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The Synthesis of Chiral Allyl Carbamates via Merger of Photoredox and Nickel Catalysis

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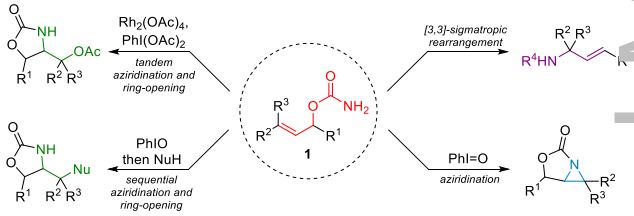
Abstract. A mild, and versatile, organophotoredox/Ni-mediated protocol was developed for the direct preparation of diverse, enantioenriched allyl carbamates. The reported approach represents a significant departure from classical step-by-step synthesis of allyl carbamates. This dual photoredox/Ni based strategy offers unrivalled capacity for convergent unification of readily available alkyl halides and chiral carbamates derived from 1-bromo-alken-3-ols with high chemoselectivity and efficiency. The reported photoredox/Ni catalyzed cross-coupling reaction is not limited to carbamates, but also to other *O*-derivatives such as esters, ethers, acetals, carbonates or silyl ethers. To demonstrate the utility of the reported protocol, the resulting allyl carbamates were transformed into functionalized non-racemic allylamines through a sigmatropic rearrangement reaction in enantiospecific manner. This approach allowed for synthesis of enantiomeric allylamines by a simple control of the geometry of a double bond of allyl carbamates.

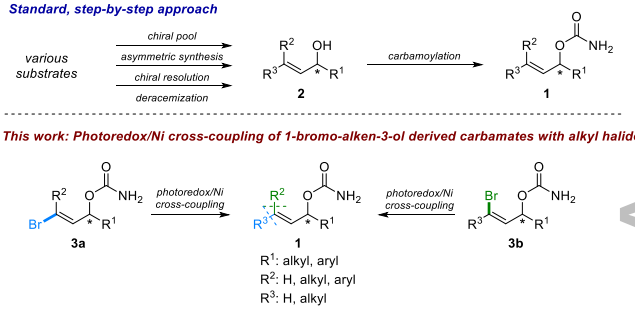
Keywords: allyl carbamates; cross-couplings; photoredox; nickel catalysis; sigmatropic rearrangements; allylamines

Introduction

Allyl carbamates **1** are an important class of compounds, valuable as synthetic intermediates as well as biologically active molecules.[1],[2],[3] Particularly, they have been found as valuable starting materials in the preparation of non-racemic allylamine derivatives through [3,3]-sigmatropic rearrangement reactions, i.e. the Ichikawa rearrangement (Scheme 1).[4],[5],[6] They are also suitable staring materials in synthesis of amino alcohols (and other β-functionalized amines) *via* aminohydroxylation,[7] aminoetherification[8] or aziridination[9] followed by a subsequent ring-opening with the corresponding nucleophiles (Scheme 1).[1a, 9-10] The classical methods for their preparation are based on the carbamoylation of allyl alcohols **2** with suitable isocyanates (e.g. trichloracetyl isocyanate,[11] chlorosulfonyl isocyanate,[11a, 12] trimethylsilyl isocyanate[13]) or through a transcarbamoylation reaction of the hydroxyl group with phenyl carbamate (Scheme 2a).[14] Of course, structural variation of allyl carbamates is determined and limited by the availability of various alcohols.



Scheme 1. Examples of allyl carbamates transformations.



Scheme 2. Strategies for the preparation of allyl carbamates

Although numerous strategies for the preparation of allyl alcohols **2**, including non-racemic ones, are known,[15] the access to their certain types is still limited, for instance multi-functionalized ones or chiral allyl alcohols bearing tri- or tetra-substituted

double bond. In results, multi-step methods of their preparation are require (with additional protection/deprotection steps).[15] Another issue is the synthesis of **1**, and thus alcohols **2**,[15] in high stereo-purity, in a term of high enantio-enrichment, as well as, a complete control of geometry of a double bond. And although various strategies, including chiral pool, asymmetric synthesis, kinetic resolution or deracemization, are known, they often have limitations, and are substrate structure dependent, what results in lack of a generality.

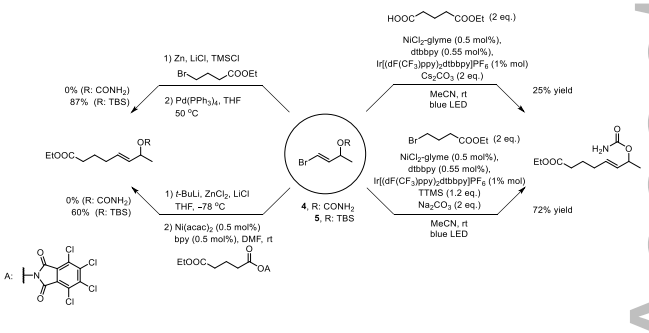
Since, non-racemic allyl carbamates **1** are of our intrest, we became interested in developing an alternative synthetic strategy for their preparation. Our goal was to develop protocol that will allow us to avoid classic parallel step-by-step of synthesis of 1. The concept adopted by us assumed the development of a method that would allow the synthesis of a wide range of carbamates **1** starting from simple, non-racemic precursors. The idea was to provide diversification of their structure at the late stage of synthesis to avoid repeating the reaction sequences (as presented in Scheme 2a) leading to subsequent alcohols **2** and then carmabates **1**. In addition, the method should exhibit high functional group tolerance, enable full control of double bond geometry, and did not provide any erosion of enantiopurity of starting materials.

These features are particularly crucial in the case when carbamates **1** are to be used in a sigmatropic rearrangement, since enantiomeric enrichment of the resulting products directly depends on both enantio- and *E*/*Z*-purity of the starting alcohol.

We sought to investigate the preparation of carbamates **1** *via* a cross-coupling strategy using readily available precursors such as vinyl halides **3a**,**b** (Scheme 2b). In recent years, the development of transition-metal mediated cross-coupling transformations for carbon–carbon bond formation has changed the way in which organic synthesis is carried out.[16],[17],[18] This includes also the coupling reactions of redox-active esters.[19] Unfortunately, most of them use palladium complexes as catalysts, which are not suitable for allyl carbamates since they can promote unwanted cyclization reactions.[20] More recently, the advent of dual-catalysis approaches based on the combination of organometallic catalysts and photosensitizers has opened new avenues in C(sp^3)−C(sp^2) bond formation.[21],[22],[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. Herein, we envisioned a photoredox/Ni-catalyzed cross-coupling of alkyl halides with vinyl bromides **3a**,**b** as coupling partners, to construct non-racemic allyl carbamates **1** directly (Scheme 2).

Results and Discussion

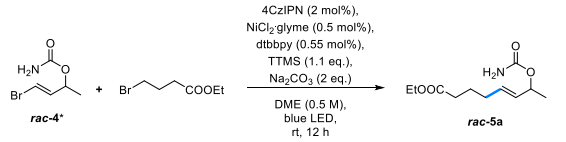
In order to investigate the feasibility of this proposal, in the initial attempt, we probed a coupling reaction of model vinyl bromide **4** with various radical precursors (Scheme 3). Compound ***rac*-4** was obtained from 3-butyn-2-ol *via* bromination/reduction and carbamoylation reaction sequence (see ESI). Decarboxylative approaches proceeded poorly and were limited mainly to α-amino and α-hydroxy acids as well as 2°/3° alkyl carboxylic acids which provide more stabilized radicals (*vide infra*). Importantly, unlike Pd-catalyzed couplings, Ni-catalyzed processes showed excellent tolerance towards vinyl precursors bearing a primary carbamate (***rac*-4** and ***rac*-5**). This resulted in the possibility of late functionalization of the core vinyl bromide, and introduction of the desired substituents. An analogous strategy based on Baran's redox-active ester chemistry[30] was not a good choice since organozinc reagents were not compatible with the carbamate reagent, and complex mixtures of products were observed. The same problem was noticed in the case of light-induced Ni-catalyzed Negishi cross-coupling under conditions reported by Alcazar and co-workers.[31] Interestingly, an application of nickel-catalyzed reductive cross-coupling[29d,e] of vinyl and alkyl bromides resulted in a formation of significant amount of 1,3-diene side-product arising from a homo-coupling reaction. Inspired by MacMillan's[29a] and König's[32] works on the alkylation of aryl bromides, we turned our attention to an analogous transformation with vinyl bromides. To our delight, under the reported conditions, vinyl bromide **4**, bearing a carbamate functionality, coupled with ethyl 4-bromobutyrate in 72% yield (Scheme 3).



Scheme 3. Initial studies on the synthesis of allyl carbamates.

Encouraged by these preliminary results, we initiated optimization studies of the coupling reaction. Factors investigated included type of photocatalyst, solvent, base, Ni source, and ligand choice (Scheme 4). Typically used photocatalysts are based on expensive metals, such as iridium (Scheme 4, ent. 3) or ruthenium (ent. 4), rendering these procedures less

sustainable and less suitable in terms of scalability. Therefore, we were interested if it was possible to replace such complexes by inexpensive organophotocatalysts. Gratifyingly, when 4CzIPN[26b, 33] was applied, the desired product ***rac*-6a** was obtained in 81% yield by using 2 mol% loading only. In the case of lower amount of the photocatalyst (1 mol%, ent. 7), the model product ***rac*-6a** was obtained in 63% yield after standard reaction time (12 h). When the reaction time was extended to 48 h, the yield increased to 75% (100% conversion of ***rac*-4**). In comparison, other typically used organic photocatalysts, such as eosin Y or rose Bengal were not effective (entries 5 and 6). The model coupling reaction in the presence of a Ru-based photocatalyst failed as well (Scheme 4, ent. 4)



Ent.	Conditions	Yield
1	no change	81%
2	$NiBr_2$·diglyme instead of $NiCl_2$·glyme	77%
3	$Ir[(dF(CF_3)ppy)_2dtbbpy]PF_6$ (1% mol) instead of 4CzIPN	72%
4	$Ru(bpy)_3(PF_6)_2$ (1 mol%) instead of 4CzIPN	0%
5	Eosin Y (2 mol%) instead of 4CzIPN	0%
6	rose Bengal (2 mol%) instead of 4CzIPN	0%
7	1% mol of 4CzIPN	63%
8	DMF as solvent	63%
9	THF as solvent	32%
10	K_2CO_3 as base	65%
11	Cs_2CO_3 as base	64%
12	dmbpy as ligand	64%
13	bpy as ligand	60%
14	1 eq. TTMS	65%
15	1.5 eq. of alkyl bromide	69%
16	0.1 M concentration	79%

4CzIPN

R: H, bpy
R: Me, dmbpy
R: t-Bu, dtbbpy

TTMS: TMS–Si(TMS)–H

Standard conditions: Vinyl bromide (0.1 mmol), ethyl 4-bromobutanoate (0.2 mmol), 4CzIPN (2 mol%), 4CzIPN (2 mol%), $NiCl_2$·glyme (0.5 mol%), dtbbpy (0.55 mol%), TTMS (0.11 mmol), Na_2CO_3 (0.2 mmol), DME (*c* 0.5 M), 2x 36 W blue LED irradiation, rt, 12 h.
* For optimization studies racemic substrate was applied.

Scheme 4. Optimization of photoredox/Ni-catalyzed cross-coupling reaction of vinyl bromide **4**.

The change of Ni source had a slight influence on the efficiency of the coupling and comparable results were obtained when $NiCl_2$ was replaced by $NiBr_2$. (Scheme 4, ent. 1 and 3). On the other hand, the type of applied ligand was crucial for the activity of the Ni complex. The change of dtbbpy to dmbpy or bpy resulted in a decrease of the coupling efficiency (Scheme 4, ent. 1, 12, 13). DME was the optimal solvent. Its replacement by DMF or THF decreased the yield of model product ***rac*-6a** significantly. Na_2CO_3 was the most suitable base for the process (compare ent. 1 vs. 10 and 11). Finally, two-fold excess of alkyl bromide and a slight excess of TTMS (1.1 eq.) were optimal.

With optimized conditions in hand, we first evaluated the coupling reactions of enantioenriched vinyl bromide **4** with simple primary, secondary, and tertiary alkyl bromides (Scheme 5). The reaction proceeded smoothly for simple alkyl bromides such as ethyl, propyl or phenethyl ones. When MeBr was applied (generated *in situ* by mixing MeOTf and LiBr), the desired product **6b** was obtained, although with lower yield. It should be stressed that the present approach had additional advantages over the standard synthetic protocols (see Scheme 2) based on carbamoylation of the corresponding alcohol, since it eliminated disadvantages related to the synthesis and handling of volatile low molecular weight alcohols.

Secondary alkyl bromides are also coupled easily, as exemplified by the formation of products **6u-6ad**. Despite their steric hindrance, also tertiary halides were good partners for the coupling reaction. However, in this case, higher loading of the Ni catalyst (10 mol%) was required to ensure complete conversion of the starting vinyl bromide, and yields of the corresponding products are slightly lower, e.g. 59% for **6ae** and 45% **6af**. Further experiments showed that in this case an efficiency of the coupling with tertiary bromides can be enhances by modification catalytic system. The replacement of bipyridine by dicarbonyl ligand (TMHD), according to Molender's report,[34] resulted in increase the yield **6af** up to 69%.

Encouraged by the above studies, we extended the strategy for the synthesis of highly valuable, structurally diverse, and unique allyl carbamates. To our delight, the investigated reaction proceeds chemoselectively and various functional groups such as ester (**6a**, **6l**), nitrile (**6f**), chloride (**6g**), boronate (**6h**), phosphonate (**6j**) or sulfone (**6k**) were tolerated. The coupling reaction proceeded well also in the case of halides bearing protected hydroxyl and amine groups. Even sensitive groups, such as epoxide (**6s**), acetal (**6o**), and electron-rich aryls (e.g. **6t**), were tolerated.

Additionally, an alkene moiety was also acceptable functionality (**6p-r**), although the coupling reaction with 6-bromohex-1-ene provided a 1:1 mixture of desired product **6r** along with product **6w** arising from 6-*endo-trig* radical cyclisation of the radical partner. No reaction proceeded for 4-bromobut-1-yne, and a starting material was recovered only. Fortunately, its TMS derivative coupled with **4** to provide product **6m** in 53% yield.

In contrast to previous examples, the reaction of **4** with benzyl bromide, allyl bromide, propargyl bromide, and ethyl bromoacetate failed. In these cases, the formation of a homo-coupling product of the alkyl bromide, e.g. 1,2-diphenylethane in the case of benzyl bromide, was observed predominantly. This indicated that for these activated halides an oxidative addition reaction is more rapid than for the starting vinyl bromide, thus, the formation of a homo-coupling product is dominant. This limitation could be overcome by a replacement of alkyl bromide by the corresponding carboxylic acid, which would provide

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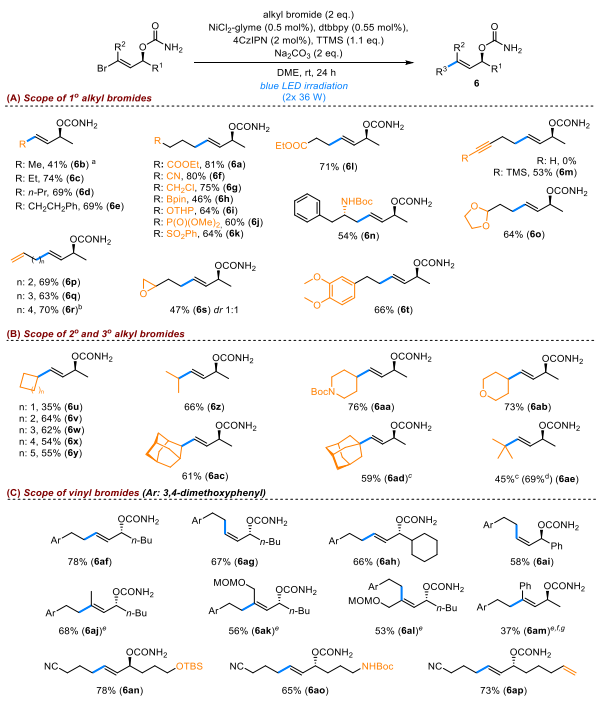
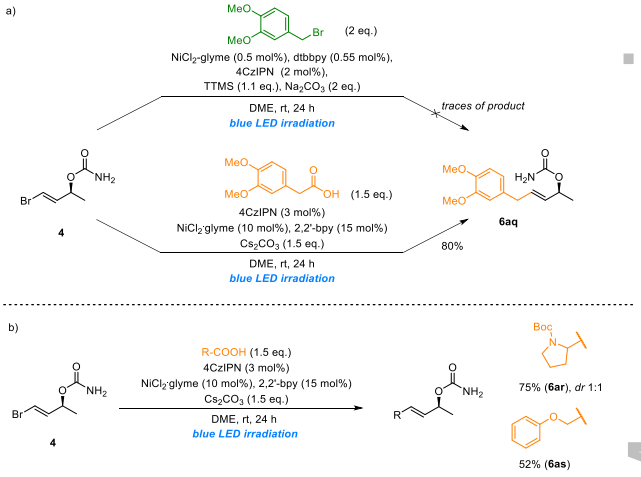
the same radical species under decarboxylative conditions (Scheme 6a). Now, under conditions showed in Scheme 6a, the desired product **6an** was obtained in 80% yield. Also other carboxylic acids were suitable precursors of radical partners. Thus, the decarboxylative approach was successfully applied also in the case of cross-coupling of vinyl bromide **4** with an *N*-Boc proline, and phenoxyacetic acid (Scheme 6b).



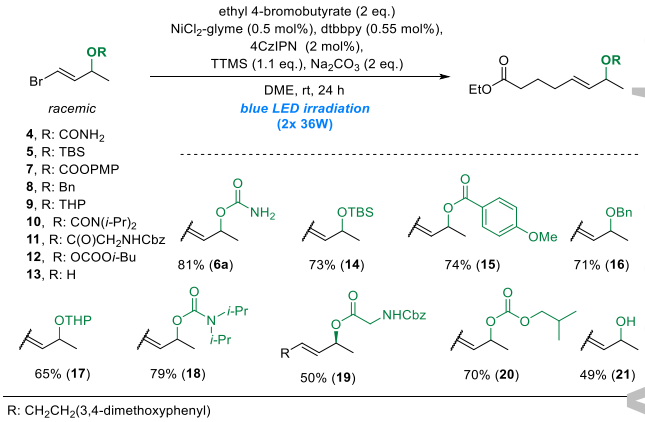
Standard conditions: Vinyl bromide (2.58 mmol), alkyl bromide (5.2 mmol), 4CzIPN (2 mol%), $NiCl_2$·glyme (0.5 mol%), dtbbpy (0.55 mol%), TTMS (2.84 mmol), Na_2CO_3 (5.2 mmol), DME (*c* 0.5 M), 2x 36 Wblue LED irradiation, rt, 12 h; Notes: [a] MeBr generated *in situ* from MeOTs (2 eq.) and LiBr (2 eq.); [b] 1:1 mixture of **6r** and **6w** was obtained; [c] $NiCl_2$-glyme (10 mol%), dtbbpy (11 mol%) were used, reaction extended to 72 h; [d] $Ni(TMHD)_2$ (10 mol%) was used; [e] $NiCl_2$ glyme (2 mol%), dtbbpy (2.2 mol%) were applied; [f] 1 eq of alkyl bromide and 1 eq. of TTMS were applied; [g] 35% of a starting material was recovered.
TTMS = tris(trimetylsilyl)silane; TMHD = 2,2,6,6-Tetramethyl-3,5-heptanedione; Ts = p-toluenesulfonyl; dtbbpy = 4,4'-di-t-butylbipyridine

Scheme 5. Scope of photoredox/Ni-catalyzed cross-coupling of vinyl bromide **4**.

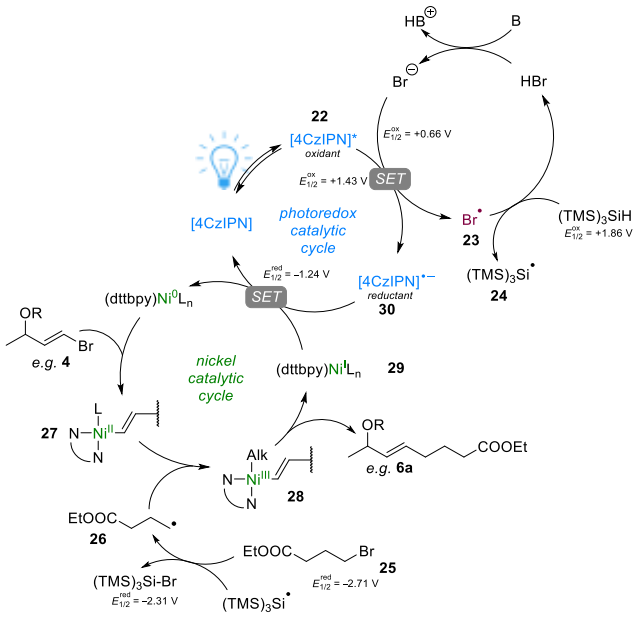
Next, the set of vinyl bromides was extended. Gratifyingly, the coupling reaction tolerated also sterically more demanding starting materials bearing *n*-butyl (**6ai**/**6ag**), cyclohexyl (**6ah**), and phenyl (**6ai**) as the R^1 group. Additional functional groups can be also incorporated into vinyl bromide cross-coupling partner structure, as indicated during the synthesis of carbamates **6an-6ap**. The cross-coupling reaction proceeded efficiently also for (*Z*)-vinyl bromides to provide the corresponding (Z)-carbamates **6ag** and **6ai**. Also trisubstituted (*E*)- and (Z)-vinyl bromides coupled smoothly to provide the isomeric carbamates **6ak** and **6al**. The access to these isomeric allyl carbamates is of particularly high interest since their sigmatropic rearrangements provides enantiomeric products (*vide infra*). The synthesis of compound **6am**, bearing a phenyl ring conjugated with a double bond, was more complicated, and provided it in lower yield, presumably due to competitive addition of radical species to styrene-type vinyl bromide. Such radical addition to activated olefins, such as styrenes is known, and results in a formation of a stabilized benzyl-type radicals.[35] ^{1}H NMR spectra of the crude reaction mixture showed the presence of multiple side-products when the mentioned vinyl bromide was applied, however, we were not to abele to isolate and assign any reasonable structure. Re-optimization of reaction conditions in this case (by reduction of the amount of TTMS to 1 eq. and alkyl bromide to 1.3 eq) afforded **6am** in 37% yield along with recovery of starting material (35%) after the standard 12 h.



Scheme 6. Decarboxylative photoredox/Ni-catalyzed cross-coupling reactions.



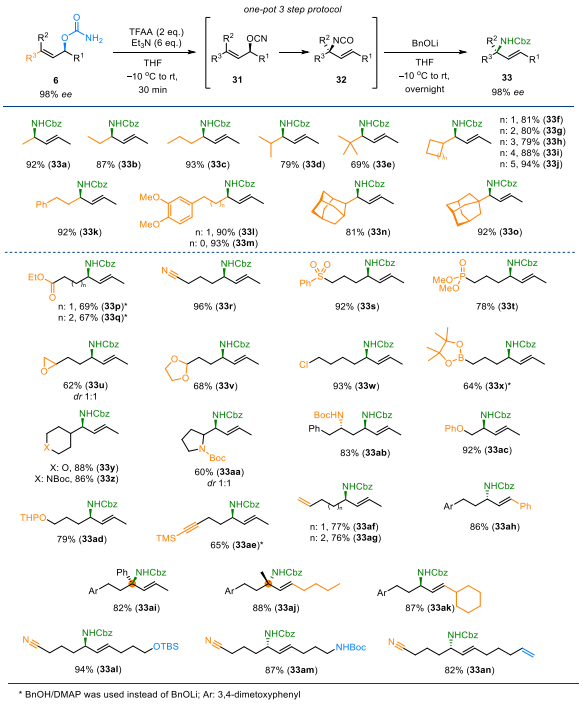
Scheme 7. Cross-coupling with other vinyl bromide substrates.



Scheme 8. Proposed mechanism for photocatalytic alkenylation of vinyl bromides.

The successful results encouraged us to extend the scope of the investigated process. Thus, a series of vinyl bromides **4**, **5** and **7**-**13** were prepared and all of them were subjected to a model coupling reaction with ethyl 4-bromobutyrate. As depicted in Scheme 7, the cross-coupling reaction proceeded smoothly also in the case of *O*-silylated (**5**), *O*-benzylated (**8**), and *O*-acylated (**15**, **19**), as well as acetal- (**17**), and carbonate-type (**20**) vinyl bromides. Amino acid-derived allylic ester **19** can serve as substrate for synthesis of highly functionalized unnatural amino acids *via* Claisen rearrangement.[36] Besides primary carbamates (**4**), also tertiary ones, such as **18**, can be efficiently coupled with ethyl 4-bromobutyrate. It is worth to underline that all of these products are valuable building blocks. For instance, type **18** carbamates can serve as substrates for lithiation-borylation reactions which have found numerous applications in organic synthesis.[37] Allyl carbonates such as **20** are valuable staring materials for various types of Tsuji-Trost reactions.[38] In contrast to *O*-protected vinyl bromides, the coupling of **13**, containing a free hydroxyl group, proceeded less efficiently, and the desired product **21** was obtained in 49% yield only.

Based related reports, the mechanism of for the cross coupling of alkyl bromides and vinyl bromides was proposed (Scheme 8).[29a][32][39] Upon LED irradiation, 4CzIPN absorbs photons to excitations to the strongly oxidizing agent [4CzIPN]* (**22**)($E_{1/2}^{ox}$ = +1.43 V[39]). This complex can oxidize bromide anion to provide bromine radical (**23**)[29a] that should abstract a hydrogen atom from (TMS)$_3$SiH ($E_{1/2}^{ox}$= +1.86 V[32]). Subsequently, the resulting silyl radical (**24**) abstracts bromine from alkyl bromide (**25**) to provide nucleophilic radical species **26** along with (TMS)$_3$SiBr. Independently, Ni^0 complex can undergo oxidative addition with vinyl bromide **4** to furnish intermediate **27**. Next, facile oxidative capture of radical **26** should provide alkyl-Ni^{III} complex **28**. Reductive elimination from **28** would provide the C(sp^3)-C(sp^2) coupling product, e.g. **6a**, and Ni^I species **29**. Finally, single-electron transfer from the available **30** species to Ni^I complex **29** ($E_{1/2}^{red}$ = –1.24 V) can reduce the latter one to Ni^0 and regenerate the ground state of photocatalysts.

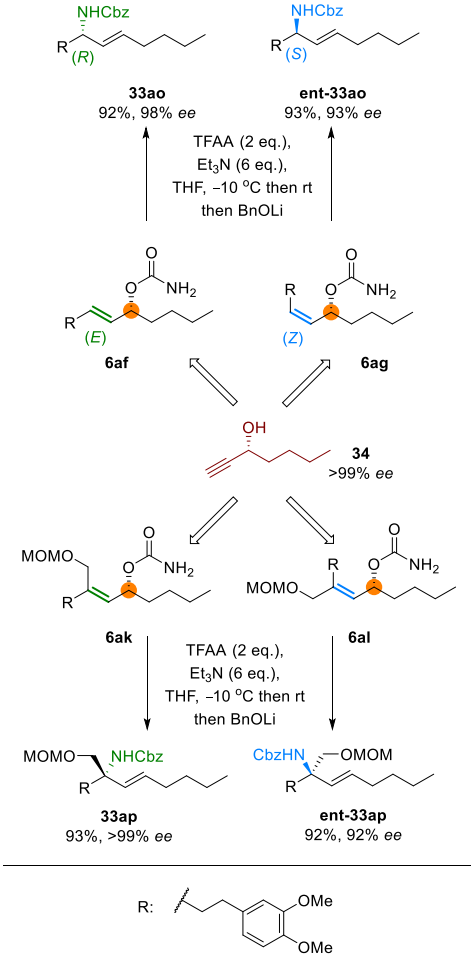


Scheme 9. [3,3]-Sigmatropic rearrangement of allyl carbamates **6**.

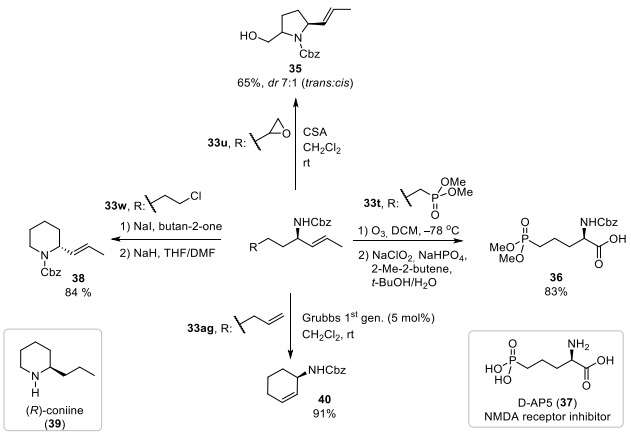
To demonstrate the utility of this mild organophotoredox/Ni-mediated method, we transformed compounds **6** into the corresponding allylamines **33** through a sigmatropic rearrangement reaction.[4-5, 14],[18],[40] Such 2° and 3° non-racemic *N*-functionalized allylamines are important structural motifs and versatile intermediates for the synthesis of a variety of products, including α-, β-, and γ-amino acids, amino alcohols, and other derivatives.[5b, 40-42]

Thus, the treatment of **6** with TFAA/Et$_3$N provided the corresponding allyl cyanates **31**, which spontaneously rearranged to allyl isocyanates **32**. The latter were directly trapped with a nucleophilic reagent, such as BnOLi, to provide *N*-Cbz protected allylamines **16** in high to excellent overall yields after 3 steps. These 3 steps are realized in a one-pot manner, what increases the efficiency of the entire process. As shown in Scheme 9, the rearrangement was

chemoselective and displayed high functional group tolerance.

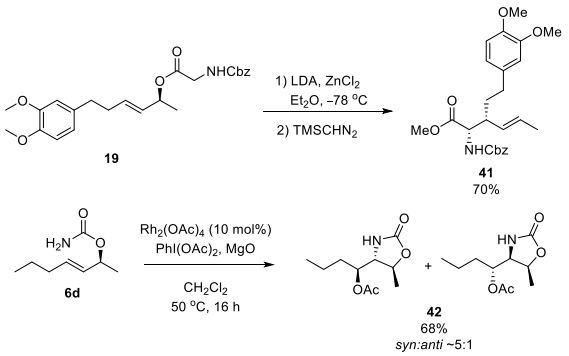


Scheme 10. Stereodivergent synthesis of enantiomeric allylamines.



Scheme 11. Further transformations of selected allylamines.

Moreover, the use of (*E*)- or (*Z*)-allyl carbamates, such as **6af** and **6ag**, or **6ak** and **6al**, bearing the same absolute configuration at the C-center, allowed for control of the stereochemical outcome of the rearrangement reaction. Thus, due to its enantiospecificity and transfer of chiral information from substrate to product, this method enables the access to enantiomeric allylamines just by a change in the geometry of the double bond (Scheme 10). It is worth to stress that all of these starting carbamates can be easily prepared from the same substrate, enantomerically enriched (*e.e.* >99%) propargyl alcohol **34**.



Scheme 12. Further transformations of selected cross-coupling products.

To further demonstrate the utility of the investigated method, we performed, under mild conditions, a series of late modifications of selected allylamines, carbamates and others to precursors of medicinal agents or important structural scaffolds. As shown in Scheme 11, acid-mediated epoxide opening/cyclization of **33u** allowed the synthesis of pyrrolidines **35** in 65% yield. Such a structural motif is present in numerous naturally occurring alkaloids.[42] The ozonolysis/oxidation of **33t** provided compound **36** which is a precursor of NMDA receptor inhibitor **37**. Intramolecular *N*-alkylation of **33w** provided piperidine **38** in 84% yield, which can be transformed directly to known toxin (*S*)-coniine **39**. It is worth to mention that under basic conditions, the same substrate may provide piperidine derivatives which can be transformed into 4-hydroxy pipecolic acid.[43] Finally, in the presence of Grubbs 1st gen. catalyst, diene **33ag** was cyclized to provide carbacyclic allyl amine **40** (Scheme 10). As mentioned before not only type **4** carbamates but also other allyl alcohol derivatives (e.g. **18-20**) synthesized according to our protocol, can serve as valuable starting materials in an organic synthesis. It can be exemplified by chelate enolate Claisen rearrangement[36] of allyl ester **19**. Upon treatment with LDA in the presence of $ZnCl_2$, this compound rearranged to the corresponding amino acid derivative. This class of compounds have found applications in the synthesis of the matrix metalloprotease MMP-2 and MMP-9 inhibitors.[44] It was not isolated but directly treated with $TMSCHN_2$ to provide amino ester **41** in 70% (Scheme 12). As described at the introduction, allyl carbamates are also suitable substrates for a preparations of amino alcohols. For example, in the presence of

$Rh_2(OAc)_4$/$PhI(OAc)_2$[10g] carbamate **6d** underwent tandem intramolecular aziridination followed by a ring-opening process to provide amino diol derivative **42**, predominantly, in 68% yield (Scheme 12).

Conclusion

In summary, a mild, versatile, and direct organophotoredox/Ni mediated protocol was developed for the preparation of diverse, enantioenriched allyl carbamates starting from commercially available non-racemic propargyl-type alcohols. The reported radical approach represents a significant departure from classical stepwise synthesis of allyl carbamates often described in the literature. This dual photoredox/Ni based strategy offers unrivalled capacity for convergent unification of readily available alkyl halides and chiral carbamates derived from 1-bromo-1-alken-3-ols, and simultaneously high chemoselectivity and efficiency. Moreover, as it was indicated, the reported photoredox/Ni catalyzed cross-coupling reaction is not limited to carbamates, but also viable for 1-bromo-1-alken-3-ols and their *O*-derivatives such as esters, ethers, acetals, carbonates or silyl ethers. Customizable by design, the simplicity and efficiency of this protocol should resonate with the organic and medicinal chemist requiring rapid access to these highly valuable and sought-after building blocks.

Experimental Section

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

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