

***Para*-Selective C–H Alkylation of Aroyl Chlorides through Organic Photoredox-Catalyzed Radical *tele*-Substitution**

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Abstract

Site-selective C(sp²)–H alkylation of arenes has served ubiquitous fragments found in pharmaceutical drugs and agrochemicals. While *ortho*- and *meta*-selective alkylation reactions have been achieved well, *para*-selective examples are scarce. Currently available methods have been designed on unique behaviors and characteristics of metals to achieve high *para* selectivity. Herein, we demonstrate *para*-selective C(sp²)–H alkylation of aroyl chlorides with alkyltrifluoroborates and trialkylphosphine through an organic photoredox-catalyzed radical *tele*-substitution. The reaction proceeds through *para*-selective addition of alkyl radicals to *in situ* generated aroyl trialkylphosphonium intermediates followed by hydrogen shift. Notably, the *para*-alkylation occurred associated with conversion of carbonyl trialkylphosphonium group to formyl group, producing *para*-alkylated benzaldehyde derivatives. This unprecedented metal-free site-selective C(sp²)–C(sp³) bond formation allows for streamlined synthesis of Siponimod and SR-31747.

Introduction

Alkylated arenes are ubiquitous and common structures found in chemical feedstocks, pharmaceutical drugs and agrochemicals. Site selective alkylation of C(sp²)–H bonds on arenes has gained much attention as an atom- and step-economical approach to alkylated arenes. Over the past three decades, significant progress in site selective C(sp²)–H alkylation has been made by transition-metal catalysts.^{1,2} Specifically, a chelation-assisted

C–H activation strategy could regulate the reaction site to *ortho*- and in some cases *meta*-position.^{3,4} In contrast, the most distal, *para*-selective C(sp²)–H alkylation has been underdeveloped. Current strategies to *para*-selective C(sp²)–H alkylation were classified to (Figure 1A): 1) *para*-selective C(sp²)–H cleavage induced by steric repulsion between bulky NHC-ligated-nickel complex and bulky Lewis acid additive-coordinated substrates;⁵ 2) *para*-selective thianthrenation followed by reductive cross-coupling with alkyl electrophiles;⁶ 3) electrophilic aromatic substitution (S_EAr) with metal carbenoid or high valent alkyl metals;^{7,8} 4) *para*-selective radical addition to metal-coordinated arenes^{9–11} and others^{4,12,13}. These reactions take advantage of transition metal-specific behaviors such as oxidative addition and reductive elimination in the cleavage of C(sp²)–H and formation of C(sp²)–C(sp²). Tunability of electronic and steric natures of metal centers by ligands leads to ease optimization. Since these characteristics of metals are unreplacable by non-metal atoms, *para*-selective C(sp²)–H alkylation without metals require an intrinsically different strategy.

Over the past few years, several groups have demonstrated metal-free *para*-selective C(sp²)–H functionalization of arenes. Tang and co-workers utilized a chiral bulky Brønsted acid catalyst for enantioselective *para*-alkylation of azobenzenes with active methylene compounds.¹⁴ Nicewicz's group demonstrated an organic photoredox catalysis enabling the *para*-alkylation of electron-rich arenes via nucleophilic addition of a diazoacetate to an arene radical cation.¹⁵ As an alternative radical-based strategy, *para*-trifluoromethylation of arylcarbamates¹⁶ and aromatic amides¹⁷, and *para*-alkylation of electron-deficient arenes¹⁸ have been disclosed. Despite such advances, the lack of diversity in the reaction limits the range of arene substrates and introducible alkyl sources. To pursue an unprecedented approach to metal-free *para*-selective C(sp²)–H functionalization, we focused on *tele*-substitution, which is defined as “a substitution reaction in which the entering group takes up a position more than one atom away from the atom to which the leaving group was attached” (Figure 1B).^{19,20} In contrast to *ipso*- and *cine*-substitution, *tele*-substitution reaction has not been explored so far. However, since the *tele*-substitution involves the addition of a nucleophile to arene ring followed by hydrogen atom transfer, this process can avoid use of transition metals. Additionally, *tele*-substitution reaction does not necessarily introduce a leaving group onto the arene ring unlike *ipso*- and *cine*-substitution reactions. For these characteristics, *tele*-substitution is a potent metal-free approach to remote C(sp²)–H functionalization. To this end, we need to ensure addition of alkyl nucleophiles to arenes

with high reactivity and *para*-selectivity and hydrogen atom transfer from *para*-carbon on arene to carbon or heteroatom on a leaving group.

To realize such functionalization, we came up with radical *tele*-substitution of aroyl trialkylphosphonium species derived from aroyl chlorides and trialkylphosphines using alkyltrifluoroborate salts and an organic photoredox catalyst (PC) (Figure 1C).²¹ Given that several cases of radical addition of carbon-centered radicals to electron-deficient arenes are known,^{22,23} an oxidatively-generated carbon-centered radical from alkyl trifluoroborates by a photoredox catalyst would undergo *para*-selective radical addition to a aroyl trialkylphosphonium intermediate.²⁴ The trialkylphosphonium could activate the arene ring through inductive effect and orbital interaction of a 3d orbital of the phosphorus and the π^* orbital of the carbonyl group.^{25,26} Also, steric bulkiness on trialkylphosphonium inhibits the radical addition at other sites, such as electronically activated carbonyl and *ortho* positions. Then, the resultant cyclohexadienyl radical is photochemically reduced to the enolate, in which phosphonium intermediate can induce the key proton transfer from *para*-position to carbonyl group through stabilization of the benzyl anion. Based on this working hypothesis, we commenced our investigation on *tele*-substitution of benzoyl trialkylphosphonium species.

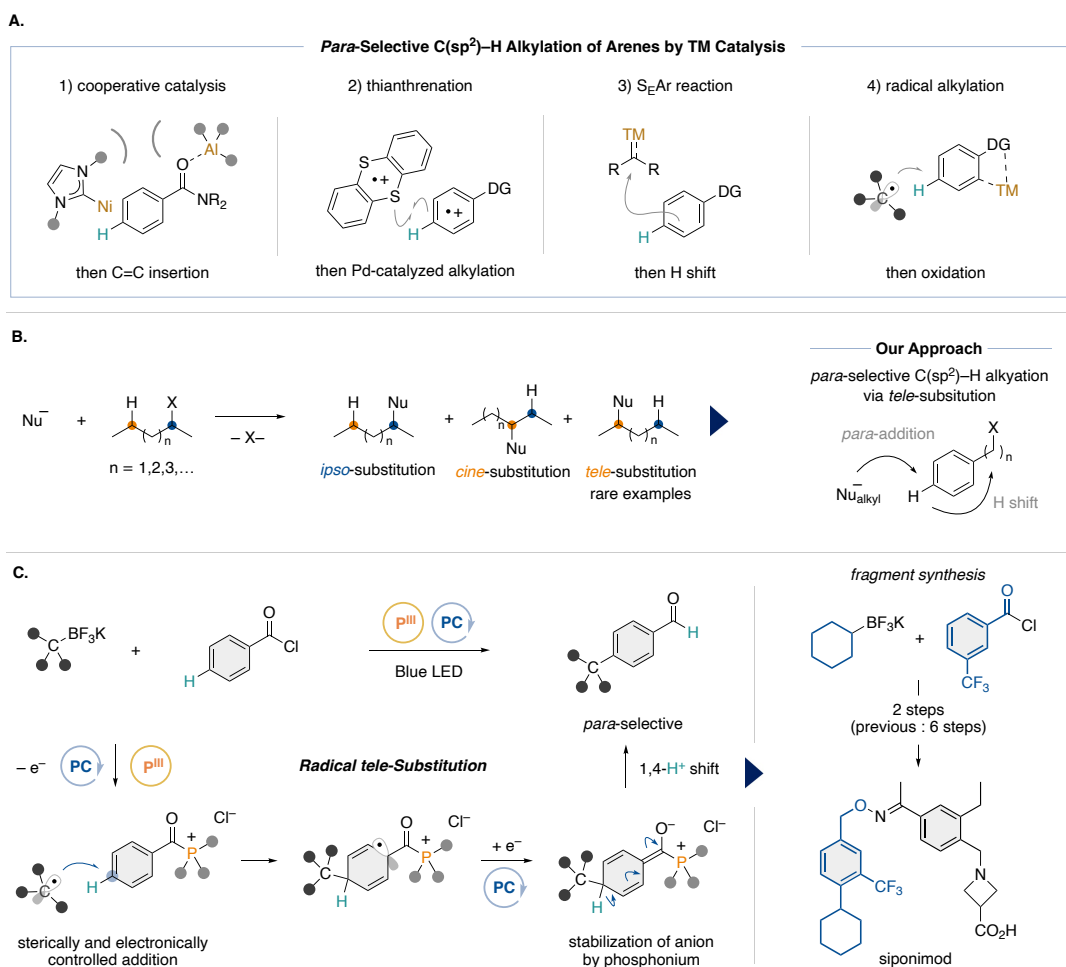


Figure 1 | Approaches to *para*-selective C(sp²)-H alkylation of arenes. A) Current strategies based on transition-metal catalysis. B) Overview of *tele*-substitution reaction. C) an organic photoredox catalyst/trialkylphosphine-mediated radical *tele*-substitution of aroyl chlorides with alkyltrifluoroborates (this work)

Results and discussion

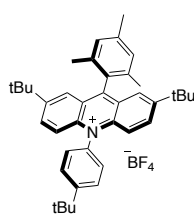
Development of the reaction. We found that the combination of tricyclohexylphosphine, acridinium type organic photoredox catalyst (**Acr 1**)²⁷ and BF₃·OEt₂ catalyst under a blue LED (440 nm) irradiation efficiently promoted the reaction between a secondary benzyltrifluoroborate **2a** and benzoyl chloride **1a** to produce *para*-alkylated benzaldehyde **3aa** in high yield (Table 1, entry 1). Although formation of benzaldehyde **1a'** was obtained, other regioisomers, such as *ipso*-, *ortho*- or *meta*-alkylated products and related carboxylic acid products were not observed at all.

The effects of organophosphorus reagents and photoredox catalysts were evaluated (Table 1). When tricyclopentylphosphine and tributylphosphine were used instead of tricyclohexylphosphine, the product yields were diminished (entries 2 and 3). Sterically encumbered tri-*tert*-butyl phosphine did not promote the reaction at all (entry 4). It might be due to the inefficient formation of the corresponding benzoyl trialkylphosphonium intermediate. Even when we substitute a cyclohexyl group of tricyclohexylphosphine, the reactivity was retained (entry 5). However, the reaction with cyclohexyldiphenylphosphine was found to be ineffective (entry 6). The low nucleophilicity did not form the benzoyl trialkylphosphonium. Although we evaluated a variety of acridinium-type photoredox catalysts **Acr2–4**^{27,28}, there were no significant differences (entries 7–9). When other organic photoredox catalysts and Ir-based photoredox catalysts were evaluated, the reaction proceeded well to afford the desired products in moderate to high yields (entries 10–13). Equimolar amounts of tricyclohexylphosphine were required for the high reactivity (entries 14–16). Even without a photoredox catalyst, the desired reaction slightly proceeded (entry 17, Figure S21). The control experiment revealed that light irradiation is essential (entry 18). Initially, we thought that additional $\text{BF}_3 \cdot \text{OEt}_2$ would facilitate the radical addition to arenes, but positive effect on the reaction between **1a** and **2a** was not observed (entry 19). This protocol was found to be suited for large scale synthesis (entry 20).

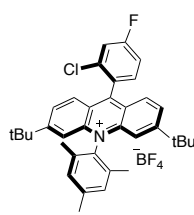
Table 1 | Screening on reaction between 1a and 2a

2a	1a	3aa	1a'
Entry	Changes from standard conditions	Yield (%) of 3aa ^b	Yield (%) of 1a' ^b
1	none	92	8
2	PCyp ₃ instead of PCy ₃	39	5
3	P ⁿ Bu ₃ instead of PCy ₃	5	trace
4	P ^t Bu ₃ instead of PCy ₃	0	trace
5	PCy ₂ Ph instead of PCy ₃	92	6

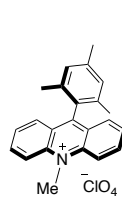
6	PCyPh ₂ instead of PCy ₃	16	2
7	Acr 2 instead of Acr 1	87	6
8	Acr 3 instead of Acr 1	88	7
9	Acr 4 instead of Acr 1	74	17
10	4Cz-IPN instead of Acr 1	56	14
11	4[Cz(CF ₃) ₂]IPN instead of Acr 1	66	9
12	Ir[dF(CF ₃)ppy] ₂ [5,5'-d(CF ₃)bpy]]PF ₆ instead of Acr 1	89	10
13	Ir[dF(CF ₃)ppy] ₂ (dtbbpy)PF ₆ instead of Acr 1	64	3
14	without PCy ₃	0	0
15	PCy ₃ (30 mol %)	8	4
16	PCy ₃ (50 mol %)	35	6
17	without photoredox catalyst, 24 h	30	4
18	without Blue LED	0	0
19	without BF ₃ ·OEt ₂	96 (96)	4
20	0.5 mmol scale	89 (86)	6



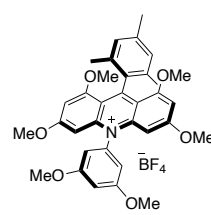
Acr 1
 $E_{\text{red}}^* = +2.18 \text{ V vs SCE}$
 $E_{\text{red}} = -0.48 \text{ V vs SCE}$



Acr 2
 $E_{\text{red}}^* = +2.32 \text{ V vs SCE}$
 $E_{\text{red}} = -0.37 \text{ V vs SCE}$



Acr 3
 $E_{\text{red}}^* = +2.06 \text{ V vs SCE}$
 $E_{\text{red}} = -0.57 \text{ V vs SCE}$



Acr 4
 $E_{\text{red}}^* = +1.65 \text{ V vs SCE}$
 $E_{\text{red}} = -0.82 \text{ V vs SCE}$

^a Each reaction was carried out with **1a** (0.1 mmol), **2a** (0.15 mmol), organophosphine (0.1 mmol), BF₃·OEt₂ (0.01 mmol) and photoredox catalyst (0.005 mmol) in DCM (2.0 mL) under blue LED irradiation (440 nm) for 3.5 h. ^b ¹H NMR yields. The number in parenthesis is isolated yield. PCy₃, Tricyclohexylphosphine. PCyp₃, Tricyclopentylphosphine.

Substrate scope. The scope of benzoyl chlorides and alkyl trifluoroborates on our organic photoredox-catalyzed *para*-alkylation was illustrated in Figure 2. Although the desired

reactions proceeded even without $\text{BF}_3 \cdot \text{OEt}_2$, the improvement of product yields was observed in some cases. Halogen substituents at *meta* position did not affect the reaction efficiency (**3ba–3da**). Electron-withdrawing groups such as trifluoromethoxy- and cyano substituents led to lowering the product yields (**3ea** and **3fa**). When the amount of tricyclohexylphosphine was decreased from 1.0 equiv. to 0.9 equiv., the product yields were drastically improved. In addition to electron-deficient substituents, methoxy and phenyl groups were tolerated (**3ga** and **3ha**). Notably, aroyl chlorides **1f** and **1h** were prepared by chlorination of the corresponding aromatic carboxylic acids **1f'** and **1h'** and directly utilized to *para*-alkylation reaction in one-pot manner (**3fa** and **3ha**). 3,5-Disubstituted benzoyl chlorides could be alkylated at 4-position (**3ia** and **3ja**). Methyl and halogen substituents at *ortho* position were tolerated albeit in low yields (**3ka–3na**). When 2,3- or 2,5-disubstituted aroyl chlorides were used as substrates, the desired products (**3oa** and **3pa**) were also obtained

The reactions between benzoyl chloride **1a** and various alkyl trifluoroborates **2** were evaluated. Electron-neutral and electron-rich secondary benzyl units could be installed to benzaldehyde products (**3ab–3ae**). However, the reactions with electron-deficient benzylic trifluoroborates were unsuccessful (Figure S28). It might be due to the high oxidation potentials and low nucleophilicity of the secondary benzylic radicals. β -Carbonyl trifluoroborates prepared by conjugate addition of bis(pinacolatodiboron) to acrylate derivatives, also participated as *para*-alkylation reagents (**3af** and **3ag**). Tertiary and secondary aliphatic groups were successfully introduced, providing complex *para*-alkylated benzaldehydes in moderate to high yields (**3ah–3al**). Although the reaction with primary benzylic trifluoroborate occurred at *para* position, the reaction with primary butyl trifluoroborate afforded *para*-alkylated product and ketone (**3am–3an**). The reaction with α -phenoxymethyl trifluoroborate furnished the tucarecol analogue (**3ao**).

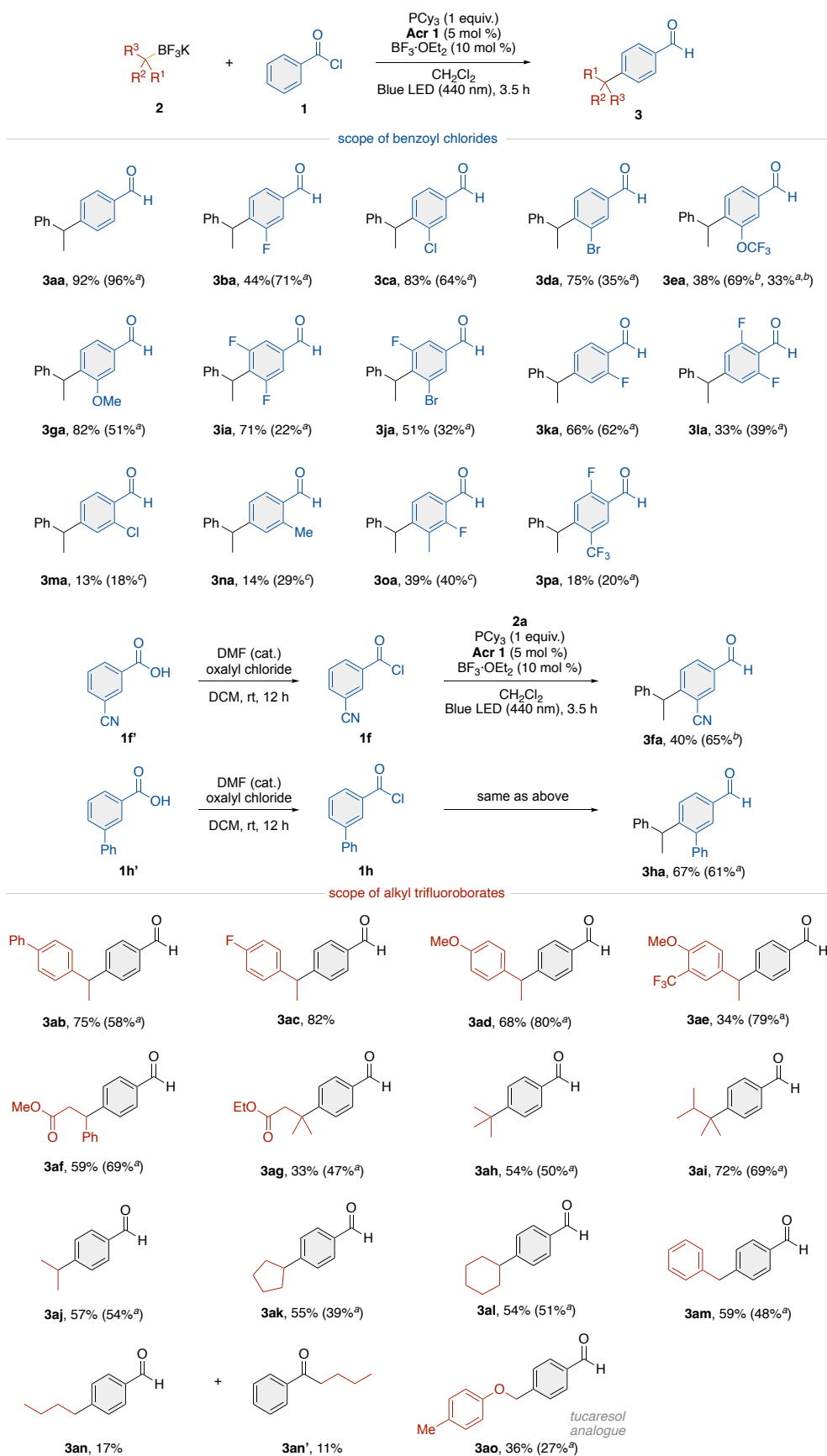


Figure 2 | Substrate scope. Each reaction was carried out with **1** (0.1 mmol), **2** (0.15 mmol), PCy_3 (0.1 mmol), $\text{BF}_3 \cdot \text{OEt}_2$ (0.01 mmol) and **Acr 1** (0.005 mmol) in

DCM (2.0 mL) under blue LED irradiation (440 nm) for 3.5 h. ^a Without BF₃·OEt₂ ^b PCy₃ (0.09 mmol) was used. ^c BF₃·OEt₂ (0.02 mmol) was used and the reaction was carried out at –20 °C.

Applications. Taking advantage of carbon-centered radical intermediate, radical addition to an alkene and hydrogen atom transfer (HAT) was envisioned to merge with our radical *tele*-substitution reaction. First, three-component coupling reaction of *tertiary* butyl trifluoroborate **2h**, styrene **4a**, and benzoyl chloride **1a** was examined (Figure 3A). Therein, a *tertiary* butyl radical undergoes radical addition to styrene prior to a benzoyl trialkylphosphonium and then the prolonged radical is introduced to *para*-position of the benzaldehyde product. The desired reaction proceeded well to afford **5aha** in moderate yield with formation of **3ah**. Subsequently, radical *tele*-substitution reaction of **1a** and ethyl benzene **6a** using *p*-anisyl trifluoroborate as a HAT reagent **7a** was performed, wherein an aryl radical from **7a** abstracts a benzylic C–H bond of **6a** and ensuing radical addition of the resultant benzyl radical to a benzoyl trialkylphosphonium occurs. Without specific modification of reaction conditions using benzyl trifluoroborate salts, **3aa** was obtained. To highlight further synthetic advantage of radical *tele*-substitution, we applied the reaction to synthesis of drug fragment. Notably, *para*-alkylated benzoyl moiety and its analogues are found in nilotinib, imatinib, pemetrexed and siponimod, that were ranked in top 200 small molecules drugs by retail sales in 2022.²⁹ Among them, synthesis of benzyl alcohol fragment of siponimod takes 6 steps in the manufacturing route (Figure 3C, top).³⁰ Thus, we aimed to improve the synthesis by use of our method. We found that the reaction between *meta*-trifluoromethyl benzoyl chloride **1o** and **2l** proceeded with slight modification of reaction conditions to afford **3ol** in moderate yield. Since **3ol** can be reduced to the desired benzyl alcohol fragment with sodium borohydride. Additionally, the *para*-alkylated benzoyl moiety was also found in synthetic intermediate in synthesis of SR-31747, a potent sigma receptor antagonist (Figure 3C, bottom).³¹ In the previous route, **3pl** was synthesized from *p*-cyclohexyl benzoic acid in 6 steps. On the other hand, our reaction provides a step-economical route from 3-chlorobenzoyl chloride **1p** and **2l**. Therefore, our approach successfully contributes to shorten the synthesis of drug molecules.

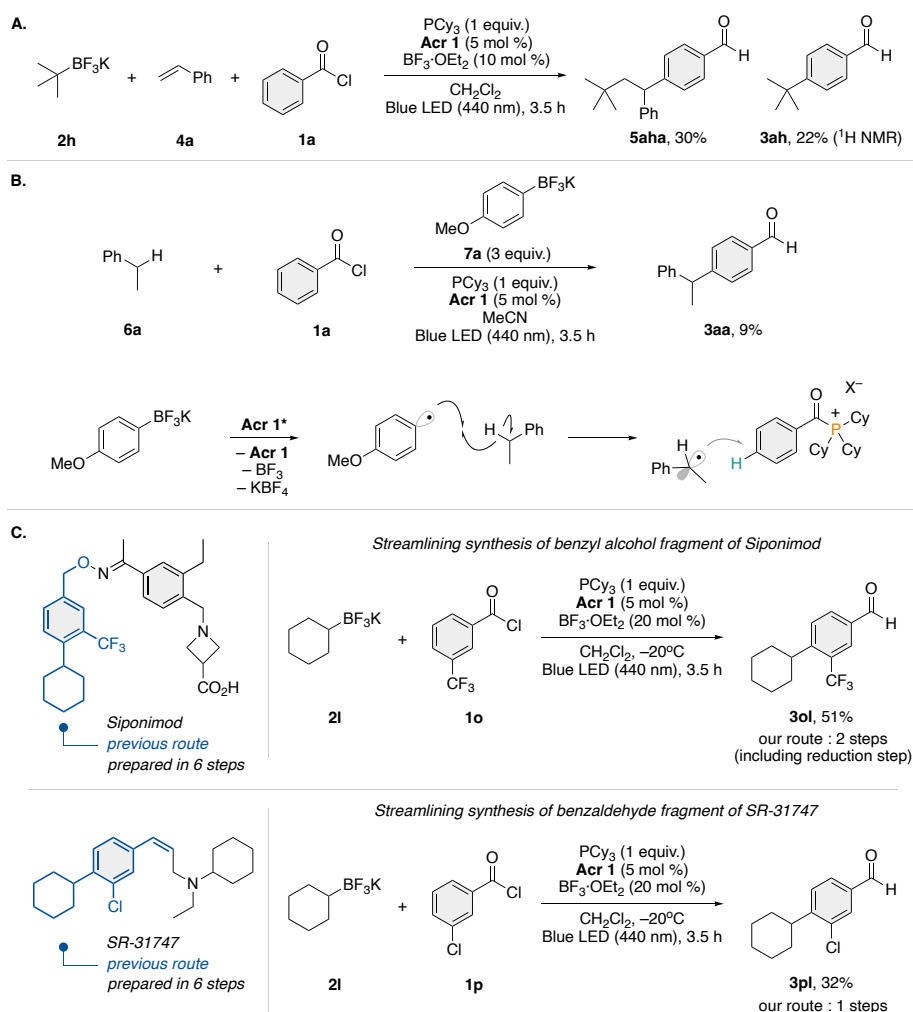


Figure 3 | Other Synthetic Applications and Fragment Synthesis of Drug Molecules. A) Three-component coupling. B) C(sp³)-H arylation. C) Fragment synthesis of Siponimod and SR-31747.

Mechanistic Studies. To gain deep insights to reaction mechanism, several experiments and DFT calculations were conducted. First, we confirmed the formation of benzoyl tricyclohexylphosphonium chloride by stoichiometric reaction of **1a** and tricyclohexylphosphine on NMR spectrum (see Supplementary Figure 5). When **2a** was added to the reaction mixture, further peak shifts were observed. This result implied the formation of an ion pair consisting of benzoyl phosphonium and benzyltrifluoroborate with release of KCl. Subsequently, we investigated whether an alkyl group from alkyl trifluoroborates was installed to benzoyl tricyclohexylphosphonium species as carbon-centered radical or carbanion and the reaction between **1a** and *tert*-butyl lithium **7a** was examined (Figure 4A). This result and successful three-component coupling shown in Figure 3A indicated our photoredox catalytic reaction would involve radical addition of a

carbon-centered radical not carbanion. Third, we investigated the origin of formyl hydrogen of *para*-alkylated products (Figure 4B). When the reaction with *p*-deuterated benzoyl chloride **1a-D** was carried out under optimal reaction conditions, the desired product **3aa** with 62%D incorporation on formyl hydrogen. To see whether intermolecular deuterium scrambling occurs or not, a competing reaction using **1a-D** and **1k** was conducted and thereby both **3aa-D** and **3ka-D** were obtained (Figure 4C). These results revealed that the reaction pathway would contain the intermolecular hydrogen (proton) transfer process.

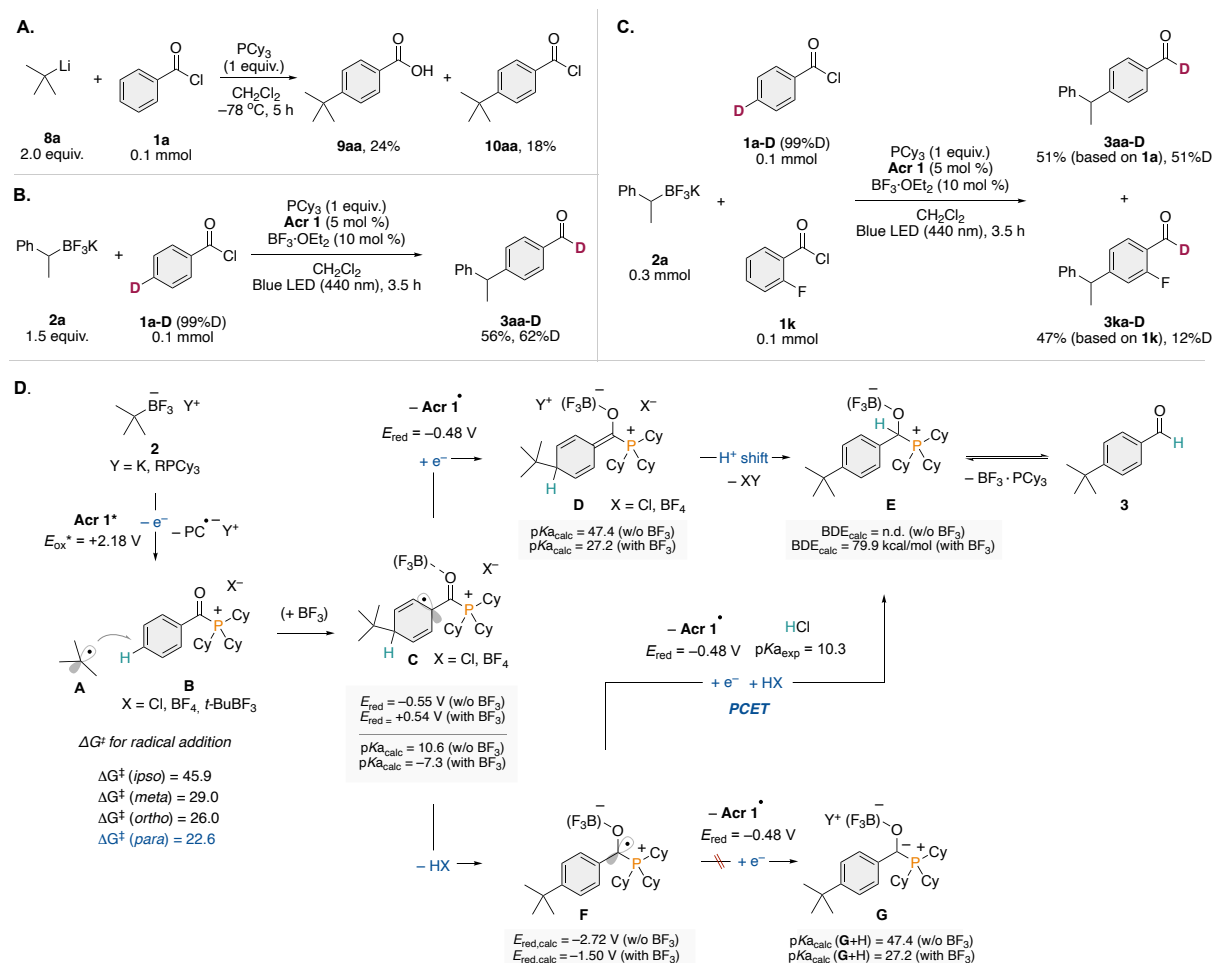


Figure 4 | Mechanistic studies and plausible reaction mechanism. A) The reaction between benzoyl tricyclohexylphosphonium and *tertiary* butyl lithium. B) The reaction with *p*-deuterated benzoyl chloride. C) The scrambling experiment. E) Plausible reaction mechanism. **PC** = **Acr 1**.

Based on mechanistic studies shown above and preliminary computational studies, plausible reaction pathway has been outlined in Figure 4D. The reaction commences with single electron oxidation of an alkyl trifluoroborate salt (**2**) ($E_{ox} = +1.26 \text{ V}$ vs SCE for

^tBuBF₃K)³² by the excited state of photoredox catalyst ($E_{\text{ox}}^*[\text{Acr } \mathbf{1}] = +2.18 \text{ V vs SCE}$)²⁵, providing the corresponding alkyl radical **A**, BF₃ and the radical anion of photoredox catalyst. Then, *para*-selective radical addition of the alkyl radical to benzoyltricyclohexylphosphonium intermediate **B** occurred to form a cyclohexadienyl radical intermediate **C**. DFT calculation predicts the lowest energy barrier for the *para* addition (Figure S31). There are two distinct reaction pathways from **C** to an enolate **D** or a ketyl radical **F** through single electron reduction by the radical anion of photoredox catalyst or deprotonation by chloride anion, respectively. In the former pathway which corresponds to our initial working hypothesis shown in Figure 1C, the single electron reduction of **C** by the radical anion of a photoredox catalyst seems to be thermodynamically feasible with or without BF₃. However, the calculation implied that the following deprotonation mediated by chloride anion sequence would not occur due to the low acidity of *para* C–H bond. **We could not rule out the pathway involving a protonation of **D** at α -phosphonium by a proton generated in the formation of **F** followed by deprotonation of a *para* C–H bond.** In the latter pathway, the *para* C–H bond is deprotonated first and then ketyl radical **F** is generated. The subsequent single electron reduction of **F** by the radical anion would be highly endothermic process. On the other hand, a concerted proton-coupled electron transfer (PCET)³³ would bypass the thermodynamic constraints to convert **F** to a phosphonium borate zwitterionic intermediate **E**. BDFE (bond dissociation free energy) (48.6 kcal/mol) achieved by combination of the radical anion of **Acr 1** ($E_{\text{red}} = -0.48 \text{ V vs SCE}$) and hydrogen chloride ($\text{p}K_{\text{a,exp}} = 10.3$ in MeCN) is sufficiently below the BDE (bond dissociation energy) of **E** (81.2 kcal/mol). These computational studies and experimental results shown in Figures 4B and 4C supported the latter reaction pathway involving **F** and **E**. Finally, elimination of tricyclohexylphosphine boron trifluoride complex leads to formation of *para*-alkylated aldehydes **3**. The NMR studies implied that the elimination is reversible (Figures S6–10), which would hinder the catalytic use of phosphine reagent. Overall, the computational studies indicated that BF₃ is essential to promote the reaction by lowering reduction potential and acidity of each reaction intermediate.

In summary, we present radical *tele*-substitution as a new strategy to *para*-selective C(sp²)–H alkylation of arene compounds. The unique steric and electronic features of trialkylphosphonium moiety in key aroyltrialkylphosphonium species realize *para*-selective radical addition and hydrogen shift from *para*- to *ipso*-position in an organic photoredox catalysis. The metal-free and site selective C(sp²)–C(sp³) bond formation would become an

environmentally benign and powerful approach to synthesis of pharmaceutical drugs and agrochemicals. Currently, other synthetic applications using a phosphonium-based directing group are ongoing.

Methods

The reaction with **3ca** in Figure 2 is representative. **Acr 1** (3.1 mg, 0.005 mmol, 5 mol%) was placed in an oven-dried screw-top 4 mL vial containing a magnetic stirring bar. The vial was then introduced in the nitrogen-filled glovebox and to this was added CH₂Cl₂ (2 mL), 3-chlorobenzoyl chloride **1c** (12.8 μL, 17.5 mg, 0.1 mmol, 1.0 equiv.) and PCy₃ (28.0 mg, 0.1 mmol, 1.0 equiv.). After stirring for 10 min, BF₃·OEt₂ (1.3 μL, 1.4 mg, 0.01 mmol, 10 mol%) in CH₂Cl₂ (100 μL) and potassium 1-phenethyltrifluoroborate **2a** (31.8 mg, 0.15 mmol, 1.5 equiv.) were added to the reaction mixture. The vial was then brought outside the glovebox. After 3.5 h stirring with a cooling fan under photoirradiation (PhotoRedOx Duo, Kessil PR160L 440 nm), the reaction mixture was evaporated under reduced pressure. The crude was purified by flash column chromatography on silica gel (100:0–94:6, hexane/AcOEt) to give **3ca** (20.3 mg, 0.083 mmol) in 83% yield.

Data availability

Details on the procedures, optimization and characterization including spectra of new compounds and compounds made using the reported method, are available in the Supplementary Information.

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AUTHOR CONTRIBUTIONS

R.O., H.S., K.N., and H.O. conceived the project. R.O., H.S., K.N., and H.O. performed the experiments and analyzed the data. K.N. and H.O. co-wrote the manuscript. All authors contributed to discussions.

DECLARATION OF INTERESTS

The authors declare no competing interests.

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at ##.

Resource availability

Lead contact

Requests for further information and resources should be directed to and will be fulfilled by the lead contact, Hirohisa Ohmiya (ohmiya@scl.kyoto-u.ac.jp).

Materials availability

Full experimental details, including optimization studies, experimental procedures, mechanistic studies, ^1H and ^{13}C NMR spectra, high-resolution mass spectrometry, and infrared, melting point, and UV-visible data, are available in the supplemental information for all new compounds. Raw data are available from the lead contact upon reasonable request.

Data and code availability

The analytical datasets generated during this study are available in the article or supplemental information.