Visible-Light-Induced Decarboxylative C–H Adamantylation of Azoles at Ambient Temperature

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Abstract The visible-light-promoted oxidant-free decarboxylative C–H adamantylation of azoles was accomplished under ambient reaction conditions. The novel acridinium photocatalyst and cobalt synergistic catalysis enabled the C–H adamantylation under oxidant-free reaction conditions. This C–H adamantylation strategy proved viable for a wide range of substituted azoles, including benzothiazole, benzoxazole, and benzimidazoles as well as caffeine derivatives, providing an expedient access to 2-adamantyl-substituted azoles.

Key words photocatalysis, C–H functionalization, decarboxylation, cobalt, acridinium salts, oxidant-free, adamantylation, azoles

Adamantane, a strain-free molecule consisting of three fused cyclohexane rings, has attracted significant attention because of its unique structural features and properties.1 For instance, the adamantyl moiety represents a key scaffold in several biologically active compounds2 and clinical therapeutics.3 The incorporation of the adamantyl group to polymers4 and functional materials5 significantly improves their physical properties, such as thermal stability and solubility.6 Furthermore, the specific features of the adamantyl scaffold, including lipophilicity, steric demand, dispersion attraction, and conformational stability and rigidity expanded their presence and influence in several other important areas of research, such as supramolecular chemistry,7 and molecular syntheses.8 Despite the great importance of adamantyl-substituted organic compounds, the incorporation of adamantyl group into organic molecules largely relies on conventional nucleophilic substitution reactions with adamantyl halides.8e,9 Recently, selected examples of C–H adamantylation were reported as the part of the scope of transition-metal-catalyzed C–H alkylation protocols.10 However, no specific methods have as of yet been reported for the C–H adamantylation of heteroarenes, in detail delineating its scope and limitations. Within our program on transition-metal-catalyzed C–H alkylation11 and photoredox catalysis,12 we have now devised an exceedingly mild method for the C–H adamantylation of azoles by a photoinduced decarboxylative14 C–H alkylation strategy.15 Notable features of our approach include (i) expedient C–H adamantylation on diversely decorated azoles, (ii) non-directing group-assisted C–H functionalization, (iii) easily accessible and inexpensive 1-adamantane carboxylic acid as a reagent, (iv) visible-light-promoted C–H functionalization, (v) no stoichiometric oxidants and iridium or ruthenium photocatalysts, (vi) key mechanistic insights, and (vii) ambient reaction temperature (Scheme 1).

We initiated our studies by examining suitable photocatalysts (PCs) (Figure 1), bases, and solvents under oxidant-free conditions, using an easily accessible cobaloxime complex16 as cocatalyst for the envisioned decarboxylative C–H adamantylation of benzothiazole (1a) with adaman- tanecarboxylic acid (2) (Table 1). Thus, among a set of representative photocatalysts, 9-mesityl-10-methylacridinium perchlorate (PC1) provided optimal results in a mixture of

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* Ambient reaction temperature
* Visible-light-promoted decarboxylation
* No stoichiometric oxidants
* No expensive Ir or Ru photocatalysts
* Ambient reaction temperature
DCE/H$_2$O (3:1) as the reaction medium (Table 1, entry 1). While a variety of bases could be utilized, the photoinduced C–H adamantylation was most effective in the presence of K$_2$HPO$_4$. The key importance of the photocatalyst, base, and light irradiation in the decarboxylative C–H adamantylation manifold was verified by probing the transformation in the absence of each component under otherwise identical reaction conditions (entries 17–19). Notably, the use of blue light was found beneficial to realize satisfactory yields (entries 20 and 21).

With the optimized reaction conditions in hand, we probed the scope of the reaction with a range of azoles 1 (Scheme 2). To our delight, the visible-light-enabled decarboxylative C–H adamantylation proved broadly applicable towards a range of azoles. Thus, differently substituted benzothiazoles 1a–h and benzoxazoles 1i–p were efficiently transformed into the desired adamantyl-substituted products 3a–p in satisfactory yields. Notably, the challenging benzimidazoles 1q and caffeine derivatives 1r,s were successfully functionalized under identical reaction conditions.

In consideration of the unique reactivity of the photoinduced decarboxylative C–H functionalization, we were attracted to delineate its mode of action. To probe the catalyst’s working mode, we performed an intermolecular competition experiment, which revealed electron-deficient benzothiazole 1e to be preferentially converted (Scheme 3a). Further, we investigated a SET-type regime by the use of typical radical scavengers TEMPO, galvinoxyl, and BHT (Scheme 3b), which significantly suppressed the catalytic efficacy.

To further elucidate the reaction mechanism of the photoinduced C–H adamantylation, we performed a series of additional experiments (Figure 2). First, we monitored the conversion profile of the photocatalytic reaction of 1a and 2 to give 3a, which revealed the reaction being completely suppressed in the absence of light (Figure 2a). These findings provided strong evidence for the beneficial influence of visible-light irradiation. Second, fluorescence-quenching experiments (Figure 2b–d) revealed no quenching of the free acid 2, while both benzothiazole and the carboxylate salt quenched the excited state of acridinium photocatalyst.
Based on these observations, we propose the single-electron transfer to occur from PC1* to adamantane carboxylate as the key step.

In light of these mechanistic findings, a plausible catalytic cycle for the photoinduced decarboxylative C–H adamantylation protocol is elaborated in Scheme 4. The acridinium photocatalyst [Arc-Mes+] is initially excited to [Arc-Mes+]* by blue light absorption, which oxidizes the adamantane carboxylate anion to the oxygen-centered carboxyl radical. Then, decarboxylation forms the adamantyl radical. Subsequently, the [Arc-Mes•] radical is re-oxidized to [Arc-Mes+] by the cobalt(III) species to complete the photo-
catalytic cycle. In the meantime, the attack of the adamantyl radical at the electrophilic C2 position of benzothiazole (1a) generates radical intermediate A. Upon deprotonation, reduction of the cobalt(II) species to cobalt(I) through SET from species A then delivers the adamantlylated product 3a. Concurrently, the cobalt(III)-hydride species could be formed from the cobalt(I) species by capturing a proton generated in the reaction. Release of H2 through a reaction with another proton will regenerate the cobalt(III) species.16c–f

In summary, we have reported on the unprecedented visible-light-enabled decarboxylative C–H adamantlylation of azoles at ambient reaction temperature. The oxidant-free decarboxylative adamantlylation was efficiently achieved by the aid of catalytic amounts of easily available cobalt oxime complex. A range of substituted azoles, including benzothiazole, benzoxazole, and benzimidazoles as well as caffeine derivatives, were well tolerated, providing a new general strategy to access adamantlylated-substituted heterocycles motifs.

Catalytic reactions were carried out in pre-dried 10 mL vials under N2 atmosphere. In cases wherein air- or moisture-sensitive reagents were used, reactions were performed under N2 atmosphere using standard Schlenk techniques. The following substrates were prepared according to previously described procedures: Benzothiazoles 1b–h,17 benzoxales 1i–p,18 benzimidazole 1q,19 [Co(dmgH)(dmgH2)Cl2],20 and tetrabutyllammonium adamantane carboxylate.21 Other chemicals were obtained from commercial sources and were used without further purification, unless otherwise noted. Yields refer to isolated products, estimated to be >95% pure as determined by 1H NMR spectroscopy. TLC: Merck TLC silica gel 60 F 254, TLC plates; detection with another proton will regenerate the cobalt(III) species.16c–f

Visible-Light-Promoted Decarboxylative C–H Adamantylation; General Procedure

To an oven-dried 10 mL vial were added the heteroarene 1 (0.40 mmol, 1.0 equiv), 1-adamantanecarboxylic acid (2; 216 mg, 1.20 mmol, 3.0 equiv), K2HPO4 (209 mg, 1.20 mmol, 3.0 equiv), 9-mesityl-10-methylacridinium perchlorate (8.2 mg, 50 mol%), and [Co(dmgH)(dmgH2)Cl2] (11.6 mg, 80 mol%). After the vial was capped with a septum, it was evacuated and refilled with N2 for three times before DCE (1.5 mL) and H2O (0.5 mL) were added sequentially. If the mixture was degassed and stirred for 24 h under visible light irradiation (Kessil A360N, see Figure S-1 in the Supporting Information). After 24 h, the mixture was diluted with CH2Cl2 (10 mL) and H2O (10 mL), and the phases were separated. The aqueous layer was extracted with CH2Cl2 (2 × 10 mL), the combined organic phases were dried (Na2SO4), and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (n-pentane or n-hexane/Et2O 20:1 to 2:1) affording the corresponding product 3.

Visible-Light-Promoted Decarboxylative C–H Adamantylation; General Procedure

To an oven-dried 10 mL vial were added the heteroarene 1 (0.40 mmol, 1.0 equiv), 1-adamantanecarboxylic acid (2; 216 mg, 1.20 mmol) for 24 h. After aqueous workup, purification by column chromatography on silica gel (n-pentane/Et2O 30:1) afforded 3a; yield: 89.3 mg (331 μmol, 83%); white solid; mp 103–104°C.

IR (ATR): 2898, 2845, 1506, 1434, 1168, 999, 965, 754, 725, 680 cm–1.


Visible-Light-Promoted Decarboxylative C–H Adamantylation; General Procedure

To an oven-dried 10 mL vial were added the heteroarene 1 (0.40 mmol, 1.0 equiv), 1-adamantanecarboxylic acid (2; 216 mg, 1.20 mmol) for 24 h. After aqueous workup, purification by column chromatography on silica gel (n-pentane/Et2O 30:1) afforded 3b; yield: 60.6 mg (214 μmol, 53%); white solid; mp 132–133°C.

IR (ATR): 2899, 2845, 1506, 1449, 1164, 1000, 835, 812, 569 cm–1.


Visible-Light-Promoted Decarboxylative C–H Adamantylation; General Procedure

To an oven-dried 10 mL vial were added the heteroarene 1 (0.40 mmol, 1.0 equiv), 1-adamantanecarboxylic acid (2; 216 mg, 1.20 mmol) for 24 h. After aqueous workup, purification by column chromatography on silica gel (n-pentane/Et2O 30:1) afforded 3c; yield: 70.2 mg (234 μmol, 59%); white solid; mp 118–119°C.

IR (ATR): 2896, 2845, 1506, 1434, 1168, 999, 965, 754, 725, 680 cm–1.


Visible-Light-Promoted Decarboxylative C–H Adamantylation; General Procedure

To an oven-dried 10 mL vial were added the heteroarene 1 (0.40 mmol, 1.0 equiv), 1-adamantanecarboxylic acid (2; 216 mg, 1.20 mmol) for 24 h. After aqueous workup, purification by column chromatography on silica gel (n-pentane/Et2O 30:1) afforded 3d; yield: 70.2 mg (234 μmol, 59%); white solid; mp 118–119°C.
The general procedure was followed using benzothiazole (3g) and 1-adamantanecarboxylic acid (2; 216 mg, 1.20 mmol) for 24 h. After aqueous workup, purification by column chromatography on silica gel (n-pentane/ EtOAc 81:19) afforded 3d; yield: 96.3 mg (285 μmol, 71%); white solid; mp 183–184 °C.

IR (ATR): 2911, 1317, 1278, 1149, 1044 (CH), 559 (CH2), 43.1 (CH2), 40.1 (CH2), 36.7 (CH2), 28.7 (CH).


The general procedure was followed using benzothiazole 1d (81.3 mg, 0.40 mmol) and 1-adamantanecarboxylic acid (2; 216 mg, 1.20 mmol) for 24 h. After aqueous workup, purification by column chromatography on silica gel (n-pentane/EtO 30:1) afforded 3d; yield: 96.3 mg (285 μmol, 71%); white solid; mp 183–184 °C.

IR (ATR): 2911, 1317, 1278, 1149, 1044 (CH), 559 (CH2), 43.1 (CH2), 40.1 (CH2), 36.7 (CH2), 28.7 (CH).


2-[(3SR,7R)-Adamantan-1-yl]-6-(trifluoromethyl)benzothiazole (3d)

The general procedure was followed using benzothiazole 1d (81.3 mg, 0.40 mmol) and 1-adamantanecarboxylic acid (2; 216 mg, 1.20 mmol) for 24 h. After aqueous workup, purification by column chromatography on silica gel (n-pentane/EtOAc 81:19) afforded 3d; yield: 96.3 mg (285 μmol, 71%); white solid; mp 183–184 °C.

IR (ATR): 2911, 1317, 1278, 1149, 1044 (CH), 559 (CH2), 43.1 (CH2), 40.1 (CH2), 36.7 (CH2), 28.7 (CH).


2-[(3SR,7R)-Adamantan-1-yl]-6-fluorobenzothiazole (3d)

The general procedure was followed using benzothiazole 1d (81.3 mg, 0.40 mmol) and 1-adamantanecarboxylic acid (2; 216 mg, 1.20 mmol) for 24 h. After aqueous workup, purification by column chromatography on silica gel (n-pentane/EtOAc 81:19) afforded 3d; yield: 96.3 mg (285 μmol, 71%); white solid; mp 183–184 °C.

IR (ATR): 2911, 1317, 1278, 1149, 1044 (CH), 559 (CH2), 43.1 (CH2), 40.1 (CH2), 36.7 (CH2), 28.7 (CH).

The general procedure was followed using 5-methylbenzoxazole 1j (53.3 mg, 0.40 mmol) and 1-adamantaneacarboxylic acid (2; 216 mg, 1.20 mmol) for 48 h. After aqueous workup, purification by column chromatography on silica gel (n-pentane/EtOAc 20:1) afforded 3n; yield: 53.0 mg (198 μmol, 50%); white solid; mp 112–114 °C. IR (ATR): 2908, 2851, 1569, 1451, 1263, 1040, 919, 809, 602 cm⁻¹. 

1H NMR (600 MHz, CDCl₃): δ = 7.63 (d, J = 2.1 Hz, 1 H), 7.37 (d, J = 8.6 Hz, 1 H), 7.23 (dd, J = 8.6, 2.1 Hz, 1 H), 2.19–2.08 (m, 9 H), 1.83–1.76 (m, 6 H). 

13C NMR (126 MHz, CDCl₃): δ = 174.2 (Cq), 148.0 (Cq), 142.3 (Cq), 129.3 (Cq), 124.5 (CH), 119.7 (CH), 110.9 (CH), 40.2 (CH₂), 36.5 (CH₂), 36.3 (Cq), 28.0 (CH). 

MS (EI): m/z (%) = 290 ([M + Na]+, 9), 268 ([M + H]+), 100. HRMS (ESI): m/z calcd for C₂₁H₂₈NO [M + H]+: 326.0645; found: 326.0648.

2-[(3R,5R,7R)-Adamantan-1-yl]-5-bromobenz[d]oxazole (3m) 

The general procedure was followed using benzoazole 1n (792 mg, 0.40 mmol) and 1-adamantaneacarboxylic acid (2; 216 mg, 1.20 mmol). After aqueous workup, purification by column chromatography on silica gel (n-pentane/EtOAc 20:1) afforded 3m; yield: 56.1 mg (169 μmol, 42%); white solid; mp 135–136 °C. IR (ATR): 2905, 2849, 1555, 1444, 1253, 1040, 907, 791, 768, 682 cm⁻¹. 

1H NMR (600 MHz, CDCl₃): δ = 7.80 (d, J = 1.9 Hz, 1 H), 7.38 (dd, J = 8.4, 1.9 Hz, 1 H), 7.34 (d, J = 8.4 Hz, 1 H), 2.14–2.11 (m, 9 H), 1.84–1.77 (m, 6 H). 

13C NMR (126 MHz, CDCl₃): δ = 174.2 (Cq), 150.0 (Cq), 143.0 (Cq), 127.3 (CH), 122.8 (CH), 116.7 (CH), 111.6 (CH), 40.3 (CH₂), 36.6 (CH₂), 36.4 (Cq), 28.1 (CH). 

MS (ESI): m/z (%) = 334 ([M + H]+, 97), 332 ([M + H]+, 100); 79[Br]. HRMS (ESI): m/z calcd for C₂₁H₁₉BrNO [M + H]+: 332.0645; found: 326.0648.
The general procedure was followed using benzoxazole 1a (61.3 mg, 0.40 mmol) as well as 1-adamantanecarboxylic acid (1b, 59.7 mg, 0.40 mmol) as 7-
[2-(methoxymethoxy)propyl]-1,3-dimethyl-3,7-dihydro-1H-purine-2,6-dione (3s). The general procedure was followed using substrate 1s (85.0 mg, 0.30 mmol) and 1-adamantanecarboxylic acid (2, 162 mg, 0.90 mmol) for 48 h. After aqueous workup, purification by column chromatography on silica gel (n-pentane/Et2O 10:1) afforded 3s; yield: 53.5 mg (129 μmol, 43%); white solid; mp 147–148 °C.

IR (ATR): 2895, 1700, 1660, 1361, 1223, 982, 743 cm⁻¹.

HR MS (EI): m/z (%) = 439 ([M + Na]+, 100), 417 ([M + H]+, 99).


**On/Off Plot**

According to the general procedure, five independent reactions were set up and placed in front of the blue LEDs. The reaction mixtures were sequentially stirred under visible light irradiation and in the absence of light. Every 2 h a reaction vial was removed from the setup and workup was performed according to the general procedure. After a total of 10 h, the obtained isolated yields were plotted with respect to the reaction time.

**Fluorescence Quenching Experiments**

Sample solutions were prepared in DCE with [Acr-Mes]⁺[ClO4]⁻ concentration of c = 1.6 × 10⁻⁵ M and varying concentrations of the respective quencher (added to each sample from a stock solution). The sample solutions were degassed prior to measurement by sparging with N₂. Stern–Volmer experiments were conducted with a fixed excitation wavelength of 430 nm and detection at 518 nm (emission maximum). Plotting of the I₀/I value against the concentration of the respective quencher resulted in the graphs (Figures 2b–d).
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Supporting Information

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