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Photocatalysis

Regio-, Diastereo-, and Enantioselective Decarboxylative Hydroaminoalkylation of Dienol Ethers Enabled by Dual Palladium/Photoredox Catalysis

Jun Zheng, Nana Tang, Hui Xie, and Bernhard Breit**

Abstract: Intermolecular photocatalytic hydroaminoalkylation (HAA) of alkenes have emerged as a powerful method for the construction of alkyl amines. Although there are some studies aiming at stereoselective photocatalytic HAA reactions, the alkenes are limited to electrophilic alkenes. Herein, we report a highly regio-, diastereo-, and enantioselective HAA of electron-rich dienol ethers and α-amino radicals derived from α-amino acids using a unified photoredox and palladium catalytic system. This decarboxylative 1,2-Markovnikov addition enables the construction of vicinal amino tertiary ethers with high levels of regio- (up to >19:1 rr), diastereo- (up to >19:1 dr), and enantioselectivity control (up to >99% ee). Mechanistic studies support a reversible hydropalladation as a key step.

Introduction

Chiral amines are ubiquitous structural motifs among bioactive alkaloids and pharmaceutical agents.[1] The development of methods that enable rapid construction enantioenriched amines from simple, cheap, and abundant precursors are highly sought after.[2] The direct addition of hydrogen and an α-amino alkyl fragment across alkenes, broadly termed the hydroaminoalkylation (HAA) reaction, is a particularly attractive approach to synthesize alkylamines, because they have the benefit of both being highly atom economic and using readily available olefin feedstocks.[3] Traditionally, HAA reactions could be achieved via transition metal catalyzed insertion of alkenes into α-C–H bonds of an amine.[4] Late transition metal catalysis preferentially enables linear selective addition with the necessity of installation of specific directing groups on the amine nitrogen;[5] while the branched selective HAAs of alkenes have been largely accomplished with early transition metal catalysis, however, *N*-methyl functionalization most often occurs.[6] The latter method also struggles with forcing reaction conditions, functional group tolerance and stereoselectivity control.[7] An alternative powerful strategy is photocatalytic HAAs with an α-amino radical.[8] Taking the advantage of the nucleophilic character of the α-amino radical, electron-deficient alkenes such as acrylates[9] or vinyl pyridines,[10] and more recently extended to styrenes are able to engage in this transformation (Figure 1A).[11] Despite these advances, the addition of α-amino radicals into electronically unbiased alkenes or even electron-rich alkenes are largely lagged behind, probably because of the polarity matching effect.[12] A recent elegant work from Rovis demonstrated that a photoredox and cobalt cocatalytic system enables the HAA with unactivated 1,3-dienes towards α-amino alkyl radicals.[13] 1,4-HAA of 1,3-dienes generate homoallylic amines preferentially with high regioselectivity but in low diastereomeric ratio (dr) when vicinal stereocenters were formed (Figure 1B). Our laboratory recently described the first enantio-, and branched-selective HAA of allenes leading to *syn*-vicinal amino secondary ethers.[14] Although good enantioselectivity has been achieved, this protocol still suffered from moderate diastereoselectivity and was restricted to *N*-Ph substituted amino acids, which diminished its practical utility in synthetic applications. Therefore, to develop an enantio-, and diastereoselective HAA of non-electrophilic alkenes with a broader scope span of α-amino radicals is still highly demanded.

In this work, we disclose a palladium and photoredox dual catalyzed highly regio-, diastereo-, and enantioselective HAA with 2-alkoxyl dienes using α-amino radicals derived from α-amino acids (Figure 1B). Theoretically, the enantioselective addition of α-amino radicals to 2-alkoxyl dienes can produce up to 22 isomers (Figure 1C). To the best of our knowledge, enantioselective variants of photocatalytic HAAs with 1,3-dienes have not been reported to date. We hypothesized that electron-rich 2-alkoxy dienes, the premier dienes for the use in Diels-Alder reaction,[15] undergo migratory insertion with a Pd–H species to form the electrophilic π-ally-Pd species, which engages in stereoselective reaction with α-amino radicals. Compared to previous work,[13,14] this umpolung based approach enables highly regioselective 1,2-Markovnikov HAA of 2-alkoxyl dienes with a variety of α-amino radicals tolerating diverse *N*-Ar

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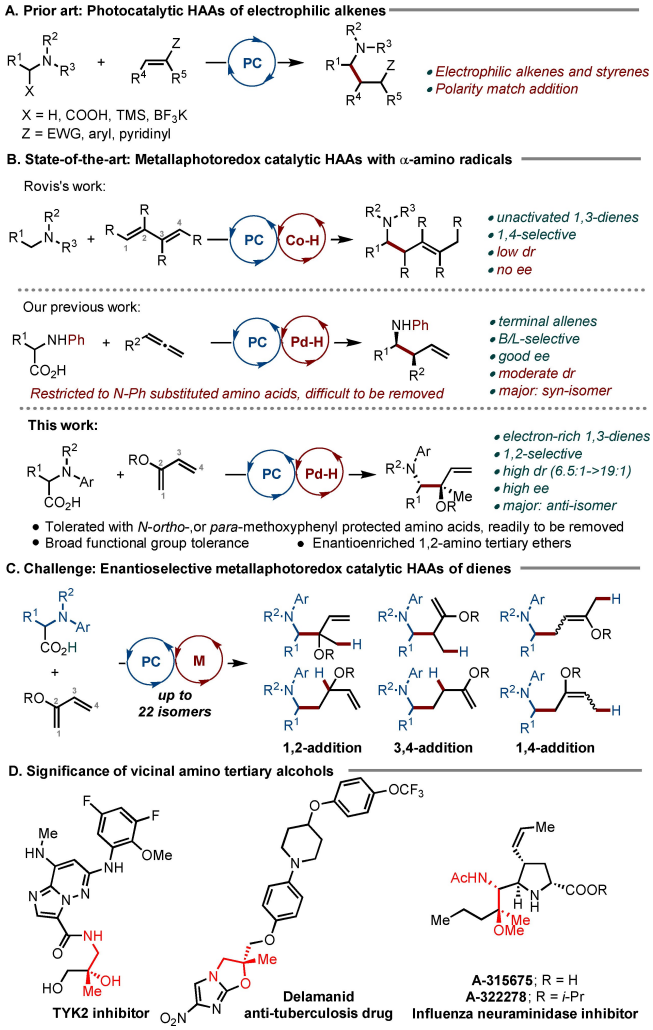


Figure 1. Concepts for asymmetric photocatalytic HAAs of alkenes and dienes and significance of vicinal amino tertiary alcohols.

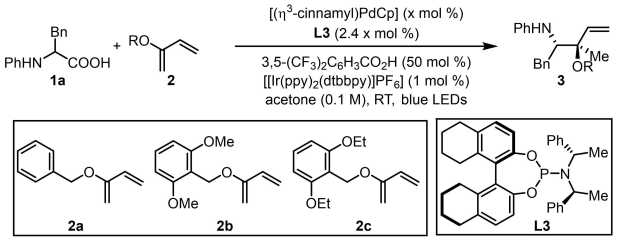
substituents, furnishing *anti*-vicinal amino tertiary alcohols in up to 99 % yield, >19:1 dr, >19:1 rr, and >99 % ee.

Vicinal amino tertiary alcohols are important structural motifs in a number of bioactive compounds and drugs (Figure 1D), but their direct catalytic enantioselective synthesis has been far less explored.[16] Current strategies mainly focus on the asymmetric addition of ketone electrophiles with α-amino alkyl building blocks, including α-amino alkyl radicals[17] and α-amino alkyl copper species.[18] We envisioned that 1,2-amino tertiary alcohols could be prepared by the deprotection of 1,2-amino ethers generated from this redox-neutral, enantio-, and diastereoselective HAA.

Results and Discussion

We therefore initiated our study with irradiation with blue LEDs of a DMF solution of *N*-phenyl-substituted phenyl alanine (**1a**) and 2-benzyloxydiene (**2a**) (Table 1). A detailed investigation of photocatalysts, chiral ligands, acid additives, palladium sources and solvents revealed that

Table 1: Optimization of reaction conditions.[a]



Entry	Diene	X	Yield [%]	dr	ee [%]
1	**2a**	5	44	5.6:1	94
2	**2a**	7	62	6.6:1	97
3	**2a**	9	64	6.7:1	97
4[b,c]	***2a***	***7***	***77(84)***	***6.7:1***	***97***
5[b,d]	**2a**	7	73	6.4:1	97
6[c,e]	**2a**	7	0	–	–
7[c,f]	**2a**	7	0	–	–
8[b,c]	***2b***	***7***	***(72)***	***11.1:1***	***99.6***
9[b,c]	**2c**	7	(48)	16.7:1	>99.9

[a] Reaction conditions (unless otherwise specified): **1a** (0.1 mmol), **2** (0.15 mmol), [(η³-cinnamyl)PdCp] (x mol %), **L3** (2.4×mol%), 3,5-$(CF_3)_2C_6H_3CO_2H$ (50 mol%), DMF (1 mL), $[[Ir(ppy)_2(dtbbpy)]PF_6]$ (1 mol%), 16 h, RT, blue LEDs. NMR yields are reported by using isoquinoline as an internal standard, the isolated yield is presented in parenthesis. Diastereomeric ratio (dr) was determined by ^{1}H NMR spectroscopy of the crude reaction mixture. For all the reactions the regioselectivity (rr) is >19:1. The enantiomeric excess (ee) was determined by chiral HPLC analysis. [b] Performed on 0.2 mmol scale. [c] 1.8 equiv **2** was used. [d] 2.0 equiv **2** was used. [e] Without $[[Ir(ppy)_2(dtbbpy)]PF_6]$. [f] Without blue LEDs.

$[Ir(ppy)_2(dtbbpy)]PF_6$ (1 mol%), $[(\eta^3$-cinnamyl)PdCp] (5 mol%), **L3** (12 mol%) and 3,5-$(CF_3)_2C_6H_4COOH$ (50 mol%) in acetone could provide vicinal amino ether **3a** in 44 % yield with 5.6:1 dr and 94 % ee (entry 1, for full details, see the Supporting Information). Pleasingly, increasing the amount of [(η³- cinnamyl)PdCp] (7 mol %) and diene (1.8 equiv) proved beneficial for the formation of **3a** in 84 % yield with >19:1 rr, 6.7:1 dr and 97 % ee (entries 2–5). The control experiments verified that photocatalyst and blue LEDs irradiation are all necessary components for a successful reaction (entries 6 and 7). Finally, an examination of protecting groups on the 2-alkoxy diene was conducted. By increasing size of the R group from benzyl to 2,6-diethoxybenzyl, diastereo-, and enantioselectivity of the related products (**3b**,**c**) increased gradually, while reactivity decreased (entries 8 and 9).

With these optimized conditions in hand, we next sought to determine the generality of this decarboxylative HAA reaction. A variety of *N*-aryl substituted natural and unnatural α-amino acids was first tested and the addition products were isolated with uniformly high regio-, diastereo- and enantioselectivity (Figure 2). In addition to *N*-phenyl phenyl alanine, *N*-2-methoxy phenyl alanine was also a suitable substrate, yielding **3d** in 79 % yield with 13.7:1 dr and 96 % ee. The 2*S*,3*R* configuration of **3d** was determined by single-crystal X-ray structural analysis.[19] Introduction of electron-withdrawing or electron-donating substituents at the *para*-, *meta*-, even *ortho*-position of the aryl ring on the

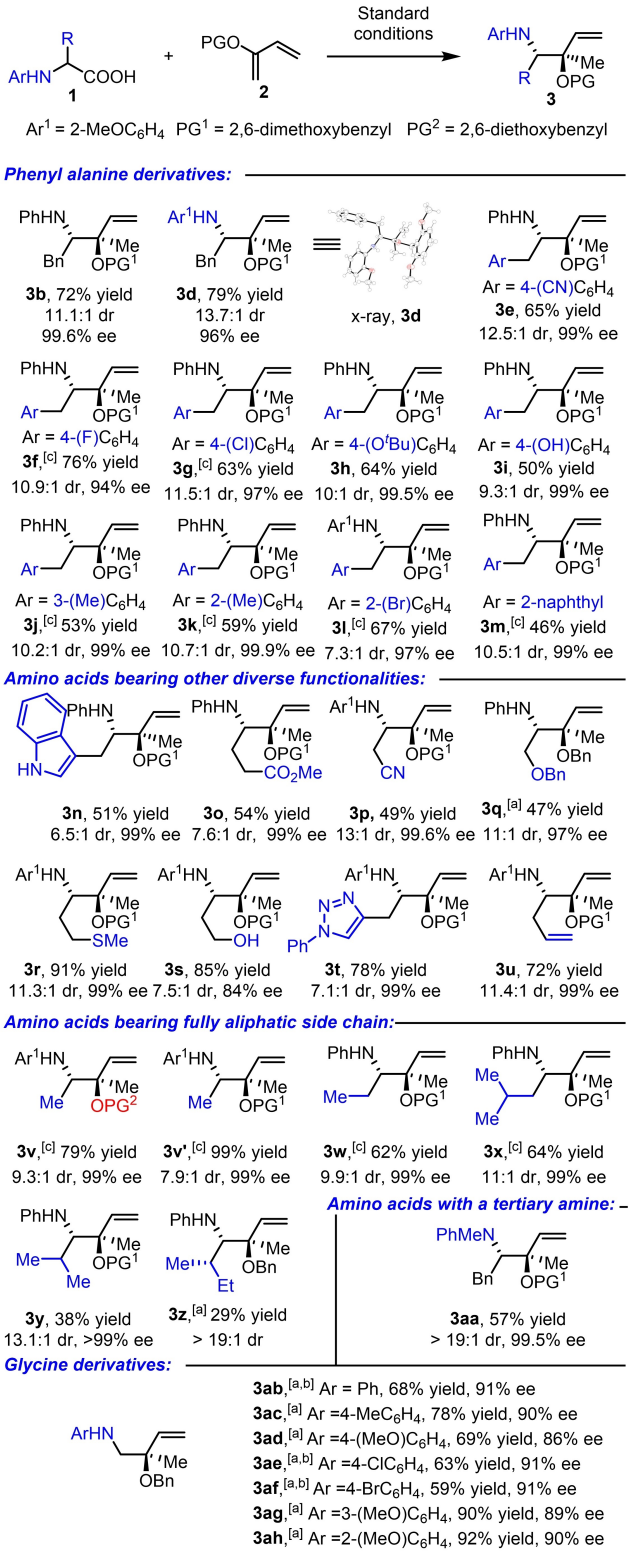


Figure 2. Scope of *N*-aryl amino acids. Reactions were carried out with reaction conditions in Table 1, entry 4, unless otherwise noted. Isolated yields are presented, and ee was determined by chiral HPLC analysis. Diastereoselectivity and regioselectivity were determined by ^{1}H NMR. Unless otherwise noted, rr > 19:1. [a] DMF was used instead of acetone. [b] 10 mol% [(η^3-cinnamyl)PdCp] and 24 mol% **L3** were used. [c] ee was determined after derivatization of corresponding compounds (see the Supporting Information).[20]

phenyl alanine was well tolerated, affording the related adducts (**3e**–**3l**) in moderate to good yields with excellent diastereo-, and enantioselectivity (7.3:1–12.5:1 dr, 94–99.5% ee). Gratefully, a 2-bromo substituent on the phenyl alanine provides a useful handle for further functionalization of **3l** through metal-catalyzed cross-couplings. Notably, tyrosine and tryptophan derivatives with an unprotected phenol and indole moieties, respectively, coupled well with **2b** to furnish allylation products **3i** and **3n** in acceptable yields with good to excellent stereoselectivity. Moreover, the reaction was compatible with the presence of a diverse array of functionalities such as carboxylic ester (**3o**), nitrile (**3p**), ether (**3q**), thioether (**3r**), hydroxyl (**3s**), 1,2,3-triazol (**3t**) and alkene (**3u**). In all cases, 1,2-amino tertiary ethers were prepared in moderate to excellent yields and stereoselectivity. Compared with the results of HAA with alanine and **2b**, 2-alkoxydiene **2c** containing a bulkier protecting group (2,6-diethoxybenzyl) resulted in a better diastereoselectivity (**3v** vs. **3v'**), albeit with a lower yield (79%). Several fully aliphatic amino acids also participated in the reaction, and the isolated yields of desired adducts (**3v**–**3z**) decreased gradually along with enlarging the bulkiness of amino acids. To our delight, 1,2-amino ether **3z** bearing three contiguous chiral centers could be formed with excellent stereoselectivity when a chiral isoleucine was employed in the reaction. In addition to α-amino radicals bearing secondary amines, this HAA also allows an α-amino radical containing a tertiary amine to react with **2b**, resulting in a tertiary amino ethers **3aa** in > 19:1 dr with 99.5% ee. Satisfactorily, *N*-aryl glycines that feature electron-withdrawing or electron-donating substituents on the aryl ring react well with **2a**, and allylated adducts **3ab**–**3ah** were obtained in 59 to 92% yields with 86 to 91% ee.

Next, the scope of the diene coupling partner was explored (Figure 3). A number of 2-benzyloxydiene derivatives reacted well with *N*-aryl glycines leading to the desired products (**4a**–**4f**) in good to excellent yields with high levels of regio- and enantioselectivities. Notably, this HAA allows the synthesis of **4a** on preparative scale (1 mmol) with slightly decreased yield and no erosion on the enantioselectivity. In addition, substrates bearing an alkyl chain with terminal functionalities including Ph, OMe, OPh, indolyl and piperidinyl groups afforded the desired products (**4g**–**4k**) in 75–95% yields with 76–89% ee. It is noteworthy that a matched/mismatched effect was investigated in this HAA with a 2-alkoxydiene bearing a chiral solketal moiety (**4l** vs. **4m**). Compared with *ent*-**L3**, **L3** provides a better outcome with reversed diastereoselectivity. This observation indicates that the chirality of the catalyst exerts major control on the stereochemical outcome of the reaction. Importantly, the mild reaction conditions and high functional group tolerance enable the formation of chiral vicinal amino ethers (**4n**–**4o**) bearing complex or bioactive fragments derived from drug (naproxen) and natural product (citronellol) in good diastereoselectivity. Unfortunately, although 2-alkyl 1,3-dienes such as isoprene can participate in the reaction, the desired product **4p** was obtained only in a modest yield because of the poor regioselectivity. This observation hints that elec-

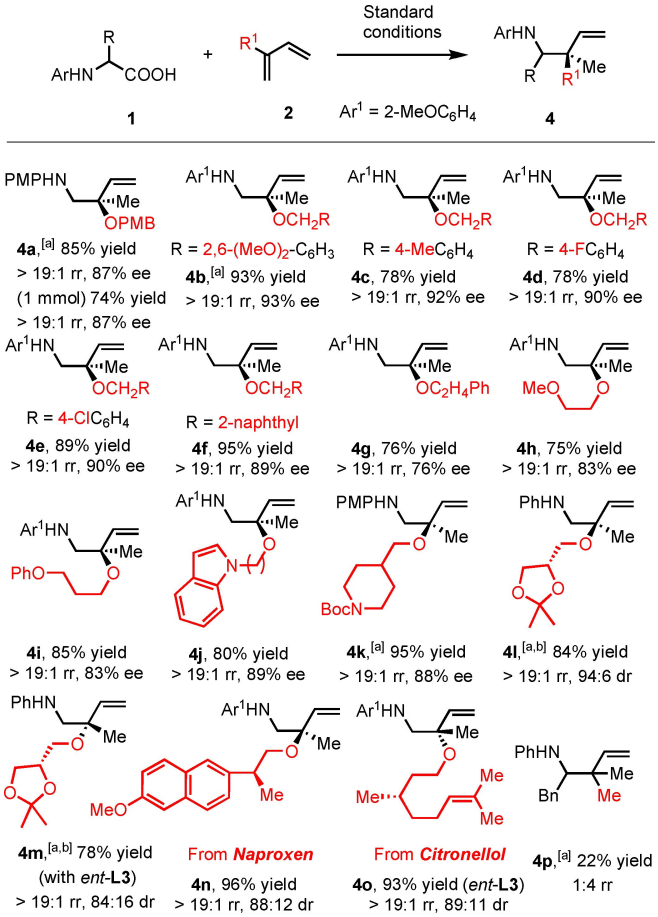


Figure 3. Scope of 1,3-dienes. Reactions were carried out with reaction conditions in Table 1, entry 4, unless otherwise noted. Isolated yields are presented, and ee was determined by chiral HPLC analysis. Diastereoselectivity and regioselectivity were determined by ^{1}H NMR or ^{13}C NMR. Unless otherwise noted, rr > 19:1. [a] DMF was used instead of acetone. [b] 10 mol% [(η^3-cinnamyl)PdCp] and 24 mol% **L3** were used.

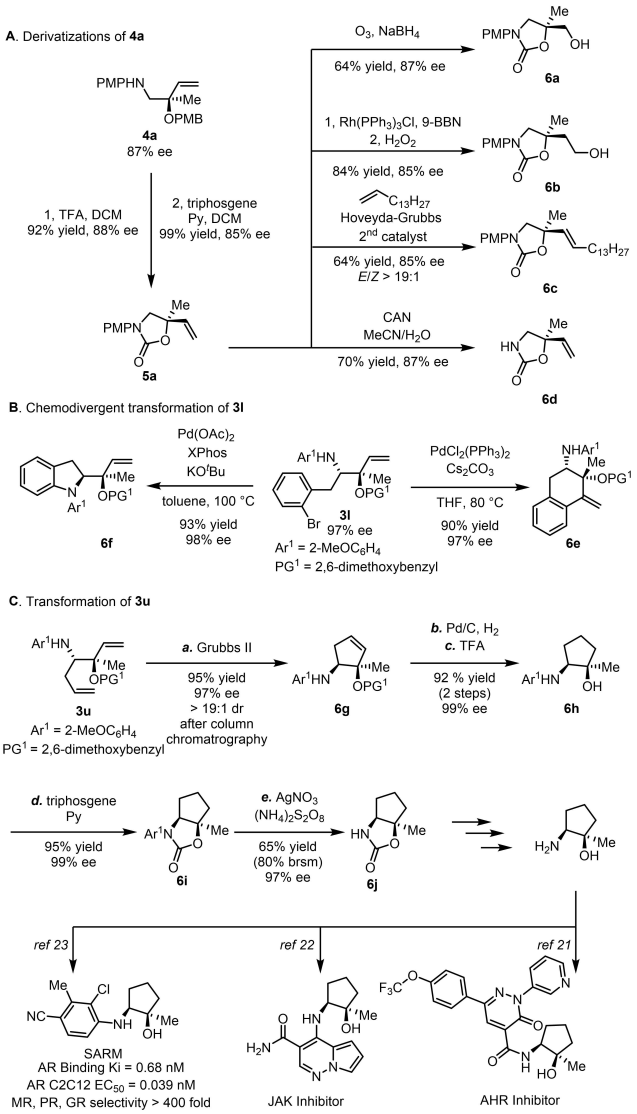


Figure 4. Synthetic applications.

tronic perturbation by oxy-substituents of dienes dictates the regioselectivities.

To verify the synthetic potential of this HAA protocol, several postcatalytic transformations were carried out (Figure 4). We first synthesized oxazolidinone **5a** via sequentially deprotection of **4a** with TFA and protection with triphosgene. Ozonolysis of **5a** followed by $NaBH_4$ reduction generated **6a** in 64% yield. Rhodium-catalyzed hydroboration followed by oxidative workup afforded alcohol **6b** in good yield. Cross metathesis between **5a** and a terminal olefin yielded an internal olefin **6c** in 64% yield. Under oxidative conditions, the PMP group on the nitrogen could be cleaved efficiently, leading to secondary amide **6d** in good yield. In all cases, no erosion of enantiopurity was observed (Figure 4A). Interestingly, a substrate bearing a bromide handle (**3l**) could undergo Buchwald-Hartwig cross coupling and Heck reaction independently under different reaction conditions, affording a chiral indoline **6f** and 6-membered cyclized product **6e**, respectively, with high levels of yields and chemoselectivity (Figure 4B).

Starting from the ring-closing-metathesis of **3u**, the corresponding amino cyclopentenol ether (**6g**) could be obtained as a single diastereoisomer in 95% yield with 97% ee after column chromatography (Figure 4C). Hydrogenation of **6g** followed by treating with TFA to product amino alcohol **6h** in 92% yield with 99% ee. Then **6h** reacted with triphosgene to generate oxazolidinone **6i** in 95% yield. Removal of *ortho*-methoxyphenyl under an oxidative condition was performed smoothly to afford **6j** in a good yield. The further deprotection of carbonyl group of **6j** might lead to chiral amino methylcyclopentanol, which is a common intermediate for the syntheses of multiple bioactive compounds, including aryl hydrocarbon receptor (AHR) inhibitor,[21] janus kinase (JAK) inhibitor[22] and transdermal selective androgen receptor modulator (SARM).[23]

To gain insights into the reaction mechanism, several mechanistic studies were carried out (Figure 5). First, D_2O (5 equiv) was added to the reaction mixture under the standard reaction conditions and deuterium was only

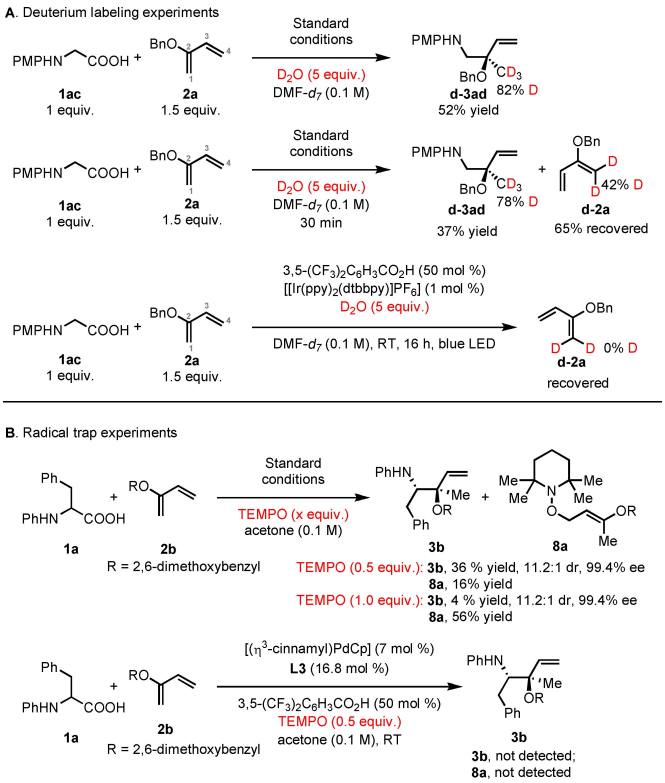


Figure 5. Mechanism investigations.

observed at C1 position of vicinal amino ether **3ad**. When the reaction was halted after 30 min, 42 % deuterium incorporation at C1 position was detected in the recovered diene **2a**. A control experiment was performed without palladium and **L3** and no deuterium incorporation was observed in recovered diene. These results indicate that hydropalladation occurs specifically at C1 position of diene and this step is reversible. Second, chiral *N*-phenyl amino acid (**L-1a**) or (**D-1a**) derived from enantiomerically pure phenyl alanine was applied in this transformation, resulting in the same stereochemical outcome, which might suggest the formation of an α-amino alkyl radical (for full details, see the Supporting Information). Moreover, the addition of a radical scavenger 2,2,6,6-tetramethylpiperidine-*N*-oxyl radical (TEMPO) into the model HAA of **2b** decreased the reactivity, and the allyl-TEMPO adduct **8a** was isolated. Neither desired product **3b** nor **8a** could be detected in the absence of photocatalysis and light irradiation, which suggests that the allyl-TEMPO adduct **8a** might not be formed through the directly nucleophilic addition of TEMPO to π-ally-Pd complex. These observations hint that an allylic radical might be formed from the π-ally-Pd complex via photoredox process.[24] A light on-off experiment was conducted and the blue LEDs irradiation throughout the reaction was found necessary for progressing this HAA smoothly. Furthermore, a low quantum yield (0.2) revealed that this transformation does not likely undergo a radical-chain propagation mechanism (for full details, see the Supporting Information).

On the basis of the aforementioned observations and previous reports on the photoredox and palladium dual-catalyzed allylic alkylation reactions,[14,24,25] a potential mechanism for this transformation is described by the cycle presented in Figure 6. The Pd^{II} precatalyst reacts with phosphoramidite ligand **L3**, following reductive elimination, generating a chiral monomeric Pd^0 species. Subsequently, oxidative addition of Pd^0 with carboxylic acid (HX) forms Pd-hydride species (**I**) (path a).[26] When the carboxylic acid is not amino acid, species **I** undergoes a ligand exchange with amino acid, leading to Pd-hydride species (**II**). Direct oxidative addition of Pd^0 with amino acid generates Pd-hydride species (**II**) is an alternative pathway (path b). After coordination with diene, a reversible hydropalladation leads to the key π-ally-Pd intermediate (**III**). Then a single electron transfer from species **III** to excited Ir^{III}* complex results in decarboxylation and the newly formed α-amino radical rebounds with π-ally-Pd intermediate, affording Pd^{III} species (**V**).[14,25c,27] After reductive elimination, a new C–C bond is formed with the release of a Pd^I species. Finally, the catalytic cycle finishes by single electron reduction of a Pd^I species with the Ir^{II} complex regenerating Pd^0.

Conclusion

In addition to enantioselectivity, diastereoselectivity remains a major challenge in radical involved cross-coupling reactions. In this work, we have developed a highly regio-, diastereo-, and enantioselective decarboxylative HAA with 2-alkoxydienes via a photoredox/palladium cocatalytic system. This dual catalysis protocol allows for facile access to synthetically useful vicinal amino ethers bearing a tertiary alcohol moiety. Mechanistic studies suggest that this transformation proceeds through a reversible hydropalladation of 1,3-dienes. Further studies aiming at extending this protocol to related synthetic applications are currently ongoing in our laboratory.

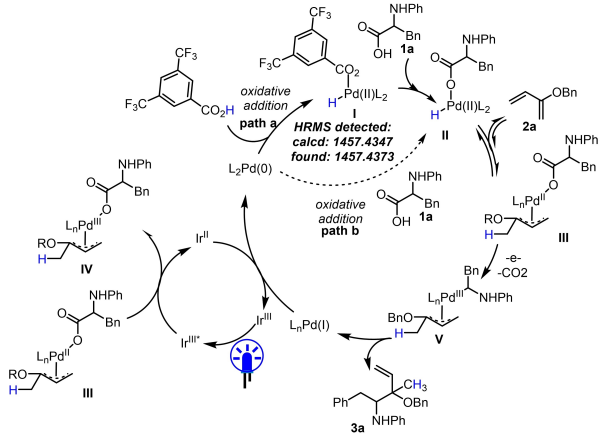


Figure 6. Proposed mechanism.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Amino Acids · Dienol Ethers · Palladium · Photoredox · Stereoselectivity

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[26] Pd-hydride species (**I**) could be detected by the high-resolution mass spectrometry, when 3,5-$(CF_3)_2$–$C_6H_3CO_2H$ was subjected to the mixture of [(η^3-cinnamyl)PdCp] and **L3**. For full details, see the Supporting Information.

[27] Control experiments in the presence of TEMPO could not detect any adducts of α-amino radical, which might hint that rebound of α-amino radical with π-allyl-Pd undergoes quickly in a solvent cage after decarboxylation process. Based on the recent reports (14, 24c) on photoredox/palladium-catalyzed decarboxylative allylation reactions, our reaction might undergo reductive quenching process.

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