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### **RESEARCH ARTICLE**

# Photocatalytic Direct *para*-selective C-H Amination of Benzyl Alcohols: Selectivity Independent of Side Substituents

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Abstract: Aminoarenes are important molecules for broad applications in nearly all modern industries that involve chemicals. Direct and site-selective C-H bond amination of arenes provides the most efficient and convenient method to prepare aminoarenes. A main challenge is to selectively install the amino group (or other functional groups) to the distal para-carbon of arenes (especially multi-substituted arenes) during the C-H bond functionalization events. Herein, we address this problem by designing a new strategy via a sequential radical dearomatization/radical amination/rearomatization process for para-selective amination of benzyl alcohols. The para-selectivity of our reaction is completely independent of the electronic and steric properties of the other substituents of the arene substrates. Aminoarenes with many substituents (up to full substitution) and diverse substitution patterns, including those difficult to synthesize previously, could be readily prepared using our protocols. Further exploration of the current strategy shall lead to other challenging C-H functionalization of arenes.

#### Introduction

Arenes are among the most prominent structural units in pharmaceuticals, agricultural chemicals, and materials. Direct C-H functionalization of arenes offers the most efficient routes in constructing complex molecules from simple feedstocks without pre-activation of arene substrates.<sup>[1]</sup> Controlling the site selectivity has long been a challenge in this area. Due to the relative remoteness and the spatial positioning between the para-position and the directing handle, achieving selective distal para-C-H bond functionalization is difficult.<sup>[2]</sup> Main methods in this area include classic electrophilic aromatic substitution (SEAr) reactions,[3-4] radical aromatic substitutions,[5-17] and chelation-assisted C-H functionalizations<sup>[1-4]</sup> (Figure 1a, left). Site-selectivity (such as ortho vs para-selectivity) in some of these strategies, such as the SEAr reactions and radical aromatic substitutions, is often determined by the inherent electronic properties of the arene substrates.<sup>[5-22]</sup> For instance, two aromatic radical reaction

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approaches have been developed for the C-H amination of arenes (Figure 1a, right) to construct aniline derivatives. One relies on the reaction of an arene radical cation with nitrogen nucleophiles.[5-9] Another one is the radical aromatic substitution process,<sup>[10-17]</sup> in which electron-rich arenes react with electrophilic nitrogencentered radical species such as amidyl radicals,[16-18] sulfamidyl radicals<sup>[19]</sup>, and aminium radical cations. <sup>[11-13,20]</sup> Except in the studies by Nicewicz, <sup>[5]</sup> Ritter, <sup>[10]</sup> and Zhao, <sup>[22]</sup> most of these works give a mixture of ortho- and para- functionalized products. Chelation-assisted C-H functionalization may override the electronic bias to achieve para-selective reactions. However, in this approach, the arene substrates need to bear suitable sites for coordination with the metal catalysts/reagents, posing significant constraints on the choices of substrates. Therefore, new concepts and robust strategies are of important need for direct selective functionalization of distal para-C-H bonds of arenes.

The persistent radical effect (PRE) that was discovered in the 1930s<sup>[23]</sup> has found numerous applications in organic synthesis via a radical-radical cross-coupling process. <sup>[24]</sup> We are interested in harnessing persistent radical species in the construction of value-added molecules. [25-28] Upon our understanding of the persistent radical effect, we designed a para-selective arene C-H functionalization strategy (Figure 1b, left). Key design in our method involves multiple key intermediates and three consecutive processes (namely radical de-aromatization, radical amination, and re-aromatization) to selectively place the functional group at the para-carbon of arenes (Figure 1b, left). Specifically, a phenyl ring tethered heteroatom-centered radical intermediate underwent ipso-addition to generate a spirocyclic 1,3cyclohexadiene radical species, which resonates with spiro 1,4cyclohexadienyl radical. Subsequent radical cross-coupling of the resultant 1,4-cyclohexadienyl radical with a persistent radical (or other radical functionalization step) enables the new bond formation. Final isomerization-induced rearomatization eventually affords the para-functionalized arenes. By using benzyl alcoholderived oxime carbonates (1) as the precursor of both phenyl ring tethered heteroatom centered radical and the persistent radical partner,<sup>[29-41]</sup> the strategy was successfully applied to an arene C-H para-selective amination reaction (Figure 1c). The current design does not rely on the electronic property of the arene substrates to set up the reactivity and regio-selectivity. Instead, both electron-rich and electron-deficient arenes are effective substrates with high para-selectivity. Compared to the previous arene C-H amination strategies whose site selectivity may be affected by the electronic effect of the side substituents, our design provides para-selectivity independent from the side substituents (Figure 1b, right). Arenes with diverse electronic properties and multiple substituents, including those that lead to fully substituted arenes are all competent substrates for our strategy, with the corresponding mono-, di-, tri-, tetra-, and pentasubstituted amination products obtained successfully (Figure 1c, right). It's worth noting that when revising our manuscript, a para-

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# **RESEARCH ARTICLE**



b. Our design: arene distal para-selective C-H amination, selectivity independent of side substituents



c. This work: photocatalytic para-selective C-H amination of (multi-substituted) arenes



3

selective C-H acylation reaction via a similar strategy was reported by Li and co-workers.  $\ensuremath{^{[42]}}$ 

### **Results and Discussion**

Reaction optimization. The key challenge to realizing the proposed para-selective aryl C-H amination process (Figure 1b &1c) was to find a suitable way to generate the benzene ringtethered heteroatom-centered radical and a persistent nitrogencentered radical under mild conditions. Considering the superior reactivity of oxime carbonates acting as bifunctional reagents to generate alkoxycarbonyloxyl and iminyl radicals via an energy transfer (EnT) process, <sup>[29, 34, 35, 38, 41]</sup> benzyl alcohol-derived oxime carbonate 1a was selected as the model substrate. Because of the higher triplet state energy of iridium-based photocatalysts compared to oxime carbonate ( $E_T \approx 45$  Kcal/mol), <sup>[43]</sup> PC-1 ( $E_T =$ 60.8 Kcal/mol)<sup>[44]</sup> was first selected as the photocatalyst. To our delight, irradiating the mixture of 1a, and PC-1 (1 mol %) in MeCN (2 mL) with a Blue LED ( $\lambda_{max}$  = 450-456 nm) for 12 hours at 35 °C resulted in the formation of para-selective amination product 2a in 44% yield together with 28% yield of 3a as a side product (Table 1, entry 1). It was envisaged that the side product 3a was formed from the dimerization of iminyl radical fragments, confirming the existence of the persistent iminyl radical intermediate in the reaction system. The structure of 2a was confirmed by X-ray diffraction analysis (CCDC 2314816). Screening of other iridiumbased photocatalysts proved PC-2 as the best one, with the desired 2a isolated in 52% vield albeit still with some 3a formed (entries 2-4). Thioxanthone, which exhibited high catalytic efficiency in various EnT-based elegant transformations,[45] however, only gave the product in 45% yield in our reaction system (entry 5). The better performance of PC-1 ( $E_T = 60.1$ Kcal/mol) to PC-3 ( $E_T = 62.0$  Kcal/mol) than PC-4 ( $E_T = 49.2$ Kcal/mol) may be attributed to their higher triplet energies.<sup>[29, 46]</sup> Screening different solvents failed to further improve the yields (entries 6). High polarity solvents such as DMSO and DMF were not competent for this transformation (entry 7). The light source was proved to have a clear influence on the yield since switching the light source into Blue LED ( $\lambda_{max}$  = 427 nm) resulted in an obviously dropped yield (entry 8). Shortening the reaction time to 6 hours could give comparable results (entry 9). However, further reducing the reaction time led to slightly reduced yields (entry 10). It was found that the reaction temperature has a significant influence on the reaction outcome. Specifically, when the reaction was conducted at 20 °C under otherwise identical conditions, the target product 2a was isolated in 73% yield, albeit still with a small amount of side product 3a formed (entry 11). Lower reaction temperature failed to further improve the reaction yield (entry 12). At last, control experiments demonstrated the crucial role of photocatalyst and light irradiation, with the transformation being completely suppressed without the presence of photocatalyst or light irradiation (entries 13 & 14).

### **RESEARCH ARTICLE**

Table 1. Optimization of the reaction conditions.<sup>a</sup>



**Substrate scope.** With the optimal reaction conditions established, we started to investigate the scope of this *para*-selective amination reaction, as outlined in Table 2. We first investigated the generality of arenes bearing various substituents and substitution patterns. The results suggested that the reaction displayed broad applicability for a wide variety of multi-substituted arenes including those that led to fully substituted arenes. For all the tested substrates, the site selectivity was independent of the side substituents, with the nitrogen-containing group specifically introduced into the *para* position to the hydroxymethyl group. This is an obvious advantage compared to the reported arene *para*-selective amination reactions, as their site selectivity is generally influenced by the pre-existing substituents.

Specifically, oxime carbonates bear substituent at ortho-position proceeded the reaction smoothly to afford the target paraaminated benzyl alcohols in moderate to good yields with specific regioselectivity (2b-2e), regardless of the electronic and steric of the substituents. It's worth noting that the bromine atom substitution resulted in a slightly dropped yield (2c). As the reaction mixture becomes complex after the reaction, the lower yields (same as 20) may be attributed to the instability of the C-Br bond in the radical system. Meta-substituted oxime carbonates were competent substrates with the disubstituted benzyl alcohols (2f-2h) afforded in good yields after simply irradiating their mixture in the presence of a catalytic amount of photocatalyst. The steric effect has little influence on the reaction as oxime carbonates with various substituents at both 2-, and 6-position were successfully converted into the desired aminated benzyl alcohols in moderate to good yields (2i-2m). It's worth noting that when 2-fluoro-6methylbenzyl alcohol-derived oxime carbonate was selected as substrate, in addition to the target 2k, a structurally novel spirocyclic compound (2k') was formed and isolated in 24% yield. Other disubstituted oxime carbonates with different substituent patterns including 2,5- (2n-2q) and 3,5- (2r-2t) proceeded the transformation smoothly, with para-aminated benzyl alcohols bearing two additional different substituents generated in moderate to high yields. It's worth noting that the low yield (35%) of 2r may be attributed to the increased steric effect-induced low conversion rate. To completely unearth the potential of the current site-selective amination reaction, tri- and tetra-substituted oxime carbonates were also investigated. For instance, (2,3,5trichlorophenyl) methanol-derived oxime carbonates proceeded with the reaction smoothly to deliver the tetra-substituted target product in 39% yield (2u). Oxime carbonate that bears two chlorine atoms and a trifluoromethyl group was successfully converted into the corresponding tetra-substituted imines (2v) up to 71% yield. At last, a 1,2,5,6-tetra-substituted oxime carbonate was also explored. As expected, the fully substituted aniline 2w was successfully prepared in 57% yield.

In addition to primary benzyl alcohols, secondary benzyl alcohols derived oxime carbonates were also investigated. Various alkyl groups including chain (**2y-2ad**) and cyclic (**2ae**) ones were explored, delivering the corresponding *para*-aminated products in good yields. The allyl group was also tolerated under the current conditions, albeit with a dropped yield (**2ad**), which may be attributed to unproductive side reactions induced by the C-C double bond. Based on our hypothesis, oxime carbonates derived from cycloalkane fused benzyl alcohols may be challenging substrates, due to the requirement of formation of a strained tricyclic intermediate. However, it is surprising to find that such types of oxime carbonates were competent for this transformation, producing aminated benzyl alcohols (**2af-2ah**) with high structural complexity, albeit sometimes with lower yields. Two diphenylmethanol-derived oxime carbonates were tested, and the

# **RESEARCH ARTICLE**



<sup>a</sup> Reaction conditions: 1a (0.1 mmol), PC-2 (1 mol %), MeCN (2.0 mL), blue LED (λ<sub>max</sub> = 440-445 nm), N<sub>2</sub> atmosphere, 20 °C, 6 h

target mono-aminated products were isolated in 67% (2ai) and 55% (2aj) yields respectively. It's worth noting that for substrate bearing two different aromatic rings, the iminyl group was exclusively introduced to the electron-rich phenyl ring (2aj). The feasibility of tertiary alcohol-derived carbonate was also explored, with the aminated tertiary alcohol (2ak) isolated in 51% yield. The norbornene unit was tolerated, with the 2al afforded in 48% yield. Heterocyclic arenes were tolerated either as substituents or reactive skeletons. Specifically, oxime carbonates bearing 2pyridyl (2am) or 2-thienyl (2an) as substituents were transformed into the aminated product successfully in moderate yields. Thiophen-2-ylmethanol-derived oxime carbonate was competent substrate to undergo the current photocatalytic amination reaction, with the iminyl group installed specifically at 5-position (2ao). Concurrently, a spirocyclic compound 2ao' was isolated in 13% yield as a side product. At last, a 4-position blocked oxime carbonate was tested. As a result, the C-N bond formation remains occurred at the *para*-position, with a dearomatized spiro cyclic compound **2ap** isolated in 23% yield, together with some unidentified side products.

Since the iminyl moiety can be readily reduced to the corresponding amine unit under mild conditions, we subsequently explored the generality of the iminyl moiety of the current photocatalytic *para*-specific amination reactions (Table 3). The electronic effect of the substituents on the phenyl ring has little influence on the reaction outcome, as both electron-donating (**4a**-**4b**) and electron-withdrawing (**4c**-**4d**) groups at the *para* position were all tolerated with the target afforded in good yields. The iminyl moieties bearing two different aromatic substituents proceeded with the reaction successfully, albeit in some cases lower yield was observed (**4e**-**4h**). It's worth noting that heteroaromatic ring-containing imines such as **4g** and **4h** could

# **RESEARCH ARTICLE**



<sup>a</sup> Reaction conditions: **1a** (0.1 mmol), **PC-2** (1 mol %), MeCN (2.0 mL), blue LED ( $\lambda_{max}$  = 440-445 nm), N<sub>2</sub> atmosphere, 20 °C, 6 h. blsolated as *E*, *Z* mixture. <sup>c</sup>Reduced by NaBH<sub>4</sub> directly after the amination reaction.

also be prepared under our standard conditions, providing opportunities for the construction of anilines with high complexity. The iminyl moieties that bear an aliphatic substituent were also investigated. The target imines were reduced directly after the photocatalytic amination reactions due to the instability of the corresponding imines. As a result, the anilines **4i** and **4k** were produced in quite low yields after the two-step-one pot operation (23% & 27%). This may be attributed to the instability of the corresponding alkyl-substituted iminyl radicals. Although the low yields, the current method provides a straightforward route to prepare such types of alkyl-substituted aniline derivatives.

Applications: To showcase the potential utility of this photocatalytic amination strategy, the late-stage transformation of natural products and drug molecules-derived oxime carbonates were investigated (Scheme 1a). Specifically, oxime carbonates derived from citronellal, and cyclamen aldehyde were successfully aminated at para-position, albeit with moderate yields (5a-5b). An insect pheromone motif-containing oxime carbonate was also competent substrate, with the aminated product 5c obtained in 53% yield. Free C-C double bond was tolerated under the standard reaction conditions, with the myrac aldehyde moiety containing product (5e) obtained in 52% yield. The cholesterol-derived substrate proceeded the site-selective amination smoothly to deliver the complex molecules 5f in 41% yield. Aniline moieties widely exist in numerous pharmaceuticals and agrochemicals, thus the synthesis of anilines with multiple different substituents and specific substitution patterns is of great importance for medical chemical screening. However, these multi-substituted anilines with specific substitution patterns are generally unaccessible or difficult to prepare with the known methods. To demonstrate the power of the current photocatalytic site-selective amination reaction, we chose Benzocaine, a local anesthetic, as a representative drug molecule for rapid synthesizing structurally diverse drug analogs (Scheme 1b). As expected, libraries of mono-, di, tri, tetra-, and even pentasubstituted anilines with different substitution patterns were prepared via the hydrolysis of our products in high yields (6a-6f). The resultant anilines (6a-6f) are readily converted into the corresponding substituted Benzocaine molecules in one step according to the reported method.<sup>[47]</sup> As such, we anticipate that our method will expedite the application of multi-substituted anilines in drug development. At last, a continuous flow process was used to scale up the current photocatalytic site-selective amination reactions (Scheme 1c). The model reaction was selected as the object of the study. After simply screening the reaction conditions including flow rate, reaction temperature, reaction concentration, and the source of light irradiation, an optimized reaction condition was finally identified. Then the reaction was scaled up to 10 mmol under this optimized reaction condition. As a result, the target **2a** was isolated in 54% yield (1.54 g) after 21 hours.

**Mechanistic studies:** According to our hypothesis and reported literatures,<sup>[29-41]</sup> possible reaction pathways were proposed, as listed in Figure 2a. The reaction started with the intermolecular energy transfer between photoexcited **PC-2** and substrate **1a** to produce excited triplet state **1a**\* and regenerate the ground state **PC-2**. Subsequent N-O bond homolysis of **1a**\* resulted in the formation of the key persistent iminyl radical (I) and the transient benzyoxycarbonyloxyl radical (II).

The oxygen-centered radical intermediate (II) may undergo ipsoaddition to the phenyl ring to form a five-membered spirocyclic 1,3-cyclohexadiene radical species III (path a), [48-49] which resonates with the 1,4-cyclohexadiene radical intermediate. Selective C(sp<sup>3</sup>)-N cross-coupling of iminyl radical I and 1,4cyclohexadienyl radical III delivers an imine group containing 1,3dioxaspiro[4.5]deca-6,9-dien-2-one IV. Such a cyclohexadiene such as 2k' and 2ao' had indeed been isolated as side products in some of our reactions. The cyclohexadiene (IV) may be converted into the para-functionalized target arene 2a via rearomatization or PC-2-involved photoredox process under our standard conditions. On the other hand, the transient benzyoxycarbonyloxyl radical (II) may undergo decarboxylation<sup>[48]</sup> before ipso-addition to the phenyl ring to generate a threemembered spirocyclic radical species VI (path b).<sup>[50]</sup> Solid evidence for the decarboxylation step was reported by Walton by EPR studies.<sup>[48,49]</sup> Subsequent selective radical cross-coupling

# **RESEARCH ARTICLE**

![](_page_6_Figure_4.jpeg)

#### Scheme 1. Application of the photocatalytic para-specific amination reaction

between the persistent iminyl radical I and 1,4-cyclohexadienyl radical VI led to the forming of the iminyl group containing 1-oxaspiro[2.5]octa-4,7-diene VII. The resultant highly strained spiro compound VII isomerized to eventually afford the target 2a spontaneously. Alternatively, a radical chain mechanism can not be excluded. Specifically, the spirocyclic radical species VI may undergo a radical addition process with the oxime ester 1a to generate the adduct VIII. Subsequent  $\beta$ -scission results in the formation of intermediate VIII and regeneration of the benzyoxycarbonyloxyl radical II.

A series of experimental studies were conducted to shed light on the reaction mechanism and distinguish the above-mentioned reaction pathways. When 1.0 equivalent of 2,2,6,6tetramethylpiperidinooxy (TEMPO) was added into the model reaction as a radical scavenger under otherwise identical conditions, the reaction was completely inhibited, with no **2a** observed (Figure 2b), confirming the radical reaction pathway. The triplet-triplet energy transfer process between iridium-based photocatalysts and oxime carbonates has been well proved by related literature.<sup>[34]</sup> Besides, the reactions that proceeded via the triplet state of substrates should also be feasible through light

direct excitation, clearly distinguishing it from the single electron transfer pathway. Therefore, a direct excitation reaction was conducted (Figure 2c). Specifically, a mixture of 1a in acetonitrile was irradiated by LED ( $\lambda_{max}$  = 365-370 nm). As expected, **2a** was obtained in 42% yield after 6 hours of irradiation, confirming the energy transfer pathway. Attempts to initiate the reaction by other radical initiators were also conducted (Figure 2d). However, all the tried radical initiators including AIBN, BPO, and DTBP failed to give the target 2a, again demonstrating the pivotal role of the To investigate the possibility of 1,3photocatalyst. dioxaspiro[4.5]deca-6,9-dien-2-one IV acting as an intermediate (path a), side product 2k' was submitted to the standard conditions (Figure 2e). However, no 2k was observed after the reaction, with most of the 2k' recovered, providing solid evidence to exclude path a. To provide evidence to support path b, a radical clock experiment was designed to prove the involvement of the benzoxyl radical species (V). Oxime carbonate-bearing threemembered ring (7) was designed and submitted to the standard condition (figure 2f). As a result, no desired para-aminated product (8) was detected. Instead, a ring-opening  $\beta$ -iminyl ketone (9) was obtained in 26% yield together with some 3a as a side

# **RESEARCH ARTICLE**

![](_page_7_Figure_4.jpeg)

other reactions supports the presence of key iminyl radical (I).

of the benzoxyl radical in our reaction system. Concurrently, the

# **RESEARCH ARTICLE**

Finally, a crossover experiment using oxime carbonates **1f** and **1a'** was conducted to further understand the reaction mechanism (Figure 2g). The detection of the crossover products (**2a** & **10**) revealed that the radical cross-coupling step is an intermolecular process. Taken together, the experimental data support the decarboxylative pathway (path b).

The radical cross-coupling of the persistent iminyl radical (I) and transient carbon radical has been widely explored by Cho, Glorius, Molander, and others,<sup>[29-41]</sup> The long lifetime of the iminyl radical (I) is supported by the isolation of their dimer **3**. However, a radical chain process can not be excluded. Most recently, Molander<sup>[36]</sup>

![](_page_8_Figure_6.jpeg)

a) Gibbs Free energy profile for the catalytic cycle

and Glorius<sup>[41]</sup> nicely proved the involvement of radical chain propagation process experimentally and computationally. To preliminary identify if the radical chain propagation is involved in the reaction, a light shutdown experiment was conducted (Figure 2h). It was found that **2a** can be formed in 17% yield after irradiation of **1a** under standard conditions for 90 seconds. Meanwhile, the reaction continued in the dark after initiating by light irradiation for 90 seconds. Specifically, **2a** was isolated in 22% (90 seconds irradiation then 1h under the dark) and 27% yields (90 seconds irradiation then 2h under the dark) respectively. Although the reaction rate dropped significantly under the dark

Figure 3. a. Gibbs free energy profile for path b, computed at SMD (acetonitrile)-M06-2X/def2-TZVP//M06-2X/def2-SVP level of theory. TDI, turnover frequency-determining intermediate; TDTS, turnover frequency-determining transition state. b. Spin density plots for selected species **X**, **TS3**, and **TS3**'. Spin density plots were visualized at an isosurface value of 0.005 au. Mulliken spin population values are given in orange, key bond distances are given in black. See Figure S1 for DFT optimized structures and Figure S2 for the spin density plots of all structures. condition, the maintained increase of the yield suggests the involvement of the radical propagation process.

# **RESEARCH ARTICLE**

path b. As depicted in Figure 3a, the carbonate radical species II formed upon the homolysis of the N-O bond in the photo-excited starting material 1a\* undergoes a homolytic C-O bond cleavage<sup>[29-41]</sup> via **TS1**, with an activation barrier of 11.4 kcal/mol, to give benzoxyl radical V, with concomitant release of a  $CO_2$ molecule. This process is highly exergonic (V is -17.7 kcal/mol downhill of II), assisted by the entropic gain as a CO<sub>2</sub> molecule is released. In addition, this step is irreversible, as the steps going forward (23.7 kcal/mol via TS3) have lower barriers than the barrier to go back from V to II (29.1 kcal/mol from V to TS1). Benzoxyl radical V subsequently undergoes ring closure to form the oxaspirocyclic intermediate VI (an intermediate also proposed in the benzoxyl radical decomposition)<sup>[50]</sup>. This step has a barrier of 13.7 kcal/mol (V to TS2) and forms VI at -5.8 kcal/mol, which is 11.9 kcal/mol thermodynamically uphill of V (Figure 3a). The formation of intermediate VI is reversible, as it can revert to V more easily (via TS2, barrier of 1.8 kcal/mol from VI to TS2) than going forward via TS3 to give intermediate VII (barrier of 11.8 kcal/mol from VI to TS3). The formation of VII and its subsequent isomerization to give the final product 2a is highly exergonic and irreversible.

To understand the regioselectivity outcome of the current amination transformations, DFT calculations on the radical crosscoupling process were conducted. we found that the TS for the C-N bond formation at the para-position (TS3) has a lower barrier than at the ortho-position (TS30) by 2.9 kcal/mol (Figure 3a). This suggests that the C-N coupling at the para-position is favored kinetically over the ortho-position by a factor of 145:1, using simple transition state theory (see SI section II.4 for details). Spin density plots for the oxaspirocyclic intermediate VI suggest that the spin density is higher at the para position (0.556, Figure 3b) than at the ortho position (0.402, Figure 3b). Thus, although the radical is delocalized over the whole structure, there is greater radical character on the para position than the ortho position. In addition, TS3 likely benefits from  $\pi$ - $\pi$  interaction between the aromatic rings due to its more favorable geometric arrangement than TS30, as suggested by the non-covalent interaction plots shown in Figure S3 (see supplementary information). Overall, DFT calculations suggest that the benzoxyl radical (V) formed upon decarboxylation of the carbonate radical is the turnover frequency (TOF)-determining intermediate (TDI), or equivalently, the resting state of the catalytic cycle, and TS3 is the TOFdetermining transition state (TDTS). This gives the energetic span for the formation of product 2a from intermediate II at 23.7 kcal/mol, which indicates that these steps are thermally feasible at 20 °C under the reaction conditions, consistent with the observed experimental reactivity. A reversible formation of an oxaspirocyclic intermediate is proposed. This species undergoes a regioselective and rate-determining radical cross-coupling to forge the C-N bond formation. The C-N cross-coupling occurs more favorably at the para-position over the ortho-position due to both greater radical character at the para position than the ortho position, and the favorable  $\pi$ - $\pi$  interaction present in the transition state for the radical cross-coupling at the para-position, but absent in the TS for coupling at the ortho-position.

To discern the influence of the electronic effect of the substituents on the regioselective outcome, additional calculations using substrates that lead to products **2i**, **2l**, **2r**, and **2t** (See SI section II.5) were performed. DFT computations show that for the electron-donating methyl substituent at the *ortho*-position forming product **2i**, the TS forming the *para* product (**TS2i\_para**) is favored over the TS forming the meta product (TS2i\_meta) by 23.7 kcal/mol, whereas for the electron-donating methyl substituent at the meta-position forming product 2r, the TS forming the para product (TS2r\_para) is favored over that forming the ortho product (TS2r\_ortho) by 3.6 kcal/mol. Similarly, for the electron-withdrawing F substituent at the ortho-position forming product 2I, the TS forming the para product (TS2I\_para) is favored over the TS forming the meta product (TS2I\_meta) by 24.2 kcal/mol, whereas for the electron-withdrawing F substituent at the meta-position forming product 2t, the TS forming the para product (TS2t\_para) is favored over that forming the ortho product (TS2t\_ortho) by 1.1 kcal/mol. We note that the formation of C-N bond via radical-radical coupling at the meta-position is highly unfavorable, since the spin at the meta-position and nitrogen atom are parallel, whereas the spins are opposite between the radical at the nitrogen atom and the para-orthoposition, thereby favoring bond formation. Overall, regardless of the electronic demands and the position of the substituents, paraselective amination products are observed.

#### Conclusion

In summary, we have designed a novel strategy for para-selective arene C-H functionalizations based on the persistent radical effect-induced radical cross-coupling event. The strategy relies on sequential radical dearomatization/radical crossа coupling/rearomatization process. By using benzyl alcoholderived oxime carbonates as the substrates, such a strategy was successfully applied in a photocatalytic para-selective arene C-H amination. The site selectivity does not rely on the electronic and steric properties of the arene substrates. Instead, both electronrich and electron-deficient arenes with multiple substituents are effective substrates with high para-selectivity. Diverse anilines including mono-, di-, tri-, and tetra-substituted ones which are not readily accessible by other methods can be easily prepared through our strategy. The successful application of this method for natural products of drug molecules derived substrates demonstrates its potential utility. Experimental and computational mechanistic studies support our proposed mechanism. Computational studies also revealed that the site selectivity was determined by the dominant radical characteristic on the paraposition of the key radical intermediate and the  $\pi$ - $\pi$  interaction presented in the transition state for the radical cross-coupling step. We believe that the current para-selective functionalization model will expedite the development of other challenging remote arene C-H functionalization.

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# **RESEARCH ARTICLE**

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### Entry for the Table of Contents

![](_page_11_Figure_6.jpeg)

A photocatalytic *para*-selective C-H amination of benzyl alcohols whose reactivity and site selectivity are independent of existing side substituents is disclosed.