

The synthesis of chiral branched allylamines through dual photoredox/nickel catalysis

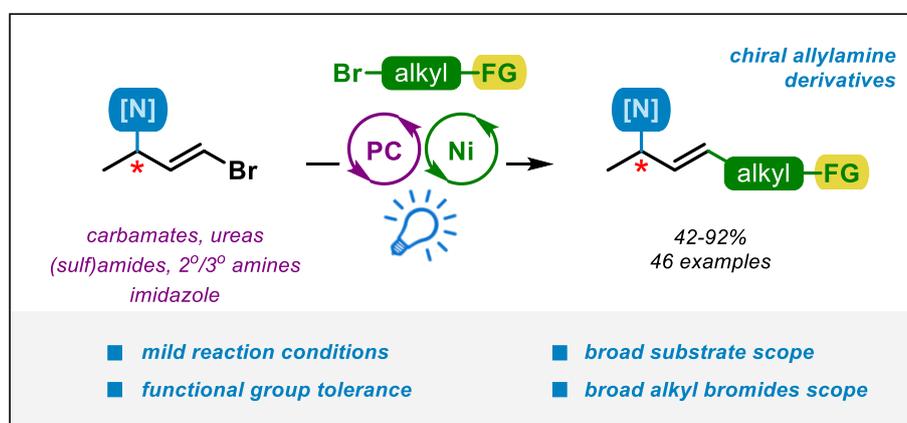
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Graphical abstract



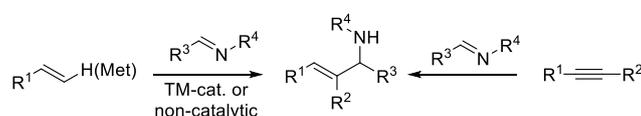
Abstract: Allylamines are versatile building blocks in the synthesis of various naturally occurring products and pharmaceuticals. In contrast to terminal allylamines, the methods of synthesis of their branched congeners with internal, stereodefined double bond are less explored. This work describes a new approach for a preparation of allylamines via cross-coupling of alkyl bromides with simple 3-bromoallylamines by merging photoredox and Ni-catalysis. The reaction proceeds under mild conditions, under blue light irradiation and in the presence of an organic dye, 4CzIPN, as a photocatalyst. The scope of suitable reaction partners is broad, including alkyl bromides bearing reactive functionalities (e.g., esters, nitriles, aldehydes, ketones, epoxides), and *N*-protected allylamines, as well as *N*-allylated secondary and tertiary amines and heterocycles. The employment of non-racemic starting materials allows for rapid and easy construction of complex multifunctional allylamine derivatives without erosion of enantiomeric purity.

Keywords: allylamines, photocatalysis, cross-coupling reactions, nickel catalysis

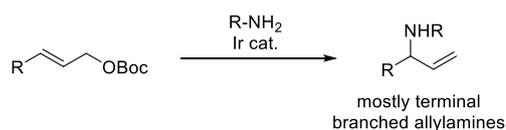
Introduction

Allylamines are versatile building blocks in the synthesis of various naturally occurring products and pharmaceuticals.^{1,2} The branched allylamines, with an internal double bond, constitute a large subgroup of this class of organic compounds, that are present in several synthetic intermediates and natural products as a structural scaffold.^{2,3} In contrast to terminal allylamines, the methods for their preparations are less explored, thus the further development of general and efficient methods for the synthesis is still a topic of considerable interest.²

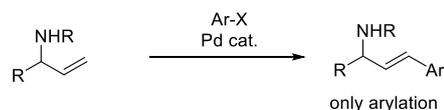
1) Addition of alkenes, alkenyl metals or alkynes to imines



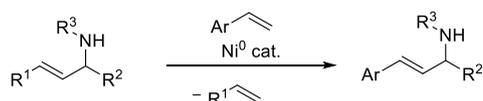
2) Allylic amination/amidation



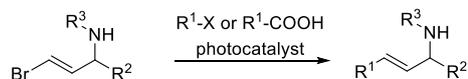
3) Mizoroki–Heck-type arylation reaction



4) Alkenyl exchange of allylamines with alkenes



5) THIS WORK: Dual photoredox/Ni-catalyzed cross coupling



Scheme 1

The common strategies rely on the addition of imines and various vinylic reagents, and represent one of the most intuitive pathways that allows to join two smaller carbon skeletons together, meaning that more-abundant and inexpensive starting materials could be used. Traditionally they are prepared by the nucleophilic addition of alkenylmetals to imines (Scheme 1),⁴ with all inconveniences connected with a generation and handling of alkenylmetals prepared from alkenyl halides⁵ or alkynes⁶ and organometallic reagents. Contemporary protocols, such as the reductive coupling⁷ or alkylative coupling⁸ of alkynes

with imines (Scheme 1), which often allow to avoid the use of sensitive alkenylmetals, still require *N*-EWG groups to enhance imines' electrophilicity. Despite the progress, the coupling of abundantly available alkenes, *via* hydroalkenylation of imines remains a scare.⁹ So far, it is limited to an introduction of styrene-like moieties.¹⁰ An installation of aliphatic-alkenyl units is scare and ineffective, due to side double bond migration leading to a mixture of allylic and homoallylic products.¹⁰

The other methods, for instance, allylic amination (Scheme 1) ^{2a, 7b, 11,11-12} hydroamination reaction,¹³ and allylic C-H amination,¹⁴ are more suitable for a preparation of branched terminal allylamines. Difficult to control regioselectivity for internal non-symmetric olefins limits applicability of these methods in a preparation of branched internal allylamines. In addition, side and competitive reactions (e.g. aziridation, telomerization), especially in the case of C-H amination and hydroamination, are another problem, thus in combination with narrow substrate pool (*N*-activated substrates) additionally limits their practical use.^{14h, 14i}

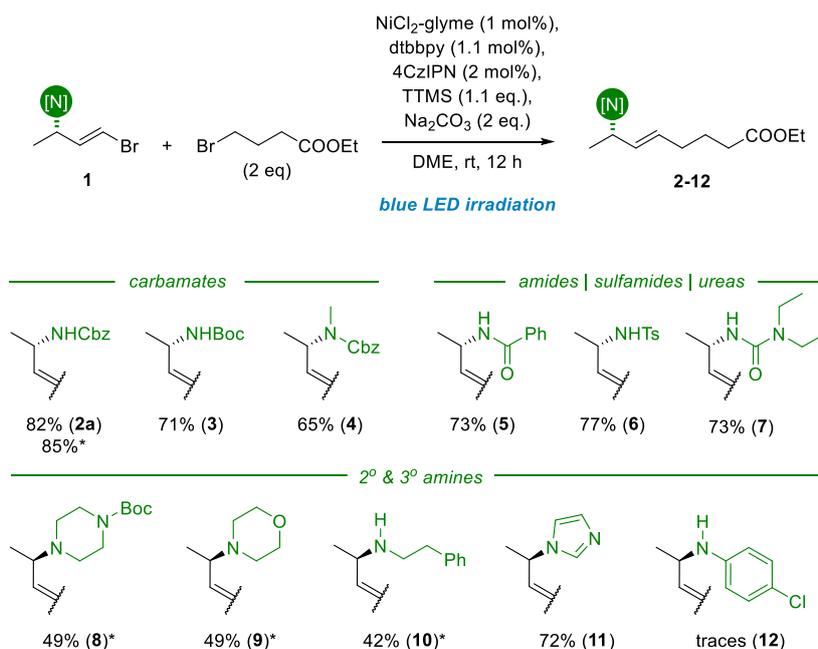
Less explored strategy for the synthesis of branched allylamines assumes an conversion of simple, readily available allylamine derivatives. Typical approach is Mizoroki-Heck-type arylation reaction (Mizoroki-Heck-type arylation reaction)^{15,16} comprising terminal allylamines and suitable coupling partners (e.g., aryl halides or pseudohalides) to assemble cinnamyl type allylamines, and there are only single examples of the preparation of branched products.¹⁷ There are also few reports on the metal-catalyzed γ -C-H arylation of allylamines by using arenes¹⁸ and the oxidative Heck-type reaction comprising allylamines and aryl boronic acids,^{17f} to afford *E*-cinnamylamines. The *Z*-selective protocols are even more rare.¹⁹ Their significant limitations are harsh reaction conditions and the requirement of directing groups responsible for a complexation of the metallic centers after a C-H insertion step. An analogue γ -alkylation reactions are almost unknown. Recently, Fan and co-workers²⁰ reported Ni-catalyzed alkenyl exchange reaction between simple allylamines and alkenes that proceeds via C-C bond cleavage and formation (Mizoroki-Heck-type arylation reaction). Despite the method being efficient for styrene type partners, in the case of alkyl based olefins poor yields of the desired products were reported. Interestingly, there are only a few examples of cross-coupling reactions of type **1** allylamines

bearing vinyl halide subunit that are limited to Sonogashira reaction and single examples of Negishi²¹ and Kumada²² coupling reactions.

We were curious whether type **1** substrates may serve as a suitable substrates for photoredox cross-coupling to provide a branched allyl amines under milder conditions than the corresponding transition metal catalyzed strategies. In last decade, the advent of dual-catalysis approaches based on the combination of organometallic catalysts and photosensitizers has opened new avenues in C(sp³)-C(sp²) bond formation.²³ Different α -heteroatom-containing carboxylic acids,²⁴ alkylborane reagents,²⁵ ammonium alkyl silicates,²⁶ O-benzyl xanthates,²⁷ 1,4-dihydropyridines,²⁸ and alkyl halides (including reductive protocols)²⁹ have been used to promote the formation of alkyl radicals. Recently, we demonstrated that vinyl bromides can be efficiently coupled with functionalised alkyl bromides to provide chemoselectively multifunctional allyl alcohol derivatives.³⁰ Taking an impetus from this reaction, and the absence of a general method for the construction of type **2** branched aliphatic allylamines, we envisaged their construction *via* Ni- and visible light mediated alkylation of 3-bromo allylamines (Scheme 1). According to our knowledge, to date such an approach has never been investigated.

Results and discussion

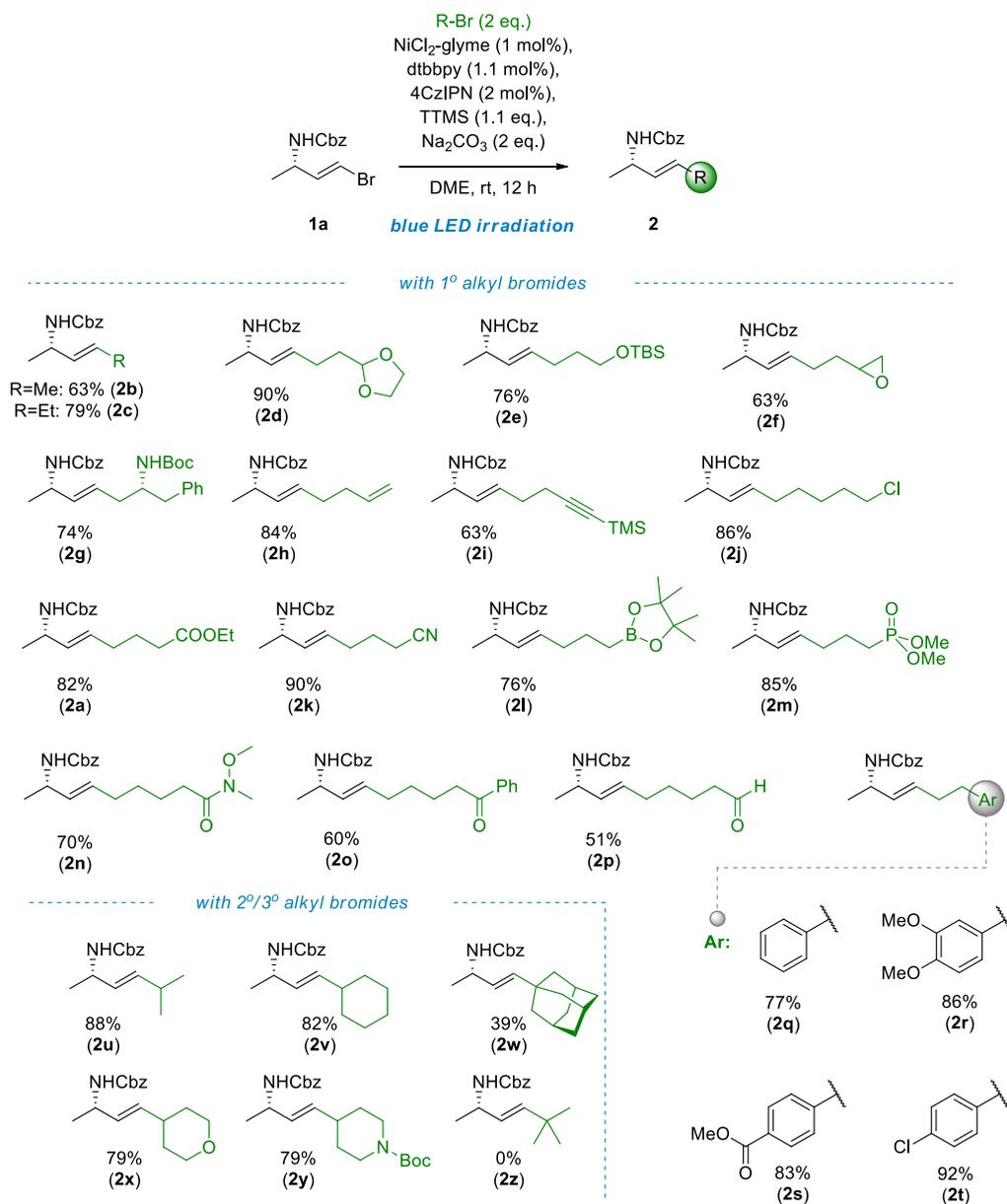
Our studies were initiated by the model cross-coupling reaction of ethyl 4-bromobutanoate and L-alanine-derived 3-bromo allylamine **1a**. In the initial experiments, the reaction conditions previously used for closely related coupling of allyl alcohol derivatives, were applied.³⁰ Thus, upon blue light irradiation, in the presence of 4CzIPN³¹ (photocatalyst) and NiCl₂/dtbbpy complex, substrate **1a** was coupled with ethyl 4-bromobutanoate to provide desired product **2a** in 82% yield. As previously, DME was found as the solvent of choice, and Na₂CO₃ was found to be the optimal base. A slightly better yield was obtained (85%) when [Ir(dF(CF₃)ppy)₂(dtbbpy)]PF₆ complex was used as photocatalyst instead of 4CzIPN, however, due to its convenience and availability, the latter was used in further studies.



* in the presence of [Ir(dF(CF₃)ppy)₂(dtbbpy)]PF₆ instead of 4CzIPN

Scheme 2

After identifying the optimized reaction conditions, we set to explore the scope of this transformation (Scheme 2). Various *N*-protected allylamines (**2a-f**) were compatible under these conditions, and provided the corresponding *N*-carbamates (**2-4**), *N*-amide (**5**), *N*-tosylate (**6**) and urea (**7**) derivatives in good yields, as well as without erosion of an enantiomeric purity. It is worth to emphasize that in the case of *N*-Ts amine **1e** only the desired product **5** was isolated. No other by-products were observed, particularly those arising from side reactions involving the amidyl radicals, which could be generated under reaction conditions via PCET. To our delight, unprotected, aliphatic allylamines also provided the desired products (**8-10**) in a moderate yield, however, Ir-catalyst had to be used instead of 4CzIPN, which provided lower yields (10–20%). On the other hand, the *N*-allyl imidazole **1k** provided the desired product **11** in 72% under standard conditions (with 4CzIPN). Finally, under standard conditions *N*-allylaniline derivative **1l** underwent complete decomposition to provide traces of the desired product **12** (detectable, but not isolated) along with a mixture of undefined by-products, plausibly due to an oxidation of nitrogen atom followed by subsequent side reactions.



Scheme 3

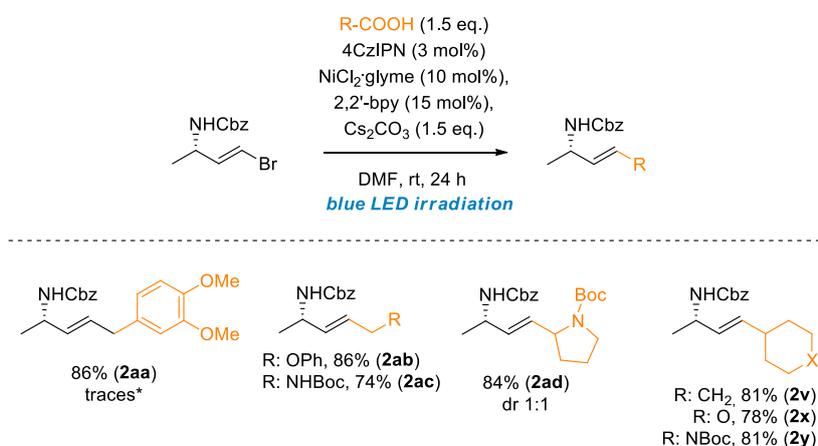
In addition to ethyl 4-bromobutanoate, the scope and versatility of alkyl bromides was investigated (Scheme 3). Methylation and ethylation of **1a** proceeded well and provided the corresponding products **2b** and **2c** in a good yield. Since in the former case, the required MeBr is generated *in situ* by direct mixing MeOTs with LiBr, the pool of suitable coupling partners can be extended to alkyl alcohol derivatives bearing a leaving group. It is worth to note that a number of electrophilic functionalities, commonly intolerant under more reactive Kumada conditions, could be employed in our approach to provide, for instance, esters (**2a**), nitrile (**2k**). Weinreb's amide functionality could also be implemented under

these conditions with compound **2n** being formed in 70% yield. To our delight, also ketone and aldehyde groups were tolerated giving the products **2o** and **2p**, respectively. Other functional groups, such as silyl ether (**2e**), *N*-protected amine (**2g**), phosphonate (**2m**), acetal (**2d**), boronate (**2l**), epoxide (**2e**) as well as alkyl chloride (**2j**) were well tolerated allowing access to the corresponding products shown in *Scheme 3* in good-to-excellent yield. Furthermore, alkyl bromide may contain multiple bonds as demonstrated for the synthesis of **2h** and **2i**. An additional either electron-rich as well as electron-deficient aryl rings are tolerated under developed conditions too, with compounds **2q-t** being formed in excellent yield.

Secondary halides, e.g., isopropyl bromide and cyclohexyl bromide, coupled smoothly to provide the corresponding products **2u** and **2v** in high yield. Furthermore, saturated heterocyclic bromides were good cross-coupling partners and allowed for a preparation of allylamines derivatives containing tetrahydropyran (**2x**) and piperidine (**2y**) rings. Disappointingly, the cross-coupling with *t*-BuBr failed to afford the desired product **2z**, even under prolonged reaction time and using an excess of alkyl bromide. Reaction resulted in the protodebromination of substrate **1a** only. In compare, the similar reaction employing 1-adamantyl bromide provided the expected product **2w** in 39% yield only along with the protodebromination product. The further re-optimization of the reaction conditions, including replacement of the photocatalyst with Ir complex, did not provide any improvement. Then, the reaction of **1a** with *t*-BuBr was run under Molander's reductive conditions³² in the presence of Ni(TMHD)₂ complex. In previous studies devoted to coupling with allyl alcohol derivatives, this catalytic system allowed to improve the yield (from 45% to 69%). However, not in the current case, only traces of the desired product **2aa** were noticed. Further attempts, including the replacement of *t*-BuBr with *t*-BuBF₃K failed too.

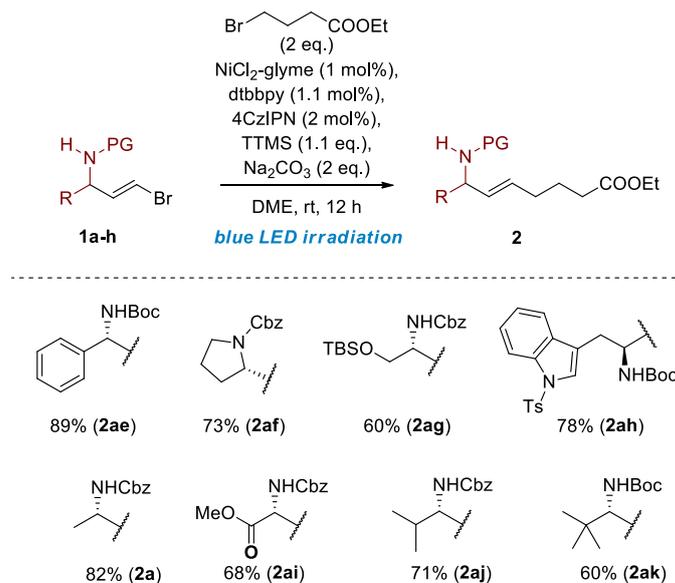
The coupling with BnBr, allyl-Br, propargyl bromide, as well as ethyl bromoacetate failed to afford the desired allylamines. These bromides provide mostly homocoupling products, since the oxidative addition of these activated halides is faster than that of vinyl bromide **1a**. Thus, to eliminate side homocoupling process, the corresponding carboxylic acids as an alkyl radical reservoir were employed, and the model substrate **1a** were subjected to a decarboxylative cross-coupling reaction under slightly modified conditions

(Scheme 4). The cross-coupling of **1a** with simple 1° and 2° carboxylic acids and amino acids proceeded smoothly, and the desired products were obtained in very good yields.



* reaction with 3,4-dimethoxybenzyl bromide, under conditions presented in Scheme 3

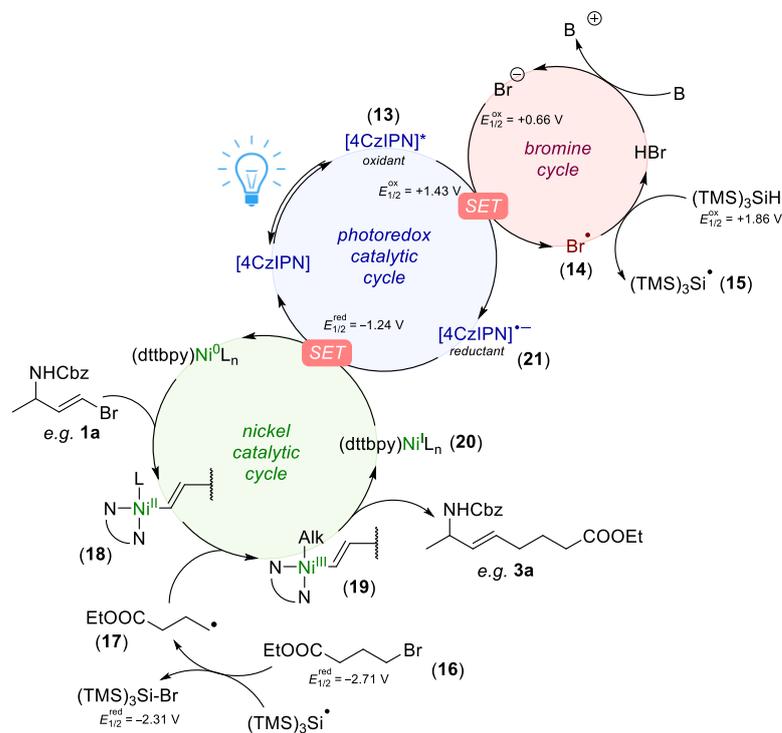
Scheme 4



Scheme 5

Finally, the scope of 3-bromoallylamines was investigated. As exemplified in Scheme 5, type **1** substrates with aliphatic or aromatic substituents, as well as additional functional groups are suitable reagents to provide the desired products **2**. Moreover, the starting materials with additional heterocyclic rings, e.g. pyrrolidine (**1c**) or indole (**1e**), are well tolerated too and deliver the corresponding products **2af** and **2ah**, respectively, in very good

yields. As presented, this method can be also utilized for functionalization of α -amino acids (**2ai**) as well as 1,2-amino alcohols (**2ag**).

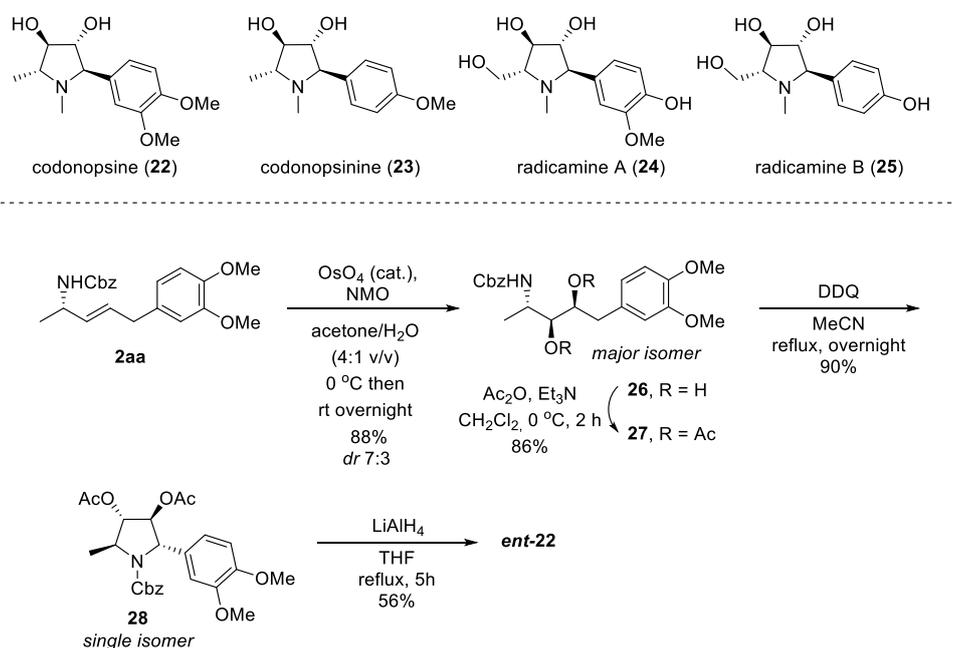


Scheme 6

The plausible mechanism of for the cross-coupling of alkyl bromides and vinyl bromides was proposed in Scheme 6.^{31,29a, 33,34} Upon LED irradiation, 4CzIPN absorbs photons with excitation to provide the strongly oxidizing agent [4CzIPN]* (**13**) ($E_{1/2}^{ox} = +1.43$ V^{31,34}). This complex can oxidize the bromide anion to provide bromine radical (**14**)^{29a} that abstracts a hydrogen atom from $(\text{TMS})_3\text{SiH}$ ($E_{1/2}^{ox} = +1.86$ V³³). Subsequently, the resulting silyl radical (**15**) abstracts bromine from alkyl bromide (**16**) to provide the nucleophilic radical species **17** along with $(\text{TMS})_3\text{SiBr}$. Independently, Ni^0 complex can undergo oxidative addition to vinyl bromide **1a** to furnish intermediate **18**. Next, facile oxidative capture of radical **17** should provide alkyl- Ni^{III} complex **19**. Reductive elimination from **19** would provide the $\text{C}(sp^3)\text{-C}(sp^2)$ coupling product, e.g., **2a**, and Ni^{I} species **20**. Finally, single-electron transfer from the available **21** species to Ni^{I} complex **20** ($E_{1/2}^{red} = -1.24$ V) can reduce the latter one to Ni^0 and regenerate the ground state of the photocatalyst.

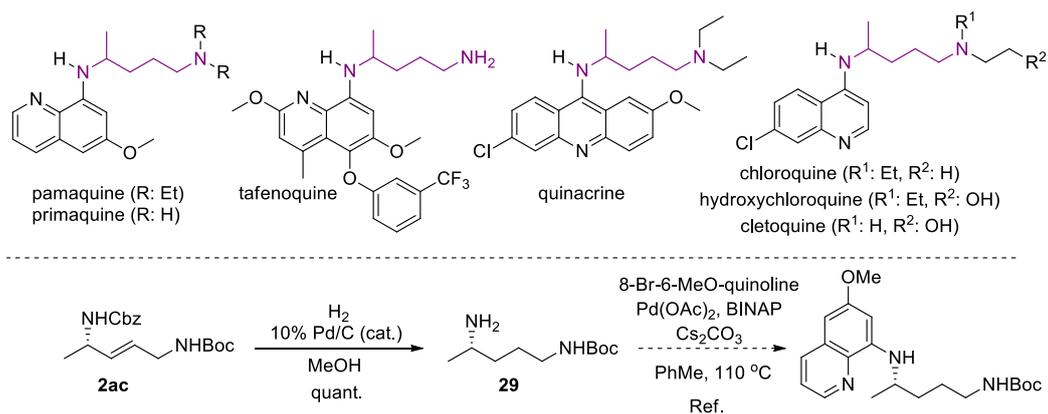
Finally, to demonstrate the high utility of the investigated protocol, the formal synthesis of codonopsine enantiomer **ent-22** was performed (Scheme 7). Codonopsine **22**

and related compounds **23–25** hydroxylated pyrrolidine alkaloid have antibiotic as well as hypotensive activity without effects on the central nervous system.³⁵ Allylamine **2aa**, prepared by a decarboxylative cross-coupling of (3,4-dimethoxyphenyl)acetic acid with **1a**, was subjected to OsO₄-catalyzed dihydroxylation reaction to provide isomeric products **26**. After diastereoisomer separation and acylation, compound **27** (major isomer) was oxidized at the benzylic position to provide tetrasubstituted pyrrolidine **28** in 90% yield as a single isomer. Finally, compound **28** was treated with LiAlH₄ to remove acetyl groups, as well as to reduce Cbz functionality to Me group, providing **ent-22** in 56% yield.



Scheme 7

Next, we focused on the 1,4-pentandiamine **29**, a structural motif present in a vast number of pharmaceuticals, such as primaquine and analogues (Scheme 8), used to treat and prevent malaria.³⁶ Among them chloroquine can be found, that became more famous recently, due expectances that this molecule could be promising drug in a COVID-19 treatment.³⁷ As demonstrated in Scheme 8, core structural motif **29** can be readily prepared by a hydrogenation of diamine **2ac**, derived of **1a** with *N*-Boc glycine. The Pd-catalyzed amination of 8-bromoquinolinie derivative³⁸ with **29** allows for an installation of heterocyclic scaffolds typical for antimalaria drugs presented in Scheme 8.



Scheme 8

In conclusion, we have demonstrated a general method for an alkylation of 3-bromo allylamines. The development of this protocol hinged on the use of the photoredox approach along with Ni catalysis. Using the conditions identified therein, an array of functionalized, unactivated alkyl halides were employed for the first time to provide branched aliphatic allylamines. These reactions generate allylamines, which are challenging to access by classical Kumada and Negishi cross-coupling due to incompatibilities with highly reactive reagents and harsh conditions. In contrast, these mild conditions tolerate a number of functional groups including electrophilic ones, for instance, aldehydes, ketones, esters, nitrile, or amides. From an allylamine diversification perspective, the reported methods allow to employ not only a broad spectrum of nucleophilic partners (alkyl bromides, carboxylic acids etc), but also the structure of the vinylic reagent can be easily modulated. Under developed conditions, starting materials bearing various *N*-functionalities, including standard *N*-protecting groups such as carbamates, amides, or sulfamides, are tolerated. Furthermore, unprotected *N*-allylated secondary and tertiary amines can be applied, including *N*-allylated heterocycles (e.g, imidazole). Tolerance of these heterocyclic moieties in visible-light driven transformations have no precedence so far, according to our knowledge. Moreover, the synthetic utility of the reported method is highlighted through the synthesis of complex multifunctional non-racemic allylamines from simple chiral building blocks, for instance, derived from amino acids.

Electronic Supporting Information

Electronic supplementary information (ESI) available: synthetic procedures, spectral characterization data.

Acknowledgements

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