

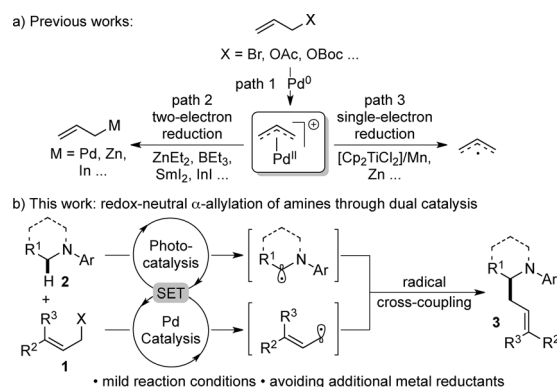
Synthetic Methods

Redox-Neutral α -Allylation of Amines by Combining Palladium Catalysis and Visible-Light Photoredox Catalysis**

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Abstract: An unprecedented α -allylation of amines was achieved by combining palladium catalysis and visible-light photoredox catalysis. In this dual catalysis process, the catalytic generation of allyl radical from the corresponding π -allylpalladium intermediate was achieved without additional metal reducing reagents (redox-neutral). Various allylation products of amines were obtained in high yields through radical cross-coupling under mild reaction conditions. Moreover, the transformation was applied to the formal synthesis of 8-oxoprotoberberine derivatives which show potential anticancer properties.

Palladium-catalyzed allylation reactions are among the most important methods for creating new chemical bonds.^[1–4] Critical to the success of this chemistry is the formation of key π -allylpalladium intermediates from allylic esters or their analogues (Scheme 1a, path 1), which can be utilized as efficient electrophilic components to react with diverse carbon or heteroatom nucleophiles.^[1,2] In contrast, reversal of reactivity of the π -allylpalladium complex can be realized through two-electron^[3] or single-electron reduction^[4] (Scheme 1a, paths 2 and 3) in the presence of stoichiometric amounts of reducing reagents (e.g., Et₃B, Et₂Zn, InI, SmI₂, or Mn powder). The resultant allylic metal complex (η^1 -type) or



Scheme 1. Palladium-catalyzed allylation reactions. Cp = cyclopentadiene.

allylic radical enables the nucleophilic addition to aldehydes, ketones, and imines,^[3] as well as radical homocoupling^[4a,d] and intramolecular radical addition reactions.^[4b–d] Despite the advances, the catalytic generation of an allylic radical from a π -allylpalladium complex without additional reductants remains a challenge. Furthermore, developing novel transformations and expanding the substrate scope of this chemistry is highly desirable.

Recently, visible-light-induced photoredox catalysis has become an important platform for the design and development of a variety of radical reactions under remarkably mild reaction conditions.^[5] More intriguingly, dual catalysis combining photocatalysis with transition-metal catalysis^[6,7] can accomplish many new chemical transformations which are impossible or not easily accessible for a single catalytic cycle. For instance, the group of Sanford successfully achieved photoredox Pd/Ru-catalyzed C–H arylation reactions using aryl diazonium and diaryliodonium salts as the radical source.^[7b,c] The key to these reactions was the oxidation of Ar–Pd^{III} to Ar–Pd^{IV} in with the high-valent Ru^{III} or Ir^{IV} species, which was generated by the oxidative quenching of the visible-light excited Ru^{II*} or Ir^{III*} complex. In contrast, we questioned whether the π -allylpalladium complex could be reduced to a neutral π -allyl radical and Pd⁰ species using the low-valent species, generated from the excited state of the photocatalyst, through reductive quenching. As part of our ongoing efforts to develop novel photocatalytic reactions,^[8] we herein disclose an unprecedented redox-neutral α -allylation of amines (Scheme 1b)^[9] through radical cross-coupling by combining palladium catalysis (to generate π -allylic radical) and photoredox catalysis (to generate α -amino radical).

Initially, cinnamyl acetate (**1a**) and *N*-phenyltetrahydroisoquinoline (**2a**) were selected as model substrates to

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examine the feasibility of the designed process. Fortunately, optimization of the reaction conditions showed that the proposed α -allylation reaction of amines did indeed occur with an 81 % yield in the presence of 5 mol % $[\text{Pd}(\text{PPh}_3)_4]$ and 2 mol % $[\text{Ir}(\text{ppy})_2(\text{dtbbpy})]\text{PF}_6$ in degassed CH_3CN under irradiation with a 3 W blue LED for 48 hours (for details of the optimization, see the Supporting Information). Control experiments indicated that the photosensitizer, palladium catalyst, visible-light irradiation, and degassing procedure are all crucial for this dual catalytic α -allylation reaction of amines (see Table S7 in the Supporting Information).

Under the optimal reaction conditions, we evaluated the generality of this photoredox Pd/Ir dual catalytic allylation reaction. As highlighted in Table 1, a wide range of allylic compounds were applicable and generally moderate to good yields were achieved. With cinnamyl alcohol as an example, not only its acetate (**1a**) but also *tert*-butoxy carbonate (**1b**) and diethyl phosphate (**1c**) proved successful for this reaction (Table 1, entries 1–3). Notably, the direct employment of allylic alcohol **1d** itself as the allyl radical precursor was also feasible with the assistance of formic acid (entry 4). When

cinnamyl bromide (**1e**) was used under best reaction conditions, the allylation product **3aa** was obtained in 45 % yield. A control experiment revealed that the absence of the palladium catalyst did not affect the reaction efficiency and a similar yield of isolated **3aa** was obtained (entry 5), presumably because **1e** can directly undergo a visible-light-induced reductive dehalogenation process to give the key allylic radical intermediate. Other substituted allylic reagents were also surveyed to explore the potential of this methodology. The results in entries 6–8 revealed that alkyl- (**1f** and **1g**) and ω -vinyl- (**1h**) substituted substrates were well tolerated under this dual catalytic system and moderate to good yields of corresponding products were obtained (**3fa–3ha**: 57–69 % yields). Notably, simple allylic esters could be employed in the reaction. With **2a** and its electron-rich analogue **2l** as the example, the Pd/Ir-catalyzed α -allylation of amines with **1i** proceeded well, thus affording desired products in good yields upon isolation (entries 8 and 9).

The experiments investigating the scope of the amine component are described in Table 2. The reaction appears to be general with a variety of *N*-aryl tetrahydroisoquinolines. For example, the substitutes on the benzene ring of tetrahydroisoquinoline can be varied, thus delivering the allylation products in satisfactory yields (**3cb**: 81 % yield and **3cc**: 62 % yield). Moreover, both electron-withdrawing groups (i.e., F, Cl, and ester) and electron-donating groups (i.e., Me and OMe) can be successfully introduced to the *para*, *meta*, and *ortho* positions of the benzene ring on the nitrogen atom, thus giving the corresponding allylation products (**3cd–3ci**) in good yields. It is important to note that the substrate **2j**, with a sensitive vinyloxy functional group, can participate in this transformation, thus giving the desired product in 51 % yield. Additionally, the *N*-alkyl substituted tetrahydroisoquinoline **2k** is suitable for this dual catalytic process, albeit with relatively low yield of the corresponding allylation product (**3ck**, 15 % yield).

The success of this dual catalysis system could be also significantly extended to the allylation reaction of secondary amines. For instance, the α -amino methyl ester **4a** and ethyl ester derivatives **4b** and **4c** can readily react with cinnamyl diethyl phosphate **1c**, and the resulting allylation products were obtained in moderate yields (Table 3). Additionally, we

Table 1: Substrate scope of allylic esters.^[a]

Entry	Substrate	Product	Yield [%] ^[b]
1			81
2			70
3			83
4 ^[c]			42
5			45 (41) ^[d]
6			60 ^[e]
7			57
8 ^[f]			69 ^[e]
9			73
10			76

[a] Reaction conditions: **1** (0.3 mmol), **2a** or **2l** (0.36 mmol), $[\text{Pd}(\text{PPh}_3)_4]$ (5 mol %), $[\text{Ir}(\text{ppy})_2(\text{dtbbpy})]\text{PF}_6$ (2 mol %), and CH_3CN (3 mL) at RT for 48 h under irradiation with a 3 W blue LED. [b] Yield of the isolated product. [c] Adding 1.0 equiv of HCO_2H . [d] Without the addition of $[\text{Pd}(\text{PPh}_3)_4]$. [e] 3:1 *E/Z* of products. [f] 6:1 *E/Z* of substrate **1g**. Ac = acetyl, Boc = *tert*-butoxycarbonyl, dtbbpy = 4,4'-di-*tert*-butyl-2,2'-bipyridine, ppy = 2-phenylpyridine.

Table 2: Substrate scope of tetrahydroisoquinolines.^[a]

Substrate	Product	Yield [%]

[a] Reaction conditions: **1c** (0.3 mmol), **2** (0.36 mmol), $[\text{Pd}(\text{PPh}_3)_4]$ (5 mol %), $[\text{Ir}(\text{ppy})_2(\text{dtbbpy})]\text{PF}_6$ (2 mol %), and CH_3CN (3 mL) at RT for 48 h under irradiation with a 3 W blue LED. Yield is that of the isolated product.

when chiral ligands were used in the reaction, made radical cross-coupling more favorable.^[15]

In conclusion, we have developed the catalytic generation of an allyl radical from a π -allylpalladium complex by combining visible-light-induced photoredox catalysis and palladium catalysis. The α -amino radical derived from the same catalytic cycle can react with the allyl radical through a cross-coupling process to afford various α -allylation products of amines in high yields. In contrast to prior reduction methods using stoichiometric amounts of additional reductants, this strategy utilized the bifunctional property of the photoredox catalyst: oxidizing amines to α -amino radical and reducing π -allylpalladium complex to allyl radical. Notably, this reaction has been successfully applied to the formal synthesis of the 8-oxoprotuberberine derivative **11**, which has potential anticancer activities. Moreover, a plausible reaction mechanism was proposed based on a series of control experiments and EPR studies.

Experimental Section

Representative procedure: **1a** (0.3 mmol), **2a** (0.36 mmol), [Ir(ppy)₃](dtbbpy)]PF₆ (0.006 mmol), [Pd(PPh₃)₄] (0.015 mmol) and dry CH₃CN (3.0 mL) were added to a 10 mL Schlenk flask equipped with a magnetic stir bar was added. The resulting mixture was degassed by using a freeze–pump–thaw procedure (3 times). The solution was then stirred at a distance of ca. 5 cm from a 3 W blue LED at room temperature for 48 h. Then, the solvent was removed by vacuum and the crude reaction mixture was purified by flash chromatography on silica gel (silica: 200 to 300; eluent: petroleum ether/CH₂Cl₂ (5:1 to 3:1) to provide pure product **3aa** as a light yellow oil in 81 % yield.

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