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Elaborating azaaryl alkanes enabled by photoredox/palladium dual catalyzed dialkylation of azaaryl alkenes

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ABSTRACT

A general process for the construction of azaaryl alkanes was achieved by employing the photoredox/palladium dual catalysis under mild visible light irradiation. The palladium catalyst ligated with a diphosphamide ligand exhibited high effectiveness in facilitating the modular three-components transformation. Furthermore, the cascade transformation was not restricted to constructing tertiary carbon centers; it also encompassed the synthesis of more challenging quaternary carbon centers with sixteen representative azaarene-derived substrates as reactants. In addition, alkyl 1,4-dihydropyridines (DHP), alkyl BF_3K, and alkyl carboxylic acids were identified as precursors for alkyl radicals. Mechanistic investigations revealed the involvement of two different active benzylic nucleophiles in the cascade transformation. One is azabenzylic radical, which generate the terminal product through an "inner sphere" reductive elimination process. The other is azabenzylic anions, generated through visible light induced radical anion cross-over, leading to the formation of terminal products *via* an "outer sphere" reaction pathway. The efficiency of current modular transformation was also demonstarted by the concise of oliceridine, a prominent USFDA drug for pain management.

Due to the distinctive pharmacological properties of drug candidates containing heteroarenes, such as the ability to lower drug lipophilicity, increase aqueous solubility, and reduce the inhibition of cytochrome P450s, the development of efficient methods to construct heteroaryl-substituted carbon centers from readily available starting materials presents a challenging yet highly attractive project in synthetic chemistry and pharmaceutical research (Fig. 1A) [1–5]. Transition-metal-catalyzed allylic alkylation at the azabenzylic position has emerged as a more efficient approach for synthesizing heteroaryl-containing compounds in recent decades [6–8]. However, most research focused on activated substrates that bear acidic benzylic C–H bonds ($pK_a < 25$). Typically, additional adjacent electron-withdrawing groups or prefunctionalization of the substrates were required to enhance the acidity of the benzylic C–H bonds [9–13]. Achieving efficient transition-metal-catalyzed allylic alkylation at unactivated azabenzylic positions remains a significant challenge, and successful examples were limited to the use of primary and secondary nucleophiles accompanied with moisture-sensitive strong bases as deprotonation reagents in most cases (Fig. 1B) [14–20], except for some well-designed substrates [21]. The groundbreaking research conducted by Trost [14], Walsh [15,16], Sawamura [17], You [18], and Newhouse [19], illustrated the significance of supporting ligands, strong bases, and appropriate substrates in transition metal-catalyzed azabenzylic allylic alkylation. The works also emphasized the difficulties in creating sterically hindered quaternary carbon centers and products containing acidic X–H bonds (X = N or O). Therefore, there is a high demand for the development of general process for the diversification of heteroaryl alkanes with transition-metal catalyzed azabenzylic allylic alkylation as the key steps.

Given the need for additional synthetic transformations to prepare heteroaryl substrates with different side chains and harsh conditions required for efficient deprotonation in previous efforts, it would be valuable to develop an efficient catalytic system that enables the cascade installation of the alkyl side chain and generation of the azabenzylic nucleophiles which could be trapped by transition metal mediated allylic cations. Recently, 1,2-substituted alkanes (aryl-arylation, alkyl-arylation) can be precisely synthesized in one operation step using versatile modular synthetic precursors by combining vicinal difunctionalization of alkenes with transition metal catalysis [22–24]. The three-components reaction based on Tsuji–Trost reaction allows for the efficient difunctionalization transformation of alkenes, but its applicability is limited to

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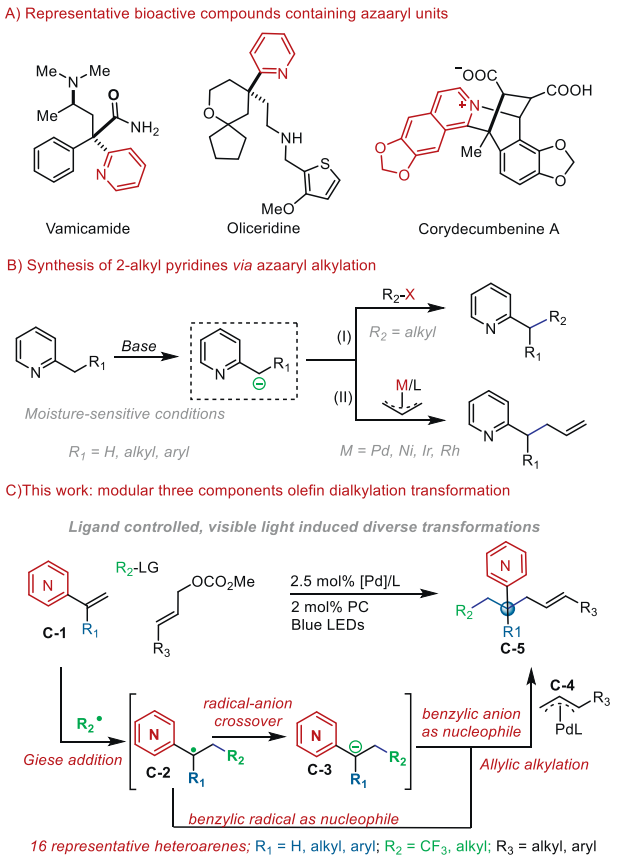

Fig. 1. (A) Representative bioactive compounds containing azaaryl units. (B) Synthesis of 2-alkyl pyridine *via* direct azabenzylic alkylation. (C) Modular three components olefin dialkylation transformation.

highly reactive Michael acceptors or specific nucleophilic reagents [25,26]. The dialkylation transformation with common used alkenes is strictly limited due to the competing allylic alkylation reaction with the pronucleophile and simple conjugate addition of the pronucleophile with the Michael acceptors [27]. Recently, alkyl radicals generated under mild visible light conditions can undergo a Gesise-type reaction with terminal double bonds. This enables efficient alkylation at the α position while generating a corresponding carbon radical at the β position [28]. In some cases, this carbon radical can be captured by transition metal-mediated cationic intermediates [29]. Additionally, these β radical intermediates can be further reduced to carbon anions, which could serve as good reaction partners for the cationic intermediates, including the transition metal-mediated allylic cations. However, the previous well-developed difunctionalization transformations based on visible light-induced radical-anion crossover process mainly limited to intramolecular cyclization, intermolecular addition reactions with carbonyl units, or protonation [30–32]. Capturing *in-situ*-generated carbon anions using transition metal-mediated cationic intermediates is rare due to the challenging matching activity between the anion and the metallic intermediate, despite the activity of the latter could be tuned by additional ligands. An notable example is the work by Wang *et al.*, who achieved the 3,4-difunctionalization of 2-aryl acrylate ester through a carbonyl group-favored benzylic radical-anion crossover strategy in 2021 [33]. Although the radical precursors were confined to specific C–H bonds and stable α-aryl enolate (corresponding ester p*Ka* $\approx$ 23.6) was generated as the terminal nucleophile [34,35], the work conveys the message that the photoinduced radical anion crossover process is fully compatible with ligand-ligated palladium catalytic systems.

In relation to our interest in the visible light induced selective transformation of olefins and palladium-catalyzed allylic alkylation with "nonstable" nucleophiles [36,37], we proposed utilizing visible light-induced radical-anion cross-over strategy to efficiently carry out palladium-catalyzed allylic alkylation transformation at the azabenzylic position. Significantly, the three-component reaction utilizing stable modular alkyl radical percussors, azaaryl alkenes (**C-1**), and allylic reagents as the reaction partners would provide a general efficient process to afford diverse azaaryl-containing alkane derivatives (Fig. 1C). However, the occurrence of Minisci-type reactions, which can result in the formation of undesired by-products or over-alkylation products [38], and the competition of the reaction between the alkyl radical and the allylic cation mediated by palladium, can pose challenges for the desired three-component transformations [39,40]. Furthermore, the unique metallophilicity of the nitrogen atom in the heteroarenes may lead to the formation of coordination complexes between metal ions and the substrates, which could impact the efficiency of the catalyst. Therefore, to achieve the desired dialkylation of heteroaryl alkenes through a visible light-enabled redox process, it is crucial to employ a well-designed ligand-ligated catalyst and carefully select radical precursors and photosensitizers.

To ensure precise introduction of the alkyl chain and diversification of the terminal products, we employed single electron transfer (SET) type radical transformation with a reductive alkyl reagent to generate the corresponding azabenzylic radical intermediate *via* Giese addition [41–47]. Considering the importance of the CF_3 group in pharmaceutical research [48,49], commercially available CF_3SO_2Na was selected as the model radical precursor for condition optimization (Fig. 2).

We first examined the ligands effect with 4CzIPN as the photosensitizer [50–52]. As shown in Fig. 2A, mono phosphine ligands predominantly gave the Giese product **4a′** with only a trace amount of the desired product **4a** observed on GC-MS (**L1**, **L2**; details see Supporting information). Encouragingly, the desired product **4a** was obtained as the major product with diphosphine **L3** (DPPE) as the ligand, and better 36% yield was achieved with DPEphos **L4**, and Xantphos **L7** could afford **4a** with a good 75% yield and only 5% yield of byproduct **4a′** was observed on GC. Inspired by the distinctive ligand effects with diphosphine ligand **L4** and **L7**, we employed diphosphamide ligand **L8** to facilitate the reaction [53]. Delightfully, the desired allylic alkylation product could be obtained with an excellent 88% yield and a trace amount of **4a′** was detected. Unfortunately, only a poor 2% enantiomeric excess (*ee*) was obtained with chiral **L8** as the supporting ligand, nor were any other chiral ligands successful (Fig. S3 in Supporting information). Since **L8** could be easily obtained on a large scale *via* simple synthetic transformations, we employed **L8** as the optimized ligand for further reaction condition screening. Polar solvents such as CH_3CN, DMSO predominantly gave the Giese product **4a′** as the major product in moderate yields. Inorganic bases were needed to sequester the generated sulfur dioxide [54], and the yield of **4a** dramatically decreased to poor 23% without additional base. Besides the well behaved Cs_2CO_3, K_3PO_4 and CsOAc also gave the desired product **4a** with slightly decreased yields. Experiments with different photosensitizers proved that the organic compounds **PC-2** and **PC-3** were suitable photocatalysts for the current transformation, while the expensive iridium complex **PC-6** gave a slightly lower but still good 72% yield. Finally, the combination of 4CzIPN/**L8**/$PdCl_2$/Cs_2CO_3 with DCM as the solvent was proven to be the optimized condition for the current visible light-induced cascade trifluoromethylation/allylic alkylation of azaaryl alkene. Then the allylic precursors with various leaving groups were studied, with the acetate, benzoate, and pivalate affording the products in slightly lower but satisfactory yields when compared to the carbonated (Fig. 2C). However, the allylic diethyl

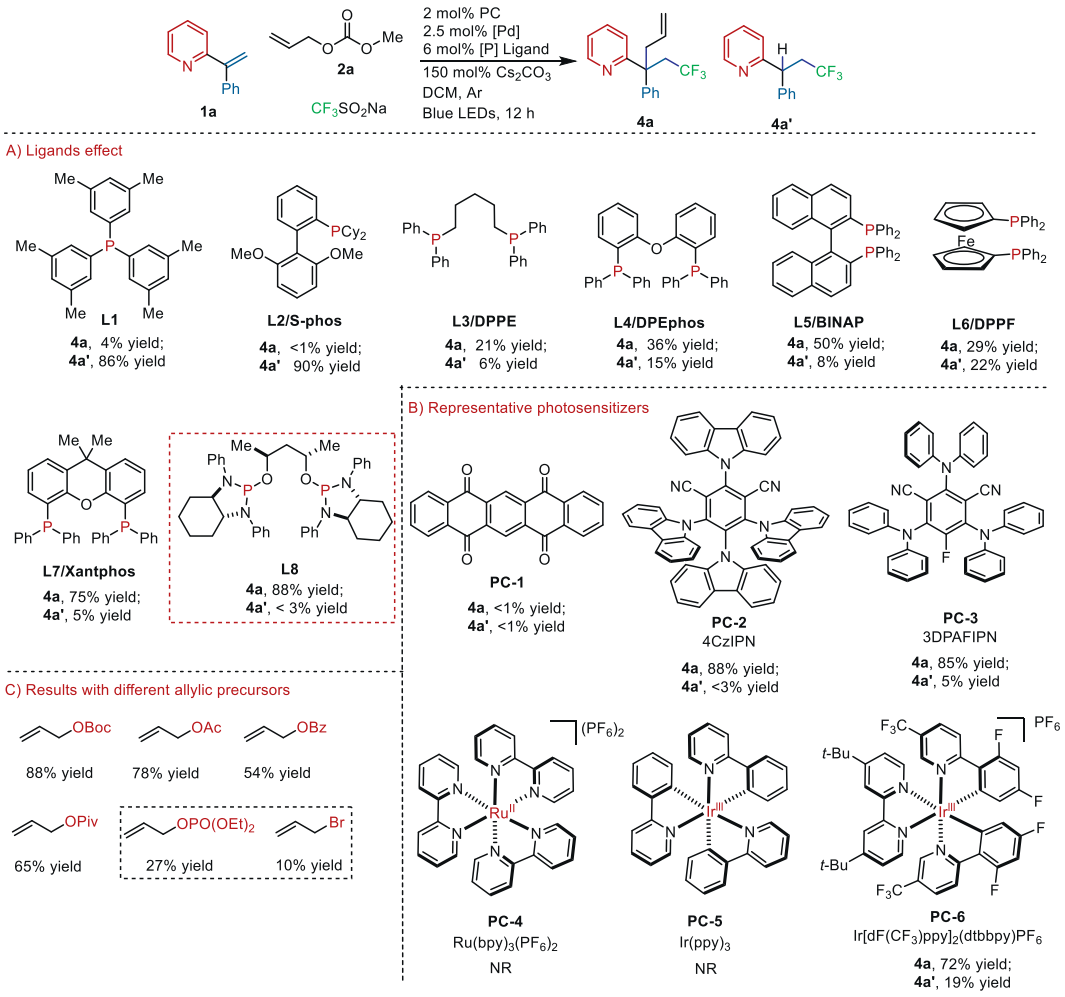

Fig. 2. Reaction optimization. (A) Ligands effect. (B) Representative photosensitizers. (C) Results with different allylic precursors.

phosphate and allylic bromide produced unsatisfactory outcomes, as the allylic reagents with good leaving groups also act as good acceptors for the alkyl radical, leading to competition with the desired Giese type transformation. Finally, the HAT process developed by Wang *et al*. was employed with **1a** as the radical acceptor, frustingly, poor 26% yield was obtained (Table S2 in Supporting information).

With the optimized conditions in hand, we first examined the scope of substrates derived from mononitrogen-containing heteroarenes using CF_3SO_2Na as the model radical precursor (Fig. 3A). Substrates bearing substituents on different positions (C3–C6) of the core pyridine ring all gave the corresponding products in good yields of 68%–84% (**4a**-**4e**). The chlorine atom, which could be a useful handle for further cross-coupling reactions, was compatible well with the palladium catalytic system (**4e**). The lower yield of 68% in this case may be due to steric hindrance from the chloride. It is notable that the acidic N–H unit in the amide (**4c**, $pK_a \approx 26$) did not interfere with the reaction. Considering the significance of 3-pyridyl and 4-pyridyl substituted compounds in pharmaceutical research [55,56], we synthesized two pyridine regio-isomers bearing the alkenyl motif on the C3 and C4 positions and subjected them to the optimized conditions. Delightfully, the corresponding products **4f** and **4g** were obtained with only slightly lower yields than the C2 isomer (**4a**). Sterically hindered quinolyl and isoquinolyl were also well tolerated in our reaction system, giving **4h** and **4i** in good yields. We then focused on substrates bearing polynitrogen-containing heteroarenes, which are useful elements in fine chemical and medicinal chemistry [57,58]. Notably, these compounds were also good acceptors for Minisci-type reactions. Delightfully, substrates such as 2-quinoxalinyl (**4j**), 2-pyrazinyl (**4k**), 2-pyramidinyl (**4l**), 2-pyridazinyl (**4m**), and 2-triazinyl (**4n**) all gave the desired products with good yields of 62%–79%. Additionally, a five-membered *N*-methyl-benzoimidazolyl substrate afforded the allylic compound **4o** with 55% yield. Furthermore, a simple thiazole derivative substrate also produced the desired product **4p** with a good 70% yield [59].

To obtain a diverse range of compounds containing heteroaryl groups, the impact of the **R1** group was then investigated using 2-pyridyl as the representative unit. Initially, various aromatic rings containing different functional groups were subjected to the optimized conditions (Fig. 3B). It was observed that electron-rich (**5a**), electron-deficient (**5c**), and sterically hindered (**5d**, **5e**) aromatic rings all gave the desired products with favorable yields. Additionally, substrates with different alkyl groups also afforded the desired products with moderate to good yields (**5f**-**5h**). Next, to establish a general procedure for the diversification of azaaryl contained compounds, the scope of radical precursors was examined with **1a** as the model acceptor (Fig. 3C). CF_2HSO_2Na was identified as an effective difluoromethyl reagent [60], leading to the desired product **6a** with a moderate yield of 55%. However, it should be noted that simple alkyl sulfinate salts, such as cyclohexanesulfinic sodium salt ($CySO_2Na$), did not produce the desired di-functionalization product.

Subsequently, we utilized alkyl radicals as efficient radical donors for the cascade transformations, and 4-alkyl 1,4-dihydropyridines (DHP) were identified as effective alkyl radical

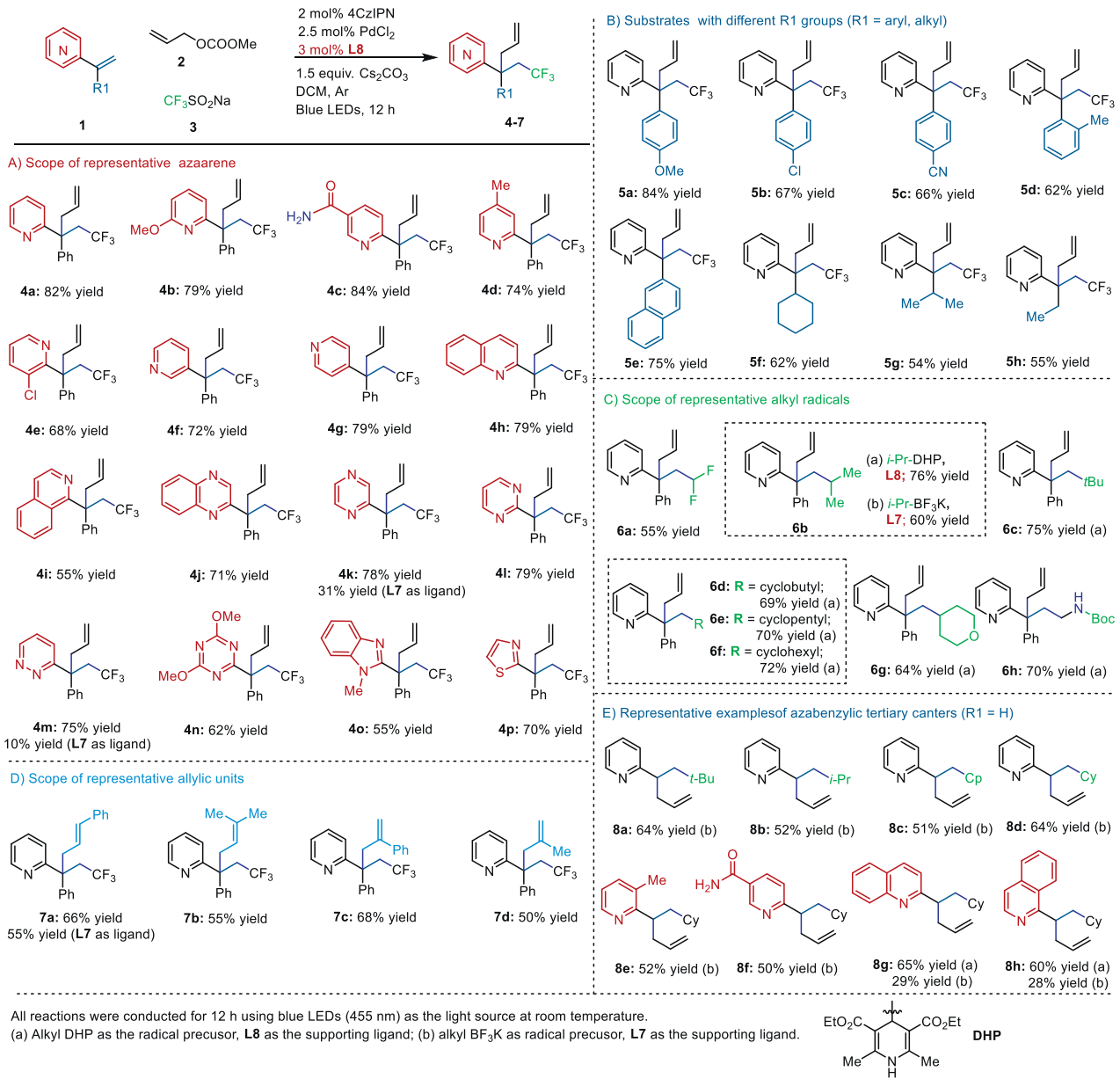

Fig. 3. Substrate scope. (A) Scope of representative azaarenes. (B) Substrates with different R1 groups (R1 = aryl, alkyl). (C) Scope of representative alkyl radicals. (D) Scope of representative allylic units. (E) Representative examples for the construction of azabenzylic tertiary canters (R1 = H).

precursors following detailed optimizations. Various substrates, including *i*-Pr (**6b**), *t*-Bu (**6c**), cyclobutyl (Cb, **6d**), Cp (**6e**), Cy (**6f**), and 4-tetrahydropyranyl (THP, **6g**), all afforded the desired dialkylation product in good yields. Interestingly, the desired product was obtained with a good 70% yield even when using a substrate containing an acidic Boc N–H unit (**6h**), suggesting the involvement of a "special" nucleophile that could not be quenched by the acidic proton in the current palladium-catalyzed allylation. The benzylic radical intermediate showed a preference for attacking the palladium-mediated allylic species rather than undergoing Giese addition to the terminal alkene, resulting in the formation of the desired product in poor yield [61–63]. Furthermore, the scope of the allylic units as useful handles for further practical transformations was examined under optimized conditions (Fig. 3D). The reaction with cinnamyl carbonate afforded the linear product **7a** in 66% yield *via* an "outer sphere" pathway. However, a branch product formed by "inner sphere" reductive elimination was also obtained with approximately 23% yield as a mixture of two isomers. This implies that the benzylic radical intermediate **C-1** may also act as a radical-type nucleophile (Fig. 1C), providing an important information for the subsequent mechanism study. The use of 2-aryl allylic carbonate afforded compounds containing the azabenzylic quaternary center with a good 68% yield (**7c**). The less reactive isopentenyl carbonate and 2-alkyl-substituted allylic carbonates also produced the desired products **7b** and **7d**, but with lower yields compared to the corresponding aryl allylic carbonate.

With the successful construction of quaternary carbon centers, our attention turned to build tertiary carbon centers (Fig. 3E), which are crucial units in bioactive compounds [64]. During the optimization of reaction conditions, we discovered that using a combination of potassium alkyltrifluoroborate and Xantphos (**L7**) produced nearly same yield with the alkyl DHPs/**L8** system. When employing 2-pyridyl styrene as the radical acceptor and *t*-BuBF_3K as the alkyl radical precursor, the desired di-functionalization product was obtained with a good 64% yield using **L7** as the supporting ligand (**8a**). We then synthesized representative potas-

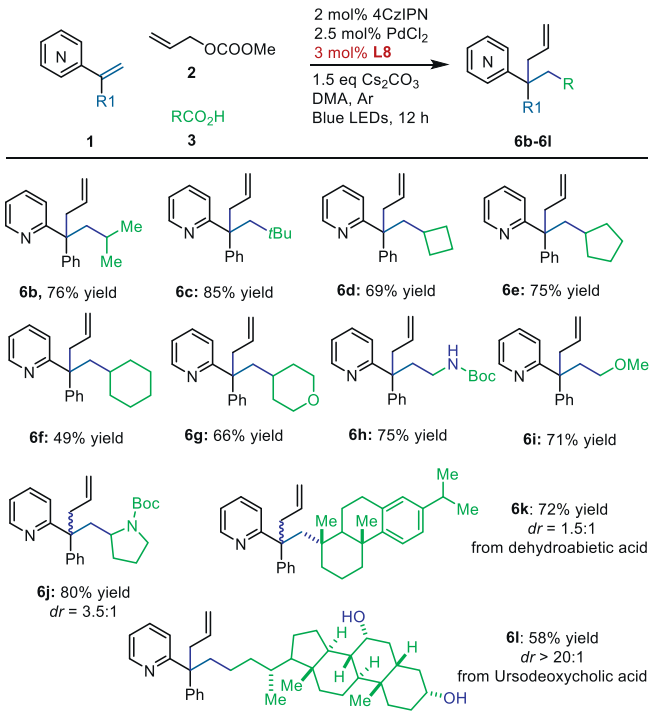

Fig. 4. Representative examples using aliphatic carboxylic acids as alkyl radical precursors.

sium alkyltrifluoroborate reagents following Molander's procedure [29,65,66] and subjected them to the standard conditions. Encouragingly, *i*-Pr (**8b**), Cp (**8c**), and Cy (**8d**) all gave the desired products in good quantities. However, 3-methyl (**8e**) and 5-amidyl (**8f**) pyridyl substrates produced terminal products with slightly lower yields, potentially due to the polymerization of pyridyl styrene initiated by the alkyl radical. The combination of potassium alkyltrifluoroborate and Xantphos (**L7**) produced the desired products from quinoline and *iso*-quinoline derived substrates with poor yields (<30%), whereas the alkyl DHPs and **L8** system provided the terminal products in good yields (**8g**, **8h**).

Considering the ready availability of carboxylic acid, we then focused on utilizing simple carboxylic acid as radical precursors for the present cascade transformations (Fig. 4) [67,68]. Encouragingly, when we used **L8** as the supporting ligand and **1a** as the acceptor, we achieved a good yield of 76% for **6b** by employing commercial *i*-PrCO_2H as the radical precursor, and the commerical ligand **L7** also could give the same results. Subsequently, we tested other representative carboxylic acids with **1a** as the model acceptor. Tertiary and secondary acids produced the desired products with yields ranging from good to excellent (**6b**-**6e**), except for the example using cyclohexanoic acid as the radical precusor (**6f**, 49% yield). Primary carboxylic acid also produced the products, one substrate derived from glycine afforded the desired product **6h** with a good 75% yield. Additionally, despite not being an ideal radical precursor as DHP and BF_3K derivatives, the substrate containing an α-oxygen atom afforded the desired products with a commendable 71% yield. The example with *N*-Boc-proline produced the product **6j** with a good 80% yield and a 3.5:1 diastereoselectivity. Furthermore, two natural products were found to be effective precursors for the current transformation. Notably, the reaction with ursodeoxycholic acid resulted in the product **6l** with an impressive diastereoselectivity of 20:1, potentially attributed to weak interactions between the hydroxyl groups and the palladium center.

Control experiments were conducted using **L8** as the supporting ligand to investigate the mechanism of the cascade transformation and elucidate the cause of the failed enantioselective attempts (Fig. 5). To rule out the possibility that the azabenzylic nucleophile was generated through *in situ* deprotonation of **4a′** with Cs_2CO_3 as base, we used **4a′** as the starting material with 1.5 equiv. of Cs_2CO_3 as the base. However, no desired product **4a** was observed, regardless of whether the reaction was performed under light or dark conditions. Furthermore, even upon addition of the radical precursor CF_3SO_2Na to the conditions, no formation of **4a** was observed (Fig. 5A). These results indicated that the key nucleophile did not originate from **4a′**. Therefore, our focus shifted towards investigating the intermediates of the Giese addition **C-2** (Fig. 1C). 2.0 equiv. TEMPO could inhibit the reaction totally and most of the staring materials was recovered, suggesting the cascade transformation was initiated by the photoinduced CF_3 radical. It should be noted that the benzylic radical intermediate **C-1** could also serve as a suitable reaction partner for the palladium-catalyzed allylic alkylation, which has been demonstrated by Tunge and Yu *et al.* [61,62]. To get information for the specific reaction intermediate, control experiments were conducted using various additives. Initially, H_2O was introduced to capture the benzylic anion intermediate (Fig. 5B). The addition of 10 equiv. of H_2O resulted in a decreased 60% yield of **4a**, while the yield of **4a′** increased to slight better 26%. Subsequently, 10 equiv. of D_2O were added, and a kinetic isotope effect was observed. The final product **4a** was obtained with an 82% yield, while **4a′** was obtained with 13% and exhibited a 66% deuteration. These findings strongly suggest that the azabenzylic anion **C-2** was one crucial intermediate in the current cascade transformations.

Then hexafluoroisopropanol (HFIP) was added to quench the nucleophile [69]. With 300 mol% HFIP, the reaction was completely inhibited. Although the yield of Giese addition product **4a′** increased (21%), there was no corresponding decrease in the yield of **4a**. This suggests that the photo-induced generation of CF_3 radical was suppressed by the excessive amount of HFIP. **4a** could be obtained with a good yield of 70% using 50 mol% HFIP as an additive, however, the yield of **4a′** was poor (4%). Taking into account that Cs_2CO_3 can neutralize the acidity of HFIP, CD_3OD was employed for further experiments. It was noteworthy that both the yield of **4a** and **4a′** decreased upon successive addition of CD_3OD. These findings suggested the existence of an active species that survives in acidic proton contained conditions and could be easily captured by the palladium-mediated allylic cation. The benzylic radical could be responsible for this observation.

To further illustrate our propose that the benzylic radical is an active nucleophile in current transformations, we conducted two additional control experiments using different allylic reagents. According to previous reports, the reaction with a benzylic radical-type nucleophile preferentially generates the branch product through the "inner sphere" reaction pathway. In comparison, the reaction with a benzylic anion of 2-pyridine as the nucleophile produces linear products *via* the "outer sphere" reaction pathway. As shown in Fig. 5C, the reaction with cinnamyl carbonate afforded two regio-isomers, with a linear to branch ratio of 1.6:1 (**9a:9a'**). Next, we used a cyclic allylic carbonate as the reaction partner, resulting in the formation of two stereoisomers with a *cis* to *trans* ratio of 1.1:1 (Fig. 5D). This ratio was consistent with the reaction using cinnamyl carbonate as allylic precursor, indicating that the benzylic radical acts as an active nucleophile to favor the *anti*-product **9b'** in the cascade transformation. Notably, the two distinct reaction pathways involved in the current transformation lead to the formation of opposite stereocarbon centers. This explains the failure of the optimizations for the enantioselective version of the transformation.

Based on previous reports and our current experimental results, we propose a tentative mechanism as illustrated in Fig. 6. When the reaction mixture was exposed to visible light, the photosensitizer 4CzIPN undergoes excitation and oxidizes CF_3SO_2Na to CF_3

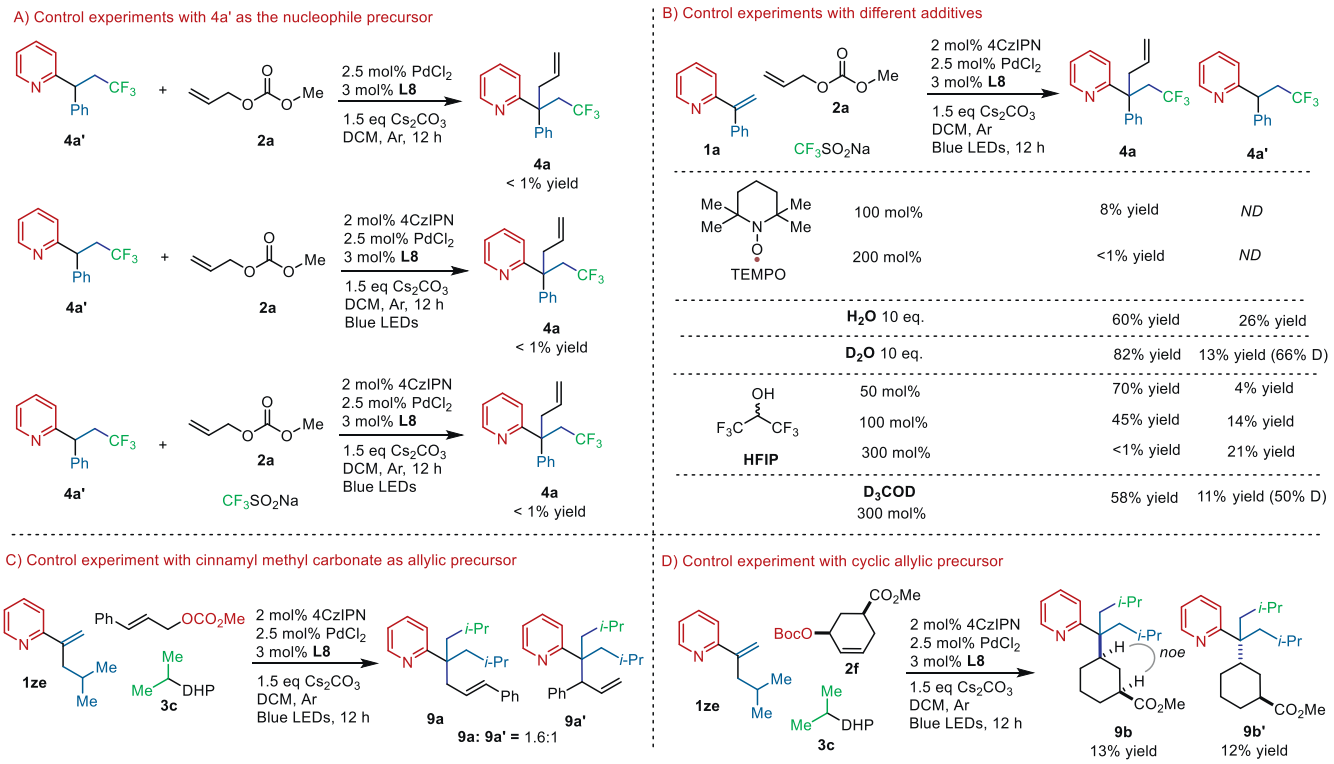

Fig. 5. Control experiments. (A) Control experiments with **4a'** as the nucleophile precursor. (B) Control experiments with different additives. (C) Control experiment with cinnamyl methyl carbonate as allylic precursor. (D) Control experiment with cyclic allylic precursor.

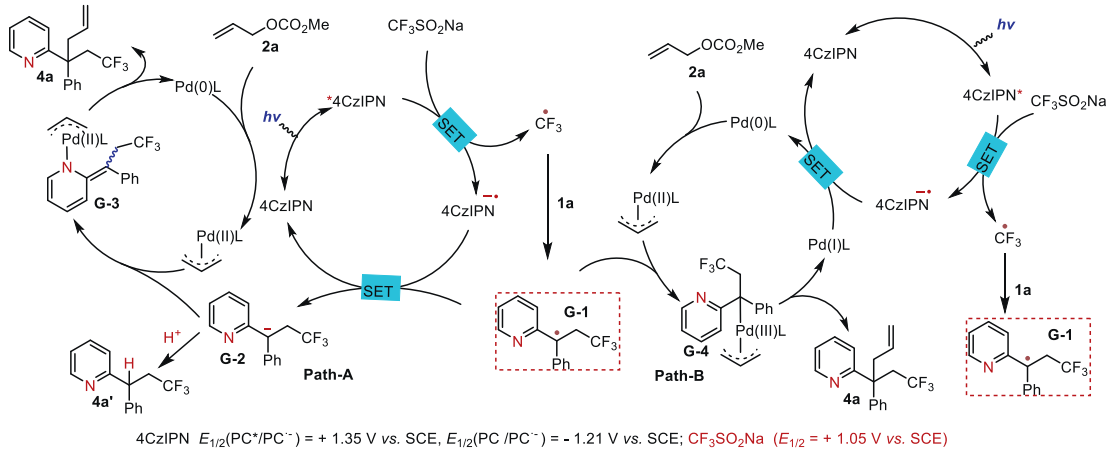

Fig. 6. Proposed mechanism.

radical. The CF_3 radical is then captured by substrate **1a** through a classic Giese reaction, resulting in the formation of the key intermediate **G-1**. Subsequently, two different reaction pathways are involved based on different reaction mechanisms. In the first pathway, **G-1** is reduced to the corresponding benzylic anion **G-2** by the reduced state of the photosensitizer. The benzylic anion **G-2** is then trapped by the **L8** ligated palladium-mediated allylic cation, leading to the formation of the key complex **G-3**. It should be noted that the configuration of the exo cyclic enamine plays a crucial role in the subsequent transformation, especially for the diastereoslective trasnformation. Ultimately, product **4a** is formed *via* conventional allylic alkylation, and the palladium(0) catalyst is regenerated for new catalytic cycle. In the second pathway (Path B), which holds equal significance, a cycle involving Pd(0)-Pd(II)-Pd(III)-Pd(I)-Pd(0) takes place [70]. The benzylic radical **G-1** can add to the palladium center due to ligand effect, forming the key palladium(III) intermediate **G-4**. Unlike "Path A", in this pathway reductive elimination through "inner sphere" is favored, resulting in the formation of the product **4a**. The generated palladium(I) is then reduced to palladium(0) by the reduced photosensitizer.

To further demonstrate the applicability of the current cascade reaction, we intend to apply our approach as a crucial step in the efficient synthesis of bioactive molecule. Oliceridine, a prominent drug developed for pain management and approved by the USFDA in 2020, is notable for its fumarate, which represents a novel class of intravenous opioid agonists that selectively activate G-protein signaling over β-arrestin recruitment [71]. This differs from conventional opioids such as morphine and oxycodone, which typically bind to and activate the μ-opioid receptor, stimulating downstream transduction mediated by β-arrestin [72]. A robust synthesis of oliceridine was first reported by Trevena, detailing a process that involves seven purification steps and 3% total yield. Ad-

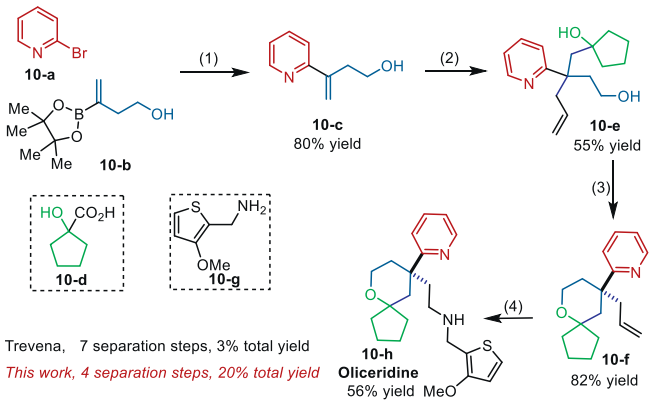

Fig. 7. Synthesis of Oliceridine. (1) 2 mol% $Pd(OAc)_2$/4 mol% S-Phos, 300 mol% K_3PO_4 H_2O, dioxane, 80 °C, 80% yield. (2) 2.5 mol% $PdCl_2$/3 mol% **L7**, 2 mol% 4CzIPN; 150 mol% Cs_2CO_3, blue LEDs, DMA, 55% yield. (3) 200 mol% TsOH, DCM, 40 °C, 82% yield. (4) (I) 2 mol% K_2OsO_4, 120 mol% NMO, 200 mol% $NaIO_4$, THF/H_2O; (II) $NaBH_4$, DCM; 56% yield for two steps.

ditionally, specific reagents such as moisture-sensitive aryl copper reagent and explosive $LiAlH_4$ are essential for efficient functional group transformations [73–75].

The core structure of oliceridine consists of a [4,5]spiro ether and one 2-pyridyl quaternary carbon center. We planed to construct the core structure using our effective method for creating 2-pyridyl quaternary carbon centers, and then finalize the molecules through straightforward functional group transformation. As shown in Fig. 7, we began our journey using commercial **10-a** and **10-b** as starting materials. Key substrate **10-c** wasobtained with good 80% yield on gram scale through classic palladium-catalyzed Suzuki cross couplings. With the key substrate in hand, we attempted the crucial three-components reaction using commercial α-hydroxyl carboxylic acid **10-d** as the radical precursor. Gratifyingly, the desired product **10-e** could be obtained with an acceptable 55% yield with **L7** as the supporting ligands, a weak coorinadation between the hydroxyl group and the palladium center may have a posotive effect for the accerlation of the termianl alyllic alkylation.

Then efficient intramolecular etherification was prompted by *p*-toluenesulfonic acid (TsOH), affording the spiro compound **10-f** in good 82% yield. The terminal double bond was transformed into an aldehyde through Os-catalyzed dioxylation and then the dioxyl was cleavaged by $NaIO_4$ directly, affording the corresponding aliphatic aldehyde which was pure enough for the further reductive amination directly. The subsequent reductive amination gave the terminal product **10-h** with 56% yield over two steps. Thus, we have efficiently synthesized oliceridine *via* four separation steps and a 20% total yield, demonstrating the efficency and promise of our synthetic process for practical applications.

In summary, we have developed a versatile catalytic system for the synthesis of azaaryl alkanes through a photo redox/palladium dual-catalyzed three-component transformation. This cascade process benefits from the ligand effect and the cooperation with suitable photosensitizer, allowing for a broad substrate scope and the production of desired products. The substrates used in this process include 16 representative heteroarenes, including mono-nitrogen-containing and poly-nitrogen-containing heteroarenes; furthermore, the substitution position on the pyridine ring is not limited to the C2-position, substrates with substitutions at the C3 and C4-positions are also effective reaction partners. Furthermore, the alkyl radical precursor is not limited to well-studied fluorine-containing compounds. Instead, commercial aliphatic carboxylic acids can also be used efficiently, providing a series of tertiary and quaternary azaaryl stereocenters in good to excellent yields.

The current transformation involves two distinct reaction paths. The first pathway involves the benzylic radical serving as the nucleophile, whereas the second pathway involves the formation of a benzylic anion through photoinduced radical-anion crossover. It is noteworthy that the modularity of radical precursors allows for easy diversification of products and excellent compatibility with functional groups under mild visible light conditions. This work presents a new method for obtaining heteroaryl-containing compounds with a broad substrate scope. It demonstrates the efficiency of combining photo-redox catalysis with palladium catalysis to figure out practical problems in synthetic chemistry.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Yunqiang Li: Methodology, Formal analysis, Data curation. **Yongxian Huang:** Methodology, Formal analysis. **Sinuo Li:** Methodology. **He Huang:** Methodology. **Zhiwei Jiao:** Writing – review & editing, Writing – original draft, Methodology, Funding acquisition, Conceptualization.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2024.110051.

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