Selective Synthesis of Functionalised Linear Aliphatic Primary Amines Using Photoredox Catalysis

Robin Cauwenbergh  
University of Antwerpen  
https://orcid.org/0000-0002-7433-0534

Prakash Sahoo  
University of Antwerpen

Rakesh Maiti  
University of Antwerp

Andrea Guidetti  
University of Antwerp

Shoubhik Das (✉️ shoubhik.das@uantwerpen.be)  
University of Antwerp

Article

Keywords:

Posted Date: September 2nd, 2022

DOI: https://doi.org/10.21203/rs.3.rs-2013443/v1

License: ☒️ This work is licensed under a Creative Commons Attribution 4.0 International License.  
Read Full License
Selective Synthesis of Functionalised Linear Aliphatic Primary Amines Using Photoredox Catalysis

Robin Cauwenbergh\textsuperscript{a,c}, Prakash Kumar Sahoo\textsuperscript{a,c}, Rakesh Maiti\textsuperscript{a,c}, Andrea Guidetti\textsuperscript{b}, and Shoubhik Das\textsuperscript{a*}

Abstract

Linear aliphatic primary amines are crucial and every year, at least, millions of tonnes are required to meet this demand. Therefore, significant interest has been shown in finding new chemical routes for the synthesis of aliphatic primary amines. However, to comply with the sustainability requirements, synthetic routes using inexpensive feedstocks are highly prioritized. In this regard, the hydroaminoalkylation (HAA) reaction, i.e. functionalization of an olefin with an aminoalkyl group and a hydrogen atom across the C=C double bond, is desirable due to the wide availability and lower price of olefins. Although photoredox catalysis is already known to synthesize amines, the synthesis of linear aliphatic amines is only limited to hydroaminomethylation (HAM) reactions i.e. functionalization of an olefin with an aminomethyl group and has never been applied to the synthesis of long chain linear aliphatic primary amines. Considering this, the synthesis of functionalized linear aliphatic primary amines is demonstrated by using a novel photoredox-mediated decarboxylative hydroaminoalkylation reaction, which exhibited a wide scope with excellent yields. The strength of this method is demonstrated by drug synthesis, late-stage modifications of complex pharmaceuticals and elaborated with detailed mechanistic studies.

Introduction

Amines are the key compounds used as bulk chemicals, materials, applied in biology, and find many more applications.\textsuperscript{1-5} Expediently, amine functionalities are present in a large number of pharmaceuticals and play crucial roles such as bypassing the blood-brain barrier to achieve biological activities, solubility, and pharmacokinetics (Figure 1A).\textsuperscript{6} In fact, >75\% of top selling drugs of the year 2021 contain amine/nitrogen moieties.\textsuperscript{7-9} Among different amines, primary amines are highly important due to their wide applications as precursors and valuable intermediates for the synthesis of advanced chemicals, pharmaceuticals, agrochemicals and materials.\textsuperscript{3,6} Particularly, linear aliphatic primary
amines are vital and every year, at least, a million-tons are required to meet this demand. Therefore, there is a significant interest in finding new chemical routes for the synthesis of aliphatic primary amines. Although a plethora of synthetic methods such as amination reactions, reductive amination reactions, Gabriel synthesis, Curtius rearrangement, Deléphine reaction and others exist, these reactions suffer from poor selectivity to attain primary amines over secondary and tertiary amines, require harsh reaction conditions, or toxic precursors. On the other hand, to comply with the sustainability requirements, synthetic routes using inexpensive feedstock and non-toxic aminating reagents are highly prioritized. In this regard, metal-catalyzed alkene hydroamination and hydroaminoalkylation provided significant opportunities due to the wide availability of olefins (Figure 1B). In these reactions, easily available alkenes, which are manufactured in tremendous scales during petroleum refining, are functionalized with an amino(alkyl) group and a hydrogen atom across the C=C double bond.

Over the past decade, photoredox catalysis has become quite popular to attain sustainability under mild reaction conditions. One way of making primary amines is through the photochemical reduction of imines and in 2018, Gilmore et al. reported an excellent chemoselective approach using benzaldehydes and ammonia to form primary amines by reducing the in situ formed iminium ion to an α-amino radical. Later, in 2020, Rovis et al. expanded this method by using preformed imines or iminium salts. They developed excellent strategies but these procedures required sacrificial and (over)stoichiometric amount of reagents and could not generate the longer chain aliphatic primary amines. Another way to synthesize primary amines is the hydroamination reactions, i.e. direct coupling of amines with alkenes. The use of primary or secondary amines underwent a single electron oxidation of the amine to form aminium radical cation - or amine centered radical intermediates, which could not generate primary amines. However, by using ammonia as the aminating source, this problem has been circumvented. It should be noted that photocatalytic hydroamination towards primary amines still remains challenging as the primary amine product is more electron-rich, thus more prone to be oxidized. Moreover, the primary amine is more nucleophilic, which provides mixtures of secondary and tertiary amines through alkylation reactions. In this respect, Nicewicz et al. successfully bypassed these problems by oxidizing alkenes to radical cation intermediates, which was reacted by the nucleophile such as ammonia. Later, Nicewicz’s procedure became the basis for the photocatalytic synthesis of amines by using the hydroamination approach. Although the photocatalytic hydroamination has
been studied extensively, still the synthesis of longer chain aliphatic primary amines could not be achieved by using hydroamination reaction.

**Figure 1.** A) Pharmaceutical compounds bearing the (amino)methyl group. B) Selected state-of-the art. C) Our Strategy.
This problem could be resolved by functionalizing alkenes with an aminoalkyl group instead of an amine group using the hydroaminoalkylation (HAA) reaction. However, in the synthesis of linear aliphatic amines within the photocatalyzed HAA reactions, only the hydroaminomethylation (HAM), where the olefin is functionalized with an aminomethyl group, has been reported till now. In fact, photocatalysis has shown highly regioselective HAM reactions under mild reaction conditions via the formation of α-aminoalkyl radicals from secondary or tertiary amines. These radicals underwent a Giese-type reaction with Michael acceptors such as malonates and malononitriles, α,β-unsaturated carbonyl compounds, esters, and alkenylpyridines. In addition, decarboxylation, desilylation and other pathways for α-aminomethyl radical generations have also been reported. Although, in general, these developed HAM reactions provided the product in high yield, these procedures still have limitations. For example, only Michael acceptors, highly activated vinylpyridines, or 1,1-diphenylethylenes reacted in the presence of, in most cases, an expensive iridium photocatalyst. Despite the achievements in photocatalytic HAM reactions, synthesis of longer chain aliphatic primary amines was still a hurdle to solve in photoredox catalysis. This problem was solved by Cresswell et al. and reported the use of unprotected primary alkylamines for the HAA of styrenes. Although a wide variety of primary alkylamines were functionalized, however, this strategy always required the presence of a tertiary α-amino radical center and limited the general synthesis of linear aliphatic amines. Therefore, a selective strategy for the general synthesis of linear aliphatic primary amines is a big challenge to solve in photocatalysis.

Considering all this information, the development of an organic photocatalyst-based strategy for the selective synthesis of linear aliphatic primary amines, is extremely important in organic synthesis. It is well known that 4CzIPN (E_{ox} = +1.35 V vs SCE) in its excited state form can readily oxidize organic molecules. We envision that a base-promoted decarboxylation of N-protected amino acids (I) could produce an aminoalkyl radical (III). We anticipate the highly nucleophilic character of this radical to readily react with the olefin to form a new radical species (IV). Due to the highly reductive nature of the catalyst (E_{red} = -1.21 V), the radical is converted to the carbanion (V), which should form the linear aliphatic amine product (VI) upon protonation. Based on this strategy, we report a 4CzIPN-mediated reaction to afford linear aliphatic primary amines which tolerated diverse functional groups and generated the desired products in excellent yields.
Results and discussion

At the outset of our reaction, 1,1-diphenylethylene (1) and boc-glycine (2) were chosen as model substrates to optimize the hydroaminomethylation reaction conditions (Table 1 and Table S1-S11). To our delight, when a solution of 1 and 2 with 1.0 eq. of cesium carbonate (Cs$_2$CO$_3$) in the presence of 5 mol% of 4CzIPN was stirred for 24 hours under a 40 W blue Kessil lamp at ambient temperature, the desired product was obtained in 94% yield (Table 1, entry 2). After a thorough base screening, similar yield was obtained (95%) when much cheaper sodium hydroxide (NaOH) was used instead of Cs$_2$CO$_3$ (Table 1, entry 1). Next, different solvents were applied (Table 1, entries 4 and 5) and among them, DMF also provided the quantitative yield, however, owing to the greener aspect, DMSO was chosen as the solvent. Unfortunately, lowering down the catalyst loading to 1 mol%, reduced the product yield substantially to 65% (Table 1, entry 7). Delighted by these results, control experiments were carried out to confirm the importance of each reagent under the optimized reaction conditions and revealed that the light source, photocatalyst (PC) and base, were all essential for this transformation (Table 1, entry 8). Interestingly, under aerobic conditions, the yield was dropped to 76%, indicating that anaerobic conditions were essential for obtaining excellent yields (Table 1, entry 9). Lastly, the reaction was performed on a gram-scale, and excitingly, 91% yield of the product was obtained (Table 1, entry 10).

Table 1. Optimization of reaction conditions. a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Deviation from standard conditions</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>None</td>
<td>95</td>
</tr>
<tr>
<td>2</td>
<td>Cs$_2$CO$_3$ (1.0 equiv.) instead of NaOH</td>
<td>94</td>
</tr>
<tr>
<td>3</td>
<td>DIPEA (1 equiv.)</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>MeCN (1 mL)</td>
<td>61</td>
</tr>
<tr>
<td>5</td>
<td>DMF (1 mL)</td>
<td>95</td>
</tr>
<tr>
<td>6</td>
<td>5 mol% 4CzIPN</td>
<td>97</td>
</tr>
</tbody>
</table>
With the optimized reaction conditions in hand, we sought to determine the substrates scope of the hydroaminoalkylation reaction for the olefin component (Scheme 1A). At the beginning, non-hindered external vinylarenes were studied (Scheme 1A, 3-18) and our focus started with the activated styrenes (3 and 4), which provided excellent yields even when an electron-withdrawing group was present (94 and 95%, respectively). To show the applicability of this transformation, the formed product was deprotected in situ to provide almost complete conversion (88%) to the linear aliphatic free amine product. After the successful transformations of activated external vinylarenes, our focus shifted towards different substituted styrenes (5-18). Delightfully, our mild reaction conditions were compatible with a wide range of substituted styrenes, involving both electron-donating and electron-withdrawing groups, which provided a versatile platform for further synthetic manipulations. This versatility in styrene substrates is a significant advancement from the previously reported HAM protocols, which only worked on Michael acceptors, highly activated 1,1-diphenylethylenes or vinylpyridines. In this regard, non-substituted styrene (5) afforded 81% yield. Further electron-withdrawing substituents such as $p$-bromo- (6), $p$-trifluoromethyl- (7), and $p$-cyano (8) substituents on styrene provided moderate to good yield (45-79% yield). After successfully exploring the electron-neutral and -withdrawing vinylarenes, curiosity drove us to explore electron-donating substrates. These substrates usually are difficult substrates for this reaction because the formed carbanion in the benzylic position gets destabilized when electron-donating groups are present in the $para$-position of styrene. Delightfully, substituents like tert-butyl (9), trimethylsilyl (10), and phenyl (11) worked with our system, provided the corresponding products in moderate to good yields (42-75%). After achieving this, ortho- (12), tri- (13), and penta-substituted (14)
styrenes worked in moderate to excellent yields (32-90% yield). Furthermore, external vinylarenes bearing α-substituents (15-18) were well tolerated and provided good to excellent yields (54-91%).

Scheme 1. *Reaction conditions A: Alkene (1 equiv.), protected amino acid (1 equiv.), 4CzIPN (0.02 equiv.), NaOH (1 equiv.), DMSO (1 mL) at rt for 24 hours under irradiation with 456 nm KESSIL lamp. *Reaction conditions B: 1 (1 equiv.), free amino acid (1.5 equiv.), Boc-anhydride (1.5 equiv.), NaOH (1 equiv.), 4CzIPN (0.04 equiv.), DMSO (2 mL) at rt for 4h and subsequently for 24 hours under irradiation with 456 nm KESSIL lamp. Optimization studies for condition B are given in Table S4-S7. *Yield given for free amine using TFA as the deprotecting agent. *48 hours. *Cs₂CO₃ was used as the base. *Reaction conditions C: performed using condition A at 70 °C for 72 hours. Optimization studies for conditions C are given in Table S8-S11. *H NMR yields are given and was determined by using 1,3,5-trimethoxybenzene as internal standard. See ESI for full experimental details.
Next, we focused on exploring our catalytic system's versatility on sterically challenging internal vinylarenes. To our delight, a plethora of bulky internal vinylarenes underwent these reactions to provide good to excellent yields. Bulky trisubstituted compounds such as triphenylethylene (19) and 3,3-diphenylacrylonitrile (20) provided moderate to good yields (48-83%). On the other hand, styrenes having α-substitution of both electron-withdrawing groups such as -CN (21), -CO₂Me (23 and 24), and donating groups such as -CH₃ (22) moiety provided excellent yields (68-80%). It is worth noting that in the case of substrates where both Michael acceptor and styrene type moieties were present in the same molecule, the α-aminoradical attacked selectively to the styrene moiety and yielded regioselective products. In addition, stilbene (25) and internal imine (26) were tolerated in this photocatalytic reaction (50 and 46% yield, respectively). Expediently, heteroaromatic vinylarenes such as 2-vinylpyridine (27), 2-(1-phenylvinyl)pyridine (28), 2-vinylbenzo[b]thiophene (29), and 4-methyl-5-vinylthiazole (30) also underwent HAM reaction, provided the product in good to excellent yields (44-87%). Compared to previous reports, the scope could be extended to other heteroaromatic olefins than 2-vinylpyridine with good to excellent yields.

The robust catalytic system not only worked with styrene derivatives, but it was also able to functionalize various Michael acceptors. Simple Michael acceptors (31, 33-38, 40 and 41) along with bulky adamentyl acrylate (32) and (vinylsulfonyl)benzene (39) provided reasonable to excellent yields (48-86% yield). Remarkably, pregabalin (38), an anticonvulsant and anxiolytic drug, was synthesized by our method in 78% yield. Our newly developed method decreased the amount of steps for the initial industrial preparation of pregabalin tremendously from more than 8 steps to only one step using the cheap and commercially available (E)-Methyl 5-methylhex-2-enoate. Further, the natural product carvone (40), which is used as an air freshening product, can also undergo HAM leading to the desired product in good yield (61%). Noteworthy, the newly developed method regioselectively underwent HAM with the conjugated double bond without interfering with the free double bond.

Further, to prove the generality of our method, different linear long-chain amino acids were investigated on 1,1-diphenylethylene (Scheme 1B). Interestingly, boc-protected 3-aminopropanoic (42), 4-aminobutanoic (43), 5-aminopentanoic (44) and 6-aminohexanoic (45) acids successfully underwent HAM reaction to yield the products in moderate to good yields (45-62%). Surprisingly, the tripeptide glycyl-glycyl-glycine (46) and γ-amino-β-hydroxybutyric acid (47) with free amine and hydroxy functional groups, respectively, were well-tolerated in our system (90 and 47%, respectively). Ultimately, the
robustness was proven when long-chain amino acids such as 4-benzamidobutanoic acid and 12-benzamidododecanoic acid were reacted with both 1, styrene (5) and 2-vinylpyridine (27) to yield the desired products in moderate to good yields (40-67%). Moreover, when methyl methacrylate (35) reacted with 12-benzamidododecanoic acid, 96% product formed proving that our method also worked with Michael acceptors and long-chain amino acid for HAA.

To further demonstrate the utility of our method, we showed effective conversion of our products into two drug molecules (prenylamine & pheniramine, Scheme 2A). Firstly, products 54 and 55 using our catalytic system were hydrolyzed separately in the presence of trifluoroacetic acid (TFA) to afford free amine containing 56 and 57. After that, the amines were used in the next step without further purification. A reductive amination of 56 with benzyl acetone provided the drug prenylamine (58) in 68% overall yield. To obtain the drug pheniramine (59), formic acid mediated dimethylation of 57 was set up, providing 59 in 74% yield.

Next, we moved to assess the applicability of our method in late-stage functionalizations (LSF). LSF is the chemoselective process of installing a particular functional group into a complex molecule. This modification facilitates the development of structure-activity relationships (SAR) and improves the physical properties such as solubility, stability etc. Since vinylarene is a common motif in various natural products and drug molecules, therefore, we selected large biomolecular derivatives for the LSF using our reaction conditions (Scheme 2B). Estrone, bexarotene, fenofibrate derivatives were functionalized with boc-protected glycine and afforded the products (60-62) in moderate to excellent yields (Scheme 2B, 56 - 81%). Interestingly, boc-protected γ-aminobutyric acid with estrone derivative also worked well (63; 48% yield). To our delight, when 12-benzamido-dodecanoic acid was employed with bexarotene using our catalytic condition, the product 64 was obtained in 50% yield, proving the generality of the reaction for the synthesis of longer aliphatic amines. In addition, bioactive picamilon, drug baclofen, and gabapentin were also functionally modified with our catalytic conditions, providing the desired products in high yields (65- 75%, 66- 77%; 67 – 78%).
After demonstrating the scope of our catalytic system, we became interested to prove the reaction mechanism (Scheme 1C). For this purpose, a series of control experiments were conducted (Scheme 3). The radical clock experiment with cyclopropane group bearing boc-protected glycine at the α-position provided the mixture of stereoisomeric ring-opened product 68, suggested that the radical cascade reaction of cyclopropane rings opened to yield the α-aminoalkyl radical (III, Scheme 1C). In fact, the presence of radicals can be further confirmed by trapping the α-aminomethyl radical (III, Scheme 1C) with (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO). In this regard, when 1 equiv. of TEMPO was added to the catalytic reaction, no desired product formed, instead, α-aminomethyl-TEMPO adduct 69 was detected in HR-MS spectrum. Additional radical suppressed experiments with the use of 2,6-di-tert-butyl-4-methylphenol (BHT, 1 equiv.) demonstrated the radical involvement in the reaction. Another interesting control experiment with D-glycine was achieved to investigate the source of the H-atom at the α-position of the product VI (Scheme 1C), which will provide the evidence of the reductive radical-polar crossover process. When in-situ formed boc-protected D-glycine molecule
underwent photocatalytic HAM reaction with 1,1-diphenylethylene as a coupling partner, 75% deuteration at the α -position of the final product (70) was observed.

Scheme 3. Mechanistic studies.

To further support this mechanism, Stern-Volmer studies were conducted to determine which reaction components were effective quenchers for the excited photocatalyst. To our delight, our proposed mechanism is consistent with these studies as the deprotonated form of boc-glycine, by means of NaOH, quenched the excited photocatalyst to the more reducing and negatively charged 4CzIPN•− (Figure 2 and Figures S2 and S3).

Figure 2. Stern-Volmer experiment between 4CzIPN and boc-glycine in the presence of NaOH as the base.
In summary, we have developed a visible-light mediated redox-neutral decarboxylative HAA reaction methodology for the synthesis of linear aliphatic amines using 4CzIPN as the organophotocatalyst. This method was successful for the synthesis of various hydroaminoalkylated products, including (heteroaromatic) vinylarenes and Michael acceptors in moderate to excellent yields. The success of this method was proven by the synthesis of long-chain linear aliphatic amines from longer chain unnatural amino acids in good to excellent yields. To the best of our knowledge, this article is the first example of a photoredox-mediated HAA reaction for the synthesis of linear aliphatic amines. Moreover, the robustness was proven by the late-stage functionalization of pharmaceuticals as well as the synthesis of drug compounds. Additionally, mechanistic studies clearly revealed the formation of radicals by the elimination of carbon dioxide from the amino acid.

Methods

Representative procedure for the hydroaminoalkylation using protected glycine.

An oven-dried microwave vial was charged with a magnetic stirring bar, the alkene (0.2 mmol), protected amino acid (1 equiv.), Cs2CO3 (1 equiv.), 4 CzIPN (0.02 equiv.) and dry DMSO (1 mL) were added under nitrogen atmosphere using standard Schlenck techniques. After, the vial was placed under KESSIL 40W 456 nm blue light irradiation for 24h at room temperature. The reaction mixture was quenched with water, extracted with EtOAc (3 times) and concentrated under reduced pressure. Finally, the desired product is obtained after purification by silica gel column chromatography with heptane/EtOAc (0 to 20%) as the eluent.

Representative procedure for the hydroaminoalkylation using unprotected amino acids.

An oven-dried microwave vial was charged with a magnetic stirring bar, the alkene (0.2 mmol), unprotected amino acid (1.5 equiv.), Boc-anhydride (1.5 equiv.), NaOH (1 equiv.), 4 CzIPN (0.04 equiv.), and dry DMSO (2 mL) were added under a nitrogen atmosphere using standard Schlenck techniques. After, the reaction mixture was stirred for 4 hours at room temperature and subsequently for 24 hours at room temperature under KESSIL 40W 456 nm blue light irradiation. The reaction mixture was quenched with water, extracted with EtOAc (3 times), and concentrated under reduced pressure. Finally, the desired product is obtained after purification by silica gel column chromatography with heptane/EtOAc (0 to 20%) as the eluent.
Representative procedure for the hydroaminoalkylation using protected longer chain amino acids.

An oven dried 20 mL Schlenk Tube was charged with 4CzIPN (0.02 equiv.), NaOH (1.0 equiv.), protected amino acid (1.0 equiv.) and a magnetic stirring bar. The reaction mixture was degassed by three freeze/pump/thaw cycles (3 min) using Schlenck techniques and refilled with nitrogen. After, olefin (0.2 mmol) and dry DMSO (2 ml) were added. After, the reaction was allowed to stir under 456 nm blue KESSIL light at 70 °C. The mixture was monitored via TLC, quenched with water and extracted with EtOAc (3 times). Lastly, the solvent was removed under reduced pressure. NMR yield was determined by adding 1,3,5-trimethoxybenzene as the internal standard. The pure compound was obtained using Flash column chromatography using heptane:EtOAc (0-50 %) as the eluent.

Data availability

Supplementary information and chemical compound information accompany this paper at www.nature.com/ncomms. The data supporting the results of this work are included in this paper or in the Supplementary Information and are also available upon request from the corresponding author.

References


Shang, T.-Y. et al. Recent advances of 1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene (4CzIPN) in photocatalytic transformations. Chemical Communications 55, 5408-5419 (2019).


Gawley, R. E. Overview of Carbanion Dynamics and Electrophilic Substitutions in Chiral Organolithium Compounds. Topics in Stereochemistry 26, 93-133 (2010).


Acknowledgements

We acknowledge FWO research grant, FWO PhD fellowship (to RC), BOF-DOCPRO (to PKS) and Odysseus grant (to SD).

Author information

Authors and affiliations

Organic Synthesis Division, Department of Chemistry, University of Antwerp, 2020 Antwerp, Belgium.

BIMEF laboratory, Department of Chemistry, University of Antwerp, 2610 Antwerp, Belgium.

R.C., P.K.S., and R.M. contributed equally.

Contributions

R.C. and S.D. conceived and designed the experiments. R.C., P.K.S. and R.M. performed the experiments, analysed the data and prepared the manuscript. R.C. and A.D. performed the Stern-Volmer experiments. R.C., P.K.S. and R.M. contributed equally to this work. All authors critically reviewed the manuscript and approved the final version.
Corresponding author

Correspondence to Shoubhik Das. Email: shoubhik.das@uantwerpen.be

Ethics declaration

The authors declare no competing interests.
Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SI.pdf