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Irradiation-Induced Palladium-Catalyzed Direct C–H Alkylation of Heteroarenes with Tertiary and Secondary Alkyl Bromides

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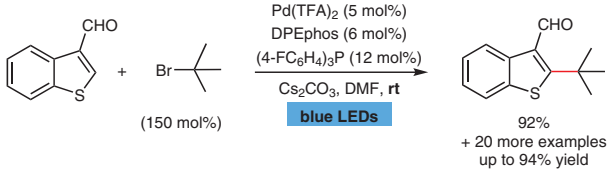

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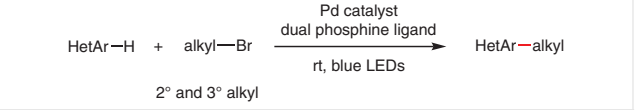
Abstract A palladium catalyst in combination with two types of phosphine ligands efficiently catalyzes direct C–H alkylation of heteroarenes with secondary and tertiary alkyl bromides under irradiation conditions. Irradiation of blue light-emitting diodes (blue LEDs) effectively excites phosphine-ligated palladium catalyst to facilitate oxidative addition with alkyl bromides, and also excites the alkylpalladium species to enable the generation of alkyl radicals to react with heteroarenes.

Key words irradiation, palladium catalysis, alkylation, heteroarenes, alkyl bromides

Alkylation of heteroarene is a useful process in pharmaceutical industry to make molecules 'escaping from the flatland',[1] and also in materials science to tune the solubility of conjugated π-materials for optoelectronic device processing.[2] Transition-metal-catalyzed direct C–H alkylation[3] is the method of choice considering the selectivity and mild conditions compared with Friedel–Crafts reactions.[4] However, alkylation using secondary and tertiary alkyl halides is challenging because of the inherent propensity of β-H elimination of alkyl organometallic species.[5] Applying secondary and tertiary alkyl bromides in palladium-catalyzed alkylation was less successful than primary alkyl bromides[6] due to the difficulty in oxidative addition[7] and the instability of the alkylpalladium intermediate due to its propensity to undergo β-H elimination.[8] Despite the existence of these problems, Zhou and co-workers reported that a radical-based mechanism could be applied to palladium-catalyzed alkylation of heteroarenes with alkyl halides under thermal conditions.[9] We recently discovered that a palladium salt in combination with two types of phosphine ligands[10,11] can be photo-excited by blue LEDs to react with tertiary and secondary alkyl bromides to deliver alkyl radical effectively.[11] We hypothesized that this irradiation-induced reactivity may also be applicable for palladium-catalyzed alkylation of heteroarene to circumvent undesired β-H elimination. We report herein the regioselective alkylation of several functionalized heteroarenes including benzothiophene, benzoxazole, benzothiazole, pyridine, indole, furan, and benzofuran with tertiary and secondary alkyl bromides by applying irradiation-induced palladium catalysis (Equation 1).[12] Though most palladium-catalyzed C–H functionalization utilizes its organometallic reactivity under thermal conditions,[13] the work presented herein demonstrates a new feasibility to operate palladium-catalyzed C–H alkylation under visible-light irradiation through a radical pathway.[14]

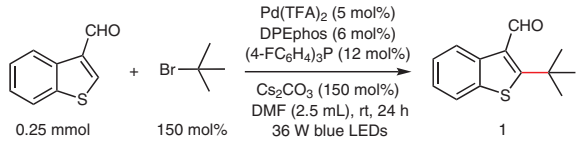


Equation 1

The optimized reaction conditions and key parameters affecting this reaction are listed in Table 1 (see Supporting Information for details of the parameter study). A transparent Schlenk tube charged with benzo[*b*]thiophene-3-carbaldehyde (0.25 mmol), *tert*-butyl bromide (0.375 mmol), palladium(II) trifluroacetate (5 mol%), bis[2-(diphenylphosphino)phenyl] ether (DPEphos, 6 mol%), tris(4-fluorophenyl)phosphane [$(4\text{-}FC_6H_4)_3P$, 12 mol%], Cs_2CO_3 as base, and DMF as solvent was irradiated with blue LEDs at room temperature for 24 hours. The *tert*-butylated product **1** was formed in 92% isolated yield with high conversion of starting material (Table 1, entry 1). For catalyst optimization, several other palladium catalysts were also examined and it turned out that $Pd(PPh_3)_4$ and $PdCl_2$ could also be used instead of $Pd(TFA)_2$ (entries 2 and 4) with slightly lower efficiency. $Pd(OAc)_2$ afforded the product in moderate yields

(entry 5) but $Pd_2(dba)_3$ gave only trace amount of the product (entry 3). The yield decreased when base or *tert*-butyl bromide was reduced to 1.2 equivalents (entries 6 and 7). The wavelength of the irradiation was crucial for this transformation. White LEDs was less effective (entry 8). Only a trace amount of product was obtained when green LEDs was used (entry 9). UV light disturbed the reaction and no desired product was formed (entry 10). Control experiments showed that the combination of $(4\text{-}FC_6H_4)_3P$ with DPEphos was essential for the high catalytic efficiency, although the desired product could be obtained in moderate yield when only $(4\text{-}FC_6H_4)_3P$ was used (entries 11 and 12). The reaction did not proceed in the absence of base or palladium catalyst (entries 13 and 14). No desired product was detected in the absence of irradiation (entry 15). Use of *tert*-butyl iodide gave the *tert*-butylated product in only 22% yield with poor conversion of heteroarene. Amide solvent such as DMF and DMA were most suitable solvents for this reaction (see Supporting Information for details on optimization of solvents).

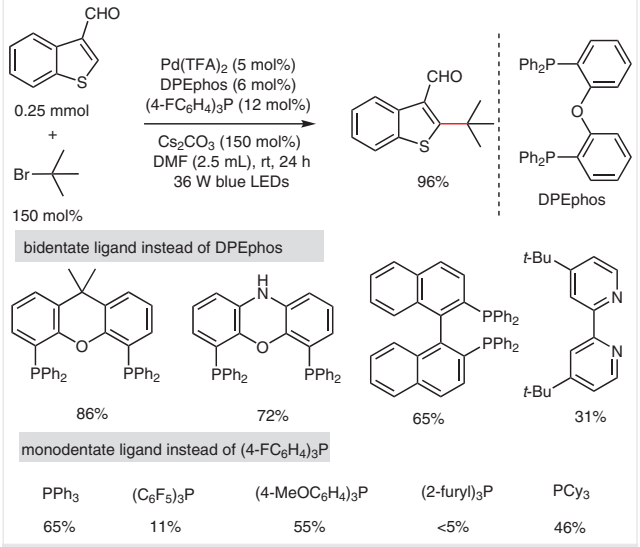
Table 1 Key Parameters Affecting C–H *tert*-Butylation of Benzo[*b*]thiophene-3-carbaldehyde



Entry	Variations from standard conditions	Yield (%)[a]	Conv. (%)[a]
1	none	96 (92)[b]	98
2	$Pd(PPh_3)_4$ instead of $Pd(TFA)_2$	86	98
3	$Pd_2(dba)_3$ instead of $Pd(TFA)_2$	trace	<10
4	$PdCl_2$ instead of $Pd(TFA)_2$	90	97
5	$Pd(OAc)_2$ instead of $Pd(TFA)_2$	68	75
6	Cs_2CO_3 (120 mol%)	65	80
7	*t*-BuBr (120 mol%)	75	85
8	36 W white LEDs instead of blue LEDs	80	92
9	36 W green LEDs instead of blue LEDs	trace	<10
10	15 W UV (254 nm) instead of blue LEDs	n.r.	65
11	without $(4\text{-}FC_6H_4)_3P$	trace	<10
12	without DPEphos	45	51
13	without Cs_2CO_3	trace	<5
14	without $Pd(TFA)_2$	n.r.	<5
15	without irradiation	n.r.	<5

[a] Yield and conversion were determined by ^1H NMR analysis using diphenylmethane as an internal standard; n.r.: no reaction.
[b] Isolated yield.

Phosphine ligands played essential role in this alkylation reaction. As shown in Scheme 1, using (9,9-dimethyl-9*H*-xanthene-4,5-diyl)bis(diphenylphosphine) (Xantphos), 4,6-bis(diphenylphosphino)-10*H*-phenoxazine (Nixantphos), and 2,2′-bis(diphenylphosphino)-1,1′-binaphthalene (BINAP) to replace DPEphos resulted in relatively lower yields. Bidentate nitrogen ligand, 4,4′-di-*tert*-butyl-2,2′-bipyridine (dtbpy), was ineffective in comparison with a control experiment (Table 1, entry 12 and Scheme 1). Interestingly, it was observed that the electronic effect on the monodentate ligand significantly affects the reaction outcome. As demonstrated in Scheme 1, using more electron-donating phosphine ligands than $(4\text{-}FC_6H_4)_3P$, such as triphenylphosphine (PPh_3), and tris(4-methoxyphenyl)phosphine $[(4\text{-}MeOC_6H_4)_3P]$ resulted in reduced yield, while more electron-deficient tris(perfluorophenyl)phosphine $[(C_6F_5)_3P]$ also dramatically reduced the alkylation efficiency. Alkylation did not occurred when tri(2-furanyl)phosphine was used instead of $(4\text{-}FC_6H_4)_3P$. Electron-rich tricyclohexylphosphine (PCy_3) with bulkiness was also less effective. The important role of the dual phosphine ligand system and the sensitivity of the reaction outcome towards the structural and electronic effect of the ligand suggest that an activated palladium(0) species coordinated with more than two phosphine atoms is responsible for activation of alkyl bromides through single-electron-transfer to generate a hybrid alkylpalladium radical intermediate,[11,12f] which reacts with heteroarene through radical addition followed by β-H elimination [or oxidation by Pd(I) followed by deprotonation] to deliver alkylated heteroarene.

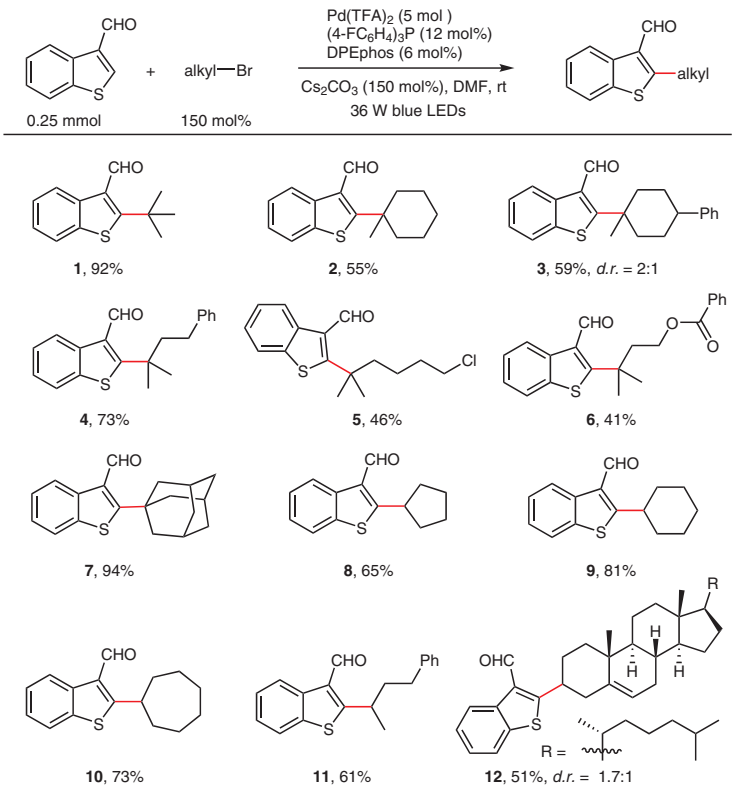


Scheme 1 Ligand effect in irradiation-induced palladium-catalyzed C–H *tert*-butylation of benzo[*b*]thiophene-3-carbaldehyde

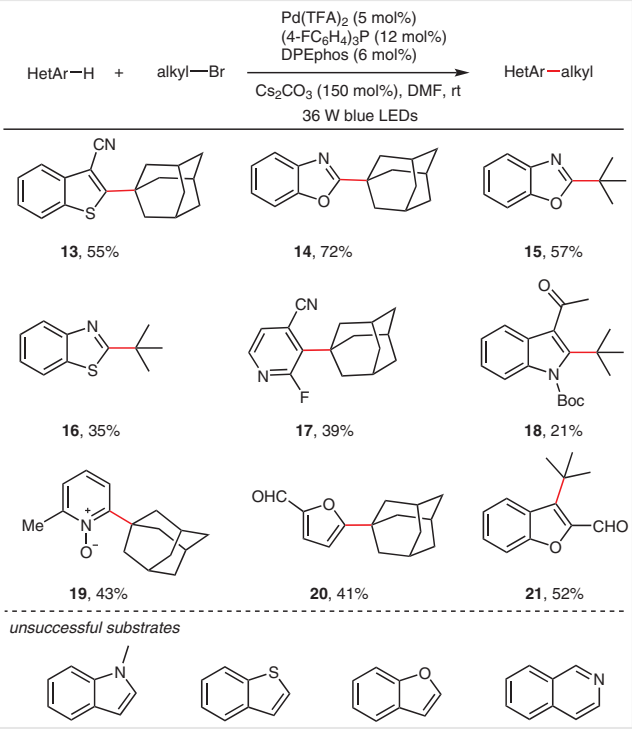
Having established the optimized reaction conditions, we next explored the reaction scope with respect to alkyl bromides (Scheme 2). A wide set of *tert*-alkyl bromides were used as amenable substrates under the optimized conditions. Both cyclic and acyclic bromides reacted well to give the desired products **1**–**6** in good to excellent yields.

The successful application of these tertiary alkyl bromides revealed undesired β-H elimination of alkylpalladium species is efficiently suppressed by irradiation to form hybrid alkylpalladium(I) radical intermediate.[15] 1-Adamantyl bromide was a good substrate to give the desired product in 94% yield. It is notable in the recent report by Yu et al. on irradiation-induced palladium-catalyzed alkylation using solely $Pd(PPh_3)_4$ as catalyst, only adamantanylation was demonstrated for intermolecular alkylation of $C(sp^2)$–H bond.[14] In addition to tertiary alkyl bromides, unactivated secondary alkyl bromides afforded the desired products **8**–**11**. The alkyl bromide derived from natural product cholesterol was also reactive to deliver the heteroarylated cholesterol **12** in moderate yield, demonstrating the method for construction of architecture of medicinal interest. It is worth mentioning that although stereoisomerically pure axial alkyl bromide was used, the heteroarylated cholesterol **12** was obtained as a diastereomeric mixture (*d.r.* = 1.7:1), supporting the formation of hybrid alkylpalladium radical intermediate.[11] Primary alkyl bromides were unreactive under the optimized reaction conditions.

Next, the substrate scope with respect to heteroarenes is examined (Scheme 3). Thus, the photo-induced palladium-catalyzed alkylation can be applied to various functionalized heteroarenes to prepare the alkylated products **13**–**18**, **20**, and **21** from benzothiophene, benzoxazoles, benzothiazole, pyridine, indole, furan, and benzofuran in moderate efficiency. The moderate yields of products in Scheme 3 were mainly due to incomplete conversion of heteroarenes, and by-products other than C–H alkylation product were not detected by GC-MS. Moreover, 2-methylpyridine *N*-oxide also coupled in moderate efficiency to give the alkylated product **19**.[16] The reaction was tolerant toward several kinds of functional groups affording products containing cyano (**13**), fluoro (**17**), ketone (**18**), and aldehyde (**20**, **21**) groups, which are useful for subsequent transformations. However, admittedly the scope of this reaction regarding to heteroarene is not ideal, as many unfunctionalized heteroarenes, such as *N*-methylindole, benzofuran, benzothiophene, and isoquinoline were not reactive. Typical substrates suitable for Minisci radical alkylation[17] failed in this reaction (such as isoquinoline). The limitation of scope regarding heteroarenes may be ascribed to the reactivity of hybrid alkylpalladium(I) radical intermediate, so that typical substrates good for free radical alkylation are not all suitable for this reaction. Nevertheless, this method provides a mild and efficient way to obtain tertiary alkylated heteroarenes, which was not easily accessible using transition-metal-catalyzed C–H functionalization.

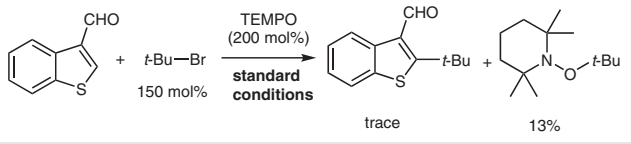


Scheme 2 Scope with respect to secondary and tertiary alkyl bromides. Yields of isolated products are shown. The reactions were conducted in front of a cooling fan in a room of constant temperature (25 ± 3 °C).



Scheme 3 Scope with respect to heteroarenes. Yields of isolated products are shown. The reactions were conducted in front of a cooling fan in a room of constant temperature (25 ± 3 °C).

Furthermore, mechanistic investigation to gain insight of the hybrid alkylpalladium(I) radical intermediate were investigated. First, a radical trapping experiment was conducted using radical scavenger. *N*-*t*-Bu-TEMPO was observed in 13% yield, which verified that alkyl radical is involved in this reaction (Scheme 4).[9] Subsequently, we tested the UV/Vis absorption of the reaction mixture of stoichiometric amount of palladium salt and ligands. As shown in Figure 1 (a), the absorption peak around 460 nm disappeared when the palladium salt was removed from the reaction mixture. The UV/Vis absorption spectrum indicated that absorption onset overlapping with blue LEDs irradiation (455–460 nm) belongs to the palladium intermediate.[10] We also conducted the electron paramagnetic resonance measurement (EPR) (Figure 1, b) of the reaction mixture (Table 1, entry 1, see Supporting Information for detailed information).



Scheme 4 Radical trapping experiment with TEMPO. Yield was determined by ^{1}H NMR spectroscopy using diphenylmethane as an internal standard.

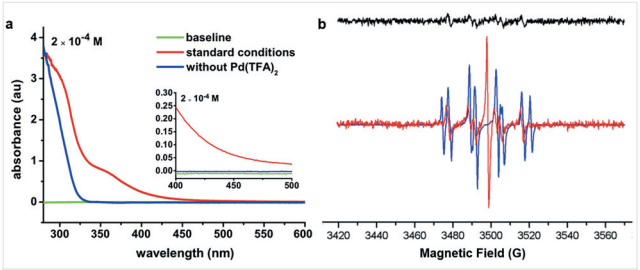


Figure 1 UV/Vis absorption (a) and EPR spectrum (b) (0.5 GHz, 298 K) of the reaction mixture using stoichiometric amount of palladium salt and ligands. 5,5-Dimethyl-1-pyrroline *N*-oxide (DMPO) was used as additive for EPR measurement.

The result of EPR measurement revealed that when the reaction mixture without heteroarene was measured in dark, EPR signals were hardly observable (black line). However, when the mixture was irradiated with blue LEDs, an obvious signal of alkyl radical trapped by DMPO (blue line) could be observed. We therefore conclude that blue LEDs can facilitate the formation of alkyl radicals from alkyl bromide. When benzo[*b*]thiophene-3-carbaldehyde was further added, a new EPR signal was detected (red line). We attribute the new EPR signal to the radical intermediate resulting from the attack of alkyl radical on the heteroarene.[14]

In summary, we have developed a mild and efficient method for direct C–H alkylation of heteroarenes with tertiary and secondary alkyl bromides using photo-excited reactivity of a palladium complex.[18] Upon irradiation with blue LEDs and applying two types of phosphine ligands, the excited palladium species undergoes oxidative addition with alkyl bromide to form hybrid alkylpalladium radical species to react with heteroarenes at room temperature. Expanding the scope of this reaction and further exploration of the diverse reactivity of hybrid alkylpalladium radical species under irradiation are our ongoing pursuits.

All reactions were carried out in oven-dried Schlenk tubes under an argon atmosphere (purity ≥99.99%), unless otherwise mentioned. Commercial reagents were purchased from TCI and Aldrich. Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. Flash column chromatographic purification of products was accomplished using forced-flow chromatography on silica gel (200–300 mesh).

^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 400 spectrometer at ambient temperature. Data for ^{1}H NMR are reported as follows: chemical shift (ppm, scale), multiplicity (standard abbreviations), coupling constant (Hz), and integration. Data for ^{13}C NMR are reported in terms of chemical shift (ppm, scale), multiplicity, and coupling constant (Hz). HRMS analysis was performed on Finnigan LCQ advantage Max Series MS System. ESI-mass data were acquired using a Thermo LTQ Orbitrap XL Instrument equipped with an ESI source and controlled by Xcalibur software.

Irradiation-Induced Palladium-Catalyzed Direct C–H Alkylation of Heteroarenes; 2-(*tert*-Butyl)benzo[*b*]thiophene-3-carbaldehyde (1); Typical Procedure

Benzo[*b*]thiophene-3-carbaldehyde (40 mg, 0.25 mmol, 1.0 equiv), $Pd(TFA)_2$ (4.2 mg, 5 mol%), $(4\text{-}FC_6H_4)_3P$ (9.5 mg, 12 mol%), DPEphos (8 mg, 6 mol%), and Cs_2CO_3 (122 mg, 0.375 mmol) were placed in a transparent Schlenk tube equipped with a stirring bar. The tube was evacuated and filled with argon for three times. Degassed DMF (2.5 mL) and *tert*-butyl bromide (51 mg, 0.375 mmol, 1.5 equiv) were added via a gastight syringe. The reaction mixture was stirred under the irradiation of 36 W blue LEDs (distance app. 2.0–3.0 cm from the bulb) at r.t. for 24 h. The mixture was quenched with brine and extracted with EtOAc (3 × 10 mL). The organic layers were combined and concentrated under reduced pressure. The product was purified by flash column chromatography on silica gel using PE or a mixture of PE and EtOAc (10:1 v/v) as eluent; yield: 50.1 mg (92%); pale yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.75 (s, 1 H), 8.68 (d, *J* = 8.1 Hz, 1 H), 7.76 (d, *J* = 8.0 Hz, 1 H), 7.47–7.43 (m, 1 H), 7.38–7.34 (m, 1 H), 1.66 (s, 9 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 185.9, 172.5, 138.7, 135.6, 129.4, 125.9, 125.0, 124.8, 121.3, 36.6, 33.3.

HRMS (ESI): *m*/*z* calcd for $C_{13}H_{15}OS^+$ [M + H]$^+$: 219.0838; found: 219.0839.

2-(1-Methylcyclohexyl)benzo[*b*]thiophene-3-carbaldehyde (2)

Yield: 35.5 mg (55%); viscous liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.76 (s, 1 H), 8.67 (d, *J* = 8.2 Hz, 1 H), 7.78 (d, *J* = 8.0 Hz, 1 H), 7.45 (t, *J* = 7.7 Hz, 1 H), 7.36 (t, *J* = 7.5 Hz, 1 H), 2.18–2.11 (m, 2 H), 2.00–1.96 (m, 2 H), 1.71–1.65 (m, 4 H), 1.62–1.60 (m, 4 H), 1.46–1.38 (m, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 186.2, 173.1, 138.7, 136.1, 129.5, 125.8, 125.0, 124.9, 121.3, 40.8, 40.4, 28.8, 25.7, 22.6.

HRMS (ESI): *m*/*z* calcd for $C_{16}H_{19}OS^+$ [M + H]$^+$: 259.1115; found: 259.1150.

2-(1-Methyl-4-phenylcyclohexyl)benzo[*b*]thiophene-3-carbaldehyde (3)

Yield: 49.3 mg (59%); viscous liquid (*d.r.* = 2:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.80 (s, 1 H), 8.68 (m, 1 H), 7.79 (d, *J* = 8.0 Hz, 1 H), 7.46 (t, *J* = 7.6 Hz, 1 H), 7.40–7.31 (m, 2 H), 7.28–7.20 (m, 3 H), 7.12 (dd, *J* = 19.3, 7.4 Hz, 1 H), 2.75–2.51 (m, 2 H), 2.32–2.13 (m, 3 H), 1.93–1.84 (m, 4 H), 1.74 (s, 2 H), 1.61 (s, 1 H).

HRMS (ESI): *m*/*z* calcd for $C_{22}H_{23}OS^+$ [M + H]$^+$: 335.1464; found: 335.1461.

2-(2-Methyl-4-phenylbutan-2-yl)benzo[*b*]thiophene-3-carbaldehyde (4)

Yield: 56.2 mg (73%); pale yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.75 (s, 1 H), 8.70 (d, *J* = 8.3 Hz, 1 H), 7.78 (d, *J* = 8.1 Hz, 1 H), 7.49–7.45 (m, 1 H), 7.40–7.36 (m, 1 H), 7.25–7.21 (m, 2 H), 7.17–7.13 (m, 1 H), 7.09 (dd, *J* = 5.1, 3.1 Hz, 2 H), 2.59–2.50 (m, 2 H), 2.29–2.21 (m, 2 H), 1.70 (s, 6 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 185.7, 170.4, 141.6, 138.7, 135.9, 129.9, 128.5, 128.4, 128.2, 126.0, 125.0, 124.9, 121.2, 48.1, 40.3, 31.6, 31.5.

HRMS (ESI): *m*/*z* calcd for $C_{20}H_{21}OS^+$ [M + H]$^+$: 309.1308; found: 309.1305.

2-(6-Chloro-2-methylhexan-2-yl)benzo[*b*]thiophene-3-carbaldehyde (5)

Yield: 33.8 mg (46%); pale yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.71 (s, 1 H), 8.69–8.66 (m, 1 H), 7.80–7.74 (m, 1 H), 7.48–7.46 (m, 1 H), 7.41–7.34 (m, 1 H), 3.47 (t, *J* = 6.6 Hz, 2 H), 2.01–1.94 (m, 2 H), 1.78–1.69 (m, 2 H), 1.65 (s, 6 H), 1.46–1.34 (m, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 185.7, 170.8, 138.7, 135.9, 129.9, 125.9, 125.1, 124.8, 121.3, 45.1, 44.6, 40.1, 32.8, 31.4, 22.3.

HRMS (ESI): *m*/*z* calcd for $C_{16}H_{20}ClOS^+$ [M + H]$^+$: 295.0918; found: 295.0917.

3-(3-Formylbenzo[*b*]thiophen-2-yl)-3-methylbutyl Benzoate (6)

Yield: 36.1 mg (41%); pale yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.69 (s, 1 H), 8.54 (d, *J* = 8.2 Hz, 1 H), 7.65 (m, 3 H), 7.36 (t, *J* = 7.6 Hz, 2 H), 7.27 (t, *J* = 7.5 Hz, 1 H), 7.18–7.13 (dd, *J* = 13.3, 5.6 Hz, 2 H), 4.29 (t, *J* = 6.6 Hz, 2 H), 2.44 (t, *J* = 6.7 Hz, 2 H), 1.66 (s, 6 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 185.5, 169.4, 166.4, 138.9, 135.9, 132.8, 129.8, 129.7, 129.3, 128.2, 126.0, 125.1, 124.6, 121.3, 61.7, 43.5, 38.8, 31.6.

HRMS (ESI): *m*/*z* calcd for $C_{21}H_{21}O_3S^+$ [M + H]$^+$: 353.1206; found: 353.1205.

2-(Adamantan-1-yl)benzo[*b*]thiophene-3-carbaldehyde (7)

Yield: 69.6 mg (94%); white solid; mp 149–150 °C.

The spectroscopic data were in accordance with those reported.[14]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.88 (s, 1 H), 8.68 (d, *J* = 8.2 Hz, 1 H), 7.78 (d, *J* = 7.9 Hz, 1 H), 7.46–7.42 (m, 1 H), 7.37–7.33 (m, 1 H), 2.29 (d, *J* = 2.9 Hz, 6 H), 2.21–2.13 (m, 3 H), 1.83 (t, *J* = 3.0 Hz, 6 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 185.9, 173.2, 138.7, 136.1, 129.3, 125.8, 125.0, 124.8, 121.4, 44.9, 39.2, 36.3, 28.9.

2-Cyclopentylbenzo[*b*]thiophene-3-carbaldehyde (8)

Yield: 37.4 mg (65%); pale yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.41 (s, 1 H), 8.60 (d, *J* = 8.2 Hz, 1 H), 7.77 (d, *J* = 8.0 Hz, 1 H), 7.47–7.43 (m, 1 H), 7.38–7.34 (m, 1 H), 4.10–4.01 (m, 1 H), 2.32–2.26 (m, 2 H), 1.94–1.77 (m, 6 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 184.4, 169.6, 137.5, 136.5, 129.7, 125.9, 125.1, 124.0, 121.8, 39.4, 36.7, 25.7.

HRMS (ESI): *m*/*z* calcd for $C_{14}H_{15}OS^+$ [M + H]$^+$: 231.0838; found: 231.0842.

2-Cyclohexylbenzo[*b*]thiophene-3-carbaldehyde (9)

Yield: 49.4 mg (81%); pale yellow solid; mp 60–62 °C.

The spectroscopic data were in accordance with those reported.[9]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.42 (s, 1 H), 8.62 (d, *J* = 8.1 Hz, 1 H), 7.81 (d, *J* = 8.0 Hz, 1 H), 7.47 (t, *J* = 7.6 Hz, 1 H), 7.38 (t, *J* = 7.6 Hz, 1 H), 3.73–3.65 (m, 1 H), 2.15–1.80 (m, 5 H), 1.67–1.28 (m, 5 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 184.2, 170.8, 137.3, 136.8, 128.6, 125.8, 125.0, 124.1, 121.8, 38.3, 36.1, 26.4, 25.6.

2-Cycloheptylbenzo[*b*]thiophene-3-carbaldehyde (10)

Yield: 47.1 mg (73%); viscous liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.41 (s, 1 H), 8.61–8.59 (m, 1 H), 7.84–7.76 (m, 1 H), 7.46–7.42 (m, 1 H), 7.40–7.32 (m, 1 H), 3.94–3.78 (m, 1 H), 2.17–2.11 (m, 2 H), 1.91–1.79 (m, 4 H), 1.77–1.70 (m, 2 H), 1.69–1.61 (m, 4 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 184.3, 172.2, 137.1, 136.8 127.9, 125.9, 125.0, 124.2, 121.8, 40.0, 37.9, 27.9, 26.9.

HRMS (ESI): *m*/*z* calcd for $C_{16}H_{19}OS^+$ [M + H]$^+$: 259.1151; found: 259.1149.

2-(4-Phenylbutan-2-yl)benzo[*b*]thiophene-3-carbaldehyde (11)

Yield: 44.8 mg (61%); pale yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.22 (s, 1 H), 8.63 (d, *J* = 8.2 Hz, 1 H), 7.80 (d, *J* = 8.0 Hz, 1 H), 7.48–7.44 (m, 1 H), 7.40–7.36 (m, 1 H), 7.30–7.24 (m, 2 H), 7.21–7.16 (m, 1 H), 7.12 (d, *J* = 6.9 Hz, 2 H), 3.97–3.72 (m, 1 H), 2.71–2.53 (m, 2 H), 2.21–1.99 (m, 2 H), 1.48 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 184.1, 170.1, 141.0, 137.2, 136.9, 129.9, 128.5, 128.3, 126.2, 125.9, 125.3, 124.3, 121.9, 41.1, 33.7, 33.0, 24.2.

HRMS (ESI): *m*/*z* calcd for $C_{19}H_{19}OS^+$ [M + H]$^+$: 295.1151; found: 295.1149.

2-{(3*S*,8*S*,9*S*,10*R*,13*R*,14*S*,17*R*)-10,13-Dimethyl-17-[(*R*)-6-methylheptan-2-yl]-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl}benzo[*b*]thiophene-3-carbaldehyde (12)

Yield: 67.6 mg (51%); pale yellow solid (*d.r.* = 1.7:1, absolute configuration of diastereomers not determined).

Diastereomer 1

^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.38 (s, 1 H), 8.61 (d, *J* = 7.9 Hz, 1 H), 7.79 (d, *J* = 7.9 Hz, 1 H), 7.50–7.42 (m, 1 H), 7.40–7.34 (m, 1 H), 5.45–5.38 (m, 1 H), 3.71–3.63 (m, 1 H), 2.69–2.57 (m, 1 H), 2.41–2.37 (m, 1 H), 2.06–1.97 (m, 4 H), 1.93–1.80 (m, 2 H), 1.65–1.48 (m, 6 H), 1.41–1.23 (m, 6 H), 1.19–1.01 (m, 11 H), 0.93 (d, *J* = 6.5 Hz, 3 H), 0.87 (dd, *J* = 6.6, 1.7 Hz, 6 H), 0.70 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 184.1, 169.6, 140.9, 137.3, 136.9, 128.9, 125.9, 125.1, 124.2, 121.9, 121.8, 56.9, 56.2, 50.3, 42.3, 42.0, 39.8, 39.6, 39.4, 39.3, 36.8, 36.2, 35.8, 32.1, 31.9, 31.8, 28.3, 24.3, 23.9, 22.8, 22.6, 20.9, 19.5, 18.8, 11.9.

Diastereomer 2

^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.42 (s, 1 H), 8.59 (d, *J* = 8.0 Hz, 1 H), 7.78 (d, *J* = 7.9 Hz, 1 H), 7.46–7.42 (m, 1 H), 7.39–7.32 (m, 1 H), 5.64–5.54 (m, 1 H), 4.34 (t, *J* = 8.0 Hz, 1 H), 3.06–2.84 (m, 1 H), 2.37–2.25 (m, 2 H), 2.17–1.98 (m, 2 H), 1.93–1.27 (m, 16 H), 1.21–1.08 (m, 10 H), 0.94–0.84 (m, 9 H), 0.71 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 184.5, 168.0, 138.6, 137.9, 136.5, 129.1, 125.8, 125.7, 124.8, 123.7, 121.5, 56.8, 56.2, 50.1, 42.4, 39.7, 39.5, 37.1, 36.9, 36.2, 35.8, 34.5, 33.8, 32.4, 31.8, 30.2, 28.3, 28.0, 24.3, 23.9, 22.8, 22.6, 19.6, 18.7, 11.9.

HRMS (ESI): *m*/*z* calcd for $C_{36}H_{51}OS^+$ [M + H]$^+$: 531.3655; found: 531.3656.

2-(Adamantan-1-yl)benzo[*b*]thiophene-3-carbonitrile (13)

Yield: 40.3 mg (55%); white solid; mp 158–159 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.89 (d, *J* = 8.1 Hz, 1 H), 7.80 (d, *J* = 9.7 Hz, 1 H), 7.50–7.44 (m, 1 H), 7.43–7.36 (m, 1 H), 2.26 (d, *J* = 2.9 Hz, 6 H), 2.16 (s, 3 H), 1.87–1.79 (m, 6 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 169.9, 139.5, 135.7, 125.6, 125.2, 122.2, 121.7, 115.4, 100.5, 42.7, 38.3, 36.2, 28.6.

HRMS (ESI): *m*/*z* calcd for $C_{19}H_{20}NS^+$ [M + H]$^+$: 294.1311; found: 294.1306.

2-(Adamantan-1-yl)benzo[*d*]oxazole (14)

Yield: 45.5 mg, (72%); white solid; mp 158–159 °C.

The spectroscopic data were in accordance with those reported.[14]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.74–7.67 (m, 1 H), 7.49–7.46 (m, 1 H), 7.31–7.26 (m, 2 H), 2.15 (t, *J* = 7.3 Hz, 9 H), 1.82 (t, *J* = 2.8 Hz, 6 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 173.0, 150.5, 141.2, 124.3, 123.9, 119.6, 110.3, 40.3, 36.5, 36.1, 28.0.

2-(*tert*-Butyl)benzo[*d*]oxazole (15)

Yield: 24.9 mg (57%); colorless liquid.

The spectroscopic data were in accordance with those reported.[9]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.72–7.68 (m, 1 H), 7.50–7.48 (m, 1 H), 7.32–7.28 (m, 2 H), 1.50 (s, 9 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 173.5, 150.8, 141.2, 124.4, 123.9 119.7, 110.3, 34.1, 28.5.

2-(*tert*-Butyl)benzo[*d*]thiazole (16)

Yield: 16.7 mg (35%); colorless liquid.

The spectroscopic data were in accordance with those reported.[9]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.02 (d, *J* = 8.1 Hz, 1 H), 7.86 (d, *J* = 7.4 Hz, 1 H), 7.48–7.44 (m, 1 H), 7.37–7.33 (m, 1 H), 1.54 (s, 9 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 182.1, 152.9, 134.8, 125.9, 124.6, 122.6, 121.5, 38.3, 30.7.

3-(Adamantan-1-yl)-2-fluoroisonicotinonitrile (17)

Yield: 25.0 mg (39%); white solid; mp 165–166 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.16 (m, 1 H), 7.44 (m, 1 H), 2.30 (s, 6 H), 2.16 (s, 3 H), 1.87–1.76 (m, 6 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 162.1 (d, *J* = 244.5 Hz), 145.1 (d, *J* = 17.5 Hz), 134.6 (d, *J* = 26.8 Hz), 127.6 (d, *J* = 4.9 Hz), 122.1 (d, *J* = 7.6 Hz), 117.7 (d, *J* = 6.3 Hz), 40.7, 38.9 (d, *J* = 6.0 Hz), 36.2, 28.6.

HRMS (ESI): *m*/*z* calcd for $C_{16}H_{17}FN_2Na^+$ [M + Na]$^+$: 279.1268; found: 279.1262.

***tert*-Butyl 3-Acetyl-2-(*tert*-butyl)-1*H*-indole-1-carboxylate (18)**

Yield: 16.5 mg (21%); colorless liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33–7.14 (m, 3 H), 7.04–6.97 (m, 1 H), 2.09 (s, 3 H), 1.56 (s, 9 H), 0.85 (s, 9 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 205.4, 153.6, 144.0, 129.5, 128.7, 124.3, 123.3, 117.5, 81.4, 69.7, 56.8, 36.4, 28.3, 26.3, 26.0.

HRMS (ESI): *m*/*z* calcd for $C_{19}H_{26}NO_3^+$ [M + H]$^+$: 316.1907; found: 316.1906.

2-(Adamantan-1-yl)-6-methylpyridine 1-Oxide (19)

Yield: 26.1 mg (43%); white solid; mp 156–158 °C.

The spectroscopic data were in accordance with those reported.[14]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.19–7.10 (m, 3 H), 2.51 (s, 3 H), 2.31 (d, *J* = 2.8 Hz, 6 H), 2.11 (s, 3 H), 1.84–1.76 (m, 6 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 157.7, 150.7, 124.8, 123.9, 121.5, 38.8, 37.5, 36.9, 28.5, 18.8.

5-(Adamantan-1-yl)furan-2-carbaldehyde (20)

Yield: 23.5 mg (41%); white solid; mp 78–80 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.52 (s, 1 H), 7.17 (d, *J* = 3.6 Hz, 1 H), 6.18 (d, *J* = 3.6 Hz, 1 H), 2.08 (s, 3 H), 1.97 (d, *J* = 2.8 Hz, 6 H), 1.82–1.72 (m, 6 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 177.2, 171.5, 151.5, 123.3, 105.5, 40.7, 36.5, 35.3, 28.0.

3-(*tert*-Butyl)benzofuran-2-carbaldehyde (21)

Yield: 26.3 mg (52%); white solid; mp 35–38 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.30 (s, 1 H), 7.96 (d, *J* = 9.9 Hz, 1 H), 7.61–7.55 (m, 1 H), 7.49–7.45 (m, 1 H), 7.31–7.27 (m, 1 H), 1.67 (s, 9 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 181.3, 155.4, 147.6, 140.8, 128.7, 127.2, 124.8, 123.0, 112.9, 34.5, 32.1.

HRMS (ESI): *m*/*z* calcd for $C_{13}H_{15}O_2^+$ [M + H]$^+$: 203.1067; found: 203.1069.

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Supporting Information

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References

(1) (a) Lovering, F.; Bikker, J.; Humblet, C. *J. Med. Chem.* **2009**, *52*, 6752. (b) Walters, W.; Green, J.; Weiss, J. R.; Murcko, M. A. *J. Med. Chem.* **2011**, *54*, 6405. (c) Taylor, A. P.; Robinson, R. P.; Fobian, Y. M.; Blakemore, D. C.; Jones, L. H.; Fadeyi, O. *Org. Biomol. Chem.* **2016**, *14*, 6611.

(2) (a) Hirase, R.; Ishihara, M.; Katagiri, T.; Tanaka, Y.; Yanagi, H.; Hotta, S. *Org. Electron.* **2014**, *15*, 1481. (b) Zhang, C.; Zhu, X. *Acc. Chem. Res.* **2017**, *50*, 1342. (c) Tsuji, H.; Nakamura, E. *Acc. Chem. Res.* **2017**, *50*, 396.

(3) (a) Dong, Z.; Ren, Z.; Thompson, S. J.; Xu, Y.; Dong, G. *Chem. Rev.* **2017**, *117*, 9333. (b) Shang, R.; Ilies, L.; Nakamura, E. *Chem. Rev.* **2017**, *117*, 9086. (c) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Chem. Rev.* **2011**, *111*, 1293. (d) Ackermann, L. *Chem. Commun.* **2010**, *46*, 4866. (e) Arockiam, P. B.; Bruneau, C.; Dixneuf, P. H. *Chem. Rev.* **2012**, *112*, 5879.

(4) (a) Olah, G. A. *Friedel–Crafts Chemistry*; Wiley: New York, **1973**. (b) Roberts, R. M.; Khalaf, A. A. *Friedel-Crafts Alkylation Chemistry: A Century of Discovery*; Marcel Dekker: New York, **1984**. (c) Iovel, I.; Mertins, K.; Kischel, J.; Zapf, A.; Beller, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 3913. (d) Mertins, K.; Iovel, I.; Kischel, J.; Zapf, A.; Beller, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 238.

(5) Frisch, A. C.; Beller, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 674.

(6) (a) Yue, W.; Li, Y.; Jiang, W.; Zhen, Y.-G.; Wang, Z.-H. *Org. Lett.* **2009**, *13*, 5430. (b) Yao, T.; Hirano, K.; Satoh, T.; Miura, M. *Chem. Eur. J.* **2010**, *16*, 12307. (c) Vechorkin, O.; Proust, V.; Hu, X. L. *Angew. Chem. Int. Ed.* **2010**, *49*, 3061.

(7) Kaga, A.; Chiba, S. *ACS Catal.* **2017**, *7*, 4697.

(8) Bräse, S.; de Meijere, A. In *Metal-catalyzed Cross-coupling Reactions*; Diederich, F.; Stang, P. J., Eds.; Wiley-VCH: Weinheim, **1998**, Chap. 3.

(9) Wu, X.-J.; See, W. J. T.; Xu, K.; Hirao, H.; Roger, J.; Hierso, J.-C.; Zhou, J. R. S. *Angew. Chem. Int. Ed.* **2014**, *53*, 13573.

(10) Wang, G.-Z.; Shang, R.; Fu, Y. *Org. Lett.* **2018**, *20*, 888.

(11) Wang, G.-Z.; Shang, R.; Cheng, W.-M.; Fu, Y. *J. Am. Chem. Soc.* **2017**, *139*, 18307.

(12) For irradiation-excited Pd catalysis, see: (a) Parasram, M.; Chuentragool, P.; Sarkar, D.; Gevorgyan, V. *J. Am. Chem. Soc.* **2016**, *138*, 6340. (b) Parasram, M.; Chuentragool, P.; Wang, Y.; Shi, Y.; Gevorgyan, V. *J. Am. Chem. Soc.* **2017**, *139*, 14857. (c) Kurandina, D.; Parasram, M.; Gevorgyan, V. *Angew. Chem. Int. Ed.* **2017**, *56*, 14212. (d) Kurandina, D.; Rivas, M.; Radzhabov, M.; Gevorgyan, V. *Org. Lett.* **2018**, *20*, 357. (e) Ratushnyy, M.; Parasram, M.; Wang, Y.; Gevorgyan, V. *Angew. Chem. Int. Ed.* **2018**, *57*, 2712. (f) Chuentragool, P.; Parasram, M.; Shi, Y.; Gevorgyan, V. *J. Am. Chem. Soc.* **2018**, *140*, 2465.

(13) (a) Thansandote, P.; Raemy, M.; Rudolph, A.; Lautens, M. *Org. Lett.* **2007**, *9*, 5255. (b) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173. (c) Verrier, C.; Hoarau, C.; Marsais, F. *Org. Biomol. Chem.* **2009**, *7*, 647. (d) Zhang, Y.-H.; Shi, B.-F.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2009**, *48*, 6097.

(14) During the preparation of this manuscript, Yu et al. reported examples of irradiation-induced palladium-catalyzed intermolecular C–H alkylation of heteroarene using 1-bromoadamantane. In Yu's report, secondary and tertiary alkyl bromides possessing eliminable β-H were not demonstrated as amenable substrates for intermolecular C(sp^2)–H alkylation of heteroarene, see: Zhou, W.-J.; Cao, G.-M.; Shen, G.; Zhu, X.-Y.; Gui, Y.-Y.; Ye, J.-H.; Sun, L.; Liao, L.-L.; Li, J.; Yu, D.-G. *Angew. Chem. Int. Ed.* **2017**, *56*, 15683.

(15) For Pd(I) generation from Pd(0) and alkyl halide under thermal condition, see: (a) McMahon, C. M.; Alexanian, E. J. *Angew. Chem. Int. Ed.* **2014**, *53*, 5974. (b) Zou, Y.; Zhou, J. R. S. *Chem. Commun.* **2014**, *50*, 3725.

(16) Xiao, B.; Liu, Z.-J.; Liu, L.; Fu, Y. *J. Am. Chem. Soc.* **2013**, *135*, 616.

(17) (a) Cheng, W.-M.; Shang, R.; Fu, Y. *ACS Catal.* **2017**, *7*, 907. (b) Cheng, W.-M.; Shang, R.; Fu, M.-C.; Fu, Y. *Chem. Eur. J.* **2017**, *23*, 2537. (c) Nuhant, P.; Oderinde, M. S.; Genovino, J.; Juneau, A.; Gagn, Y.; Allais, C.; Chinigo, G. M.; Choi, C.; Sach, N. W.; Bernier, L.; Fobian, Y. M.; Bundesmann, M. W.; Khunte, B.; Frenette, M.; Fadeyi, O. O. *Angew. Chem. Int. Ed.* **2017**, *56*, 15309.

(18) For references on irradiation-induced transition metal catalysis, see: (a) Weiss, M. E.; Kreis, L. M.; Lauber, A.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2011**, *50*, 11125. (b) Weiss, M. E.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2011**, *50*, 11501. (c) Kreis, L. M.; Krautwald, S.; Pfeiffer, N.; Martin, R. E.; Carreira, E. M. *Org. Lett.* **2013**, *15*, 1634. (d) Parasram, M.; Gevorgyan, V. *Chem. Soc. Rev.* **2017**, *46*, 6227.