6, d), which suggests only minor positive charge buildup in the transition state of the product selective step of the reaction. Assuming that this step is the C–N bond forming event, the relatively small rho-value correlates better with radical-based amination mechanisms than carbocationic ones.³¹

Collectively, these results are consistent with the results previously obtained for our aminochlorination reaction.^{17a} However, the complete lack of stereoretention may indicate that the putative carbon-centered radical intermediate is slightly more long-lived in the aminoazidation case. Based on these experiments, we propose a mechanism in which the hydroxylamine-derived reagent is first reductively cleaved by an iron catalyst. The resulting, putative *N*-centered radical³² or iron-nitrenoid³³ could then add to an alkene. The resulting

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

C-centered radical is then trapped by an iron-coordinated azido ligand to release the product.

Conclusion

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.

ASSOCIATED CONTENT

The Supporting Information is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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