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
carcatalysis, C–H functionalization, decarboxylation, cobalt, acridinium salts, oxidant-free, adamantanoylation, azoles

Adamantane, a strain-free molecule consisting of three fused cyclohexane rings, has attracted significant attention because of its unique structural features and properties. For instance, the adamantyl moiety represents a key scaffold in several biologically active compounds and clinical therapeutics. The incorporation of the adamantyl group to polymers significantly improves their physical properties, such as thermal stability and solubility. 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 and molecular syntheses. 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. Recently, selected examples of C–H adamantylation were reported as the part of the scope of transition-metal-catalyzed C–H alkylation protocols. 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 alkylation and photoredox catalysis, we have now devised an exceedingly mild method for the C–H adamantylation of azoles by a photoinduced decarboxylative C–H alkylation strategy. 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 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 complex as cocatalyst for the envisioned decarboxylative C–H adamantylation of benzothiazole (1a) with adamantane carboxylic acid (2) (Table 1). Thus, among a set of representative photocatalysts, 9-mesityl-10-methylacridinium perchlorate (PC1) provided optimal results in a mixture of DCE/H2O, 25–30 °C, 24 h.

Scheme 1 Visible-light-induced decarboxylative C–H adamantylation
DCE/H₂O (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 K₂HPO₄. 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 (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 benzimidazole 1q and caffeine derivatives 1r,s were successfully functionalized under identical reaction conditions.

Table 1 Optimization Studies

<table>
<thead>
<tr>
<th>Entry</th>
<th>PC</th>
<th>Base (equiv)</th>
<th>Solvent</th>
<th>Yield (%)</th>
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<tr>
<td>1</td>
<td>PC1</td>
<td>K₂HPO₄ (3)</td>
<td>DCE/H₂O (3:1)</td>
<td>83</td>
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<tr>
<td>2</td>
<td>PC2</td>
<td>K₂HPO₄ (3)</td>
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<td>3</td>
<td>PC3</td>
<td>K₂HPO₄ (3)</td>
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<tr>
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<td>PC4</td>
<td>K₂HPO₄ (3)</td>
<td>DCE/H₂O (3:1)</td>
<td>0</td>
</tr>
<tr>
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<td>DCE/H₂O (3:1)</td>
<td>0</td>
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<tr>
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<td>PC1</td>
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<td>74</td>
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<td>CHCl₃/H₂O (3:1)</td>
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<td>K₂HPO₄ (3)</td>
<td>H₂O</td>
<td>7</td>
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</tr>
<tr>
<td>21</td>
<td>PC1</td>
<td>K₂HPO₄ (3)</td>
<td>DCE/H₂O (3:1)</td>
<td>15°</td>
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</table>

a Reaction conditions: benzothiazole (1a, 0.4 mmol), 1-adamantanecarboxylic acid (2a, 1.2 mmol), photocatalyst PC (5.0 mol%), K₂HPO₄ (3.0 mol%), solvent (2.0 mL), 24 h under blue light irradiation (λ_max = 458 nm), yield of isolated product.

b Reaction performed in the dark.

c 22 W CFL.
d 2 W green LED.

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 2a 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 photodecarbonylation of azoles.

Scheme 2
Visible-light-induced decarboxylative C–H adamantylation of azoles

Scheme 3
Key mechanistic findings

Scheme 4
Proposed mechanism for the decarboxylative C–H adamantylation
catalytic cycle. In the meantime, the attack of the adamantanyl 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 adamantylated product 3a. Concurrently, the cobalt(III)-hydride species could be formed from the cobalt(II) species by capturing a proton generated in the reaction. Release of H2 through a reaction with another proton will regenerate the cobalt(III) species.

In summary, we have reported on the unprecedented visible-light-enabled decarboxylative C–H adamantylation of azoles at ambient reaction temperature. The oxidant-free decarboxylative adamantylation was efficiently achieved by the aid of catalytic amounts of easily available cobalt oxime derivatives, were well tolerated, providing a new general strategy to access adamantyl-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–l,18 benzimidazole 1q,19 [Co(dmgH)(dmgH₂)Cl₂]20 and tetrabutylammonium adamantane carboxylate.21 Other chemicals were obtained from commercial sources and were used without further purification, unless otherwise noted. Yields refer to isolated compounds, estimated to be >95% pure as determined by 1H NMR spectroscopy. TLC: Merck TLC silica gel 60 F254 TLC plates; detection under UV light at 254 nm. Chromatography: Separations were carried out on Merck Geurdan® Silica 60 (0.040–0.063 mm, 70–230 mesh ASTM) using distilled solvents. Melting points: Stuart melting point apparatus SMP3, Bariworld Scientific; the reported values are not corrected. NMR: Spectra were recorded on Varian VX 300, Varian VN-MRS 300, Bruker Avance 300, Bruker Avance 400 and 500 or Varian Inova 500 and 600 spectrometers in the solvent indicated; chemical shifts (δ) are given in ppm and referenced to the residual solvent peak. All IR spectra were recorded on a Bruker ATR FT-IR Alpha device. MS: ESI-MS-spectra as well as high-resolution mass spectrometry (HRMS) were recorded with a micrOTOF (ESI-TOF-MS), Bruker Daltonics; EI-spectra were recorded with an AccuTOF (EI-TOF) instrument from Jeol. Fluorescence emission data in solution were recorded on a Jasco® FP-8500 spectrofluorometer. The widths of excitation and emission slits were held constant at 2.5 and 5.0 nm, respectively. The scan speed was adjusted to 500 nm/min.

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

To an oven-dried 10 mL vial were added the heteroarene (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] (8 mg, 0.5 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 heterocyclic substrate 1 was a liquid, it was added at this point. 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.

**2-[(3R,5R,7R)-Adamantan-1-yl]benzo[d]thiazole (3a)**

The general procedure was followed using benzothiazole (1a; 54.1 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/Et₂O 30:1) afforded 3a; yield: 89.3 mg (331 μmol, 83%); white solid; mp 103–104 °C.

**IR (ATR):** 2928, 2845, 1506, 1168, 999, 963, 725, 680 cm⁻¹.

**1H NMR (400 MHz, CDCl₃):** δ = 8.00 (ddd, J = 8.2, 1.2, 0.7 Hz, 1 H), 7.86 (ddd, J = 7.2, 1.2, 0.7 Hz, 1 H), 7.44 (ddd, J = 8.2, 7.2, 1.2 Hz, 1 H), 7.32 (ddd, J = 8.2, 7.2, 1.2 Hz, 1 H), 2.18–2.12 (m, 9 H), 1.86–1.81 (m, 6 H).

**13C NMR (101 MHz, CDCl₃):** δ = 182.3 (C₂), 153.3 (C₆), 134.5 (C₅), 125.8 (CH), 124.5 (CH), 122.8 (CH), 121.7 (CH), 43.1 (CH₂), 40.3 (C₃), 36.7 (CH₃), 28.7 (CH).

**MS (ESI):** m/z [%] = 270 ([M + H]+, 100).

**HRMS (ESI):** calcd for C₁₇H₂₀NS+ [M + H]⁺: 270.1311; found: 270.1313.

The analytical data are in accordance with those reported in the literature.¹⁰

**2-[(3R,5R,7R)-Adamantan-1-yl]-6-methylbenzo[d]thiazole (3b)**

The general procedure was followed using benzothiazole 1b (59.7 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/Et₂O 30:1) afforded 3b; yield: 60.6 mg (214 μmol, 53%); white solid; mp 132–133 °C.

**IR (ATR):** 2899, 2845, 1506, 1434, 1168, 999, 963, 725, 680 cm⁻¹.

**1H NMR (400 MHz, CDCl₃):** δ = 7.87 (d, J = 8.2 Hz, 1H), 7.32 (ddd, J = 8.2, 1.7, 0.6 Hz, 1H), 2.46 (s, 3H), 2.16–2.11 (m, 9 H), 1.83–1.80 (m, 6 H).

**13C NMR (101 MHz, CDCl₃):** δ = 181.2 (C₂), 151.4 (C₆), 134.6 (C₅), 134.5 (C₄), 127.3 (CH), 122.2 (CH), 121.4 (CH), 43.1 (CH₂), 40.2 (C₃), 36.7 (CH₃), 28.7 (CH₂), 21.6 (CH₃).

**MS (ESI):** m/z [%] = 284 ([M + H]+, 100).

**HRMS (ESI):** calcd for C₁₈H₂₂NS⁺ [M + H]⁺: 284.1467; found: 284.1471.

The analytical data are in accordance with those reported in the literature.²²

**2-[(3R,5R,7R)-Adamantan-1-yl]-6-methoxylbenzo[d]thiazole (3c)**

The general procedure was followed using benzothiazole 1c (66.1 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/Et₂O 25:1) afforded 3c; yield: 70.2 mg (234 μmol, 59%); white solid; mp 118–119 °C.

**IR (neat):** 2904, 1467, 1450, 1435, 1261, 1223, 1028, 1000, 834, 827 cm⁻¹.
The general procedure was followed using benzothiazole (0.40 mmol) and 1-adamantanecarboxylic acid (2.16 mmol, 1.20 mmol) for 24 h. After aqueous workup, purification by column chromatography on silica gel (1.20 mmol) for 24 h. After aqueous workup, purification by column chromatography on silica gel (n-pentane/Et2O 30:1) afforded 3d; yield: 71.8 mg (236 μmol, 71%); white solid; mp 183–184 °C.

IR (ATR): 2989, 2844, 1514, 1435, 1259, 1097, 999, 802, 768, 680 cm⁻¹.

1H NMR (400 MHz, CDCl₃): δ = 7.88 (dd, J = 8.9, 0.4 Hz, 1 H), 7.31 (d, J = 2.5 Hz, 1 H), 7.03 (dd, J = 8.9, 2.5 Hz, 1 H), 3.85 (s, 3 H), 2.15–2.11 (m, 9 H), 1.82–1.79 (m, 6 H).

IR (ATR): 2898, 2844, 1514, 1435, 1259, 1097, 999, 802, 768, 680 cm⁻¹.

1H NMR (400 MHz, CDCl₃): δ = 7.88 (dd, J = 8.7, 0.4 Hz, 1 H), 7.81 (dd, J = 2.1, 0.4 Hz, 1 H), 7.38 (dd, J = 8.7, 2.1 Hz, 1 H), 2.16–2.11 (m, 9 H), 1.84–1.79 (m, 6 H).

IR (ATR): 2907, 2852, 1560, 1455, 1264, 1240, 1044, 736, 704 cm⁻¹.

The general procedure was followed using benzothiazole (0.40 mmol) and 1-adamantanecarboxylic acid (2.16 mmol, 1.20 mmol) for 24 h. After aqueous workup, purification by column chromatography on silica gel (n-pentane/Et2O 30:1) afforded 3f; yield: 71.8 mg (236 μmol, 59%); white solid; mp 145–146 °C.
The general procedure was followed using benzoxazole 1m (792 mg, 0.40 mmol) and 1-adamantanecarboxylic acid (2; 216 mg, 1.20 mmol). After aqueous workup, purification by column chromatography on silica gel (n-pentane/Et2O 20:1) afforded 3n; yield: 56.1 mg (169 μmol, 42%); white solid; mp 135–136 °C.

IR (ATR): 2906, 2849, 1561, 1480, 1452, 1272, 1041, 924, 800 cm–1.

HRMS (ESI): m/z (%) = 334 ([M + H]+, 2); 332 ([M + H]+, 100); 79Br. HRMS (ESI): m/z calcld for C17H20NO Br+ [M + Br]+: 330.2645; found: 330.2648.

2-[(3R,5R,7R)-Adamantan-1-yl]-5-chlorobenzo[d]oxazole (3k)
The general procedure was followed using benzoxazole 1k (533 mg, 0.40 mmol) and 1-adamantanecarboxylic acid (2; 216 mg, 1.20 mmol) for 48 h. After aqueous workup, purification by column chromatography on silica gel (n-pentane/Et2O 20:1) afforded 3k; yield: 78.2 mg (198 μmol, 50%); white solid; mp 150–152 °C.

IR (ATR): 2915, 2851, 1609, 1564, 1460, 1039, 819, 800, 702, 599 cm–1.

HRMS (ESI): m/z (%) = 267 ([M + H]+, 100), 135 (60). HRMS (ESI): m/z calcld for C18H22NO+ [M + H]+: 268.1696; found: 268.1702.

2-[(3R,5R,7R)-Adamantan-1-yl]-5-bromobenzo[d]oxazole (3m)
The general procedure was followed using benzoxazole 1m (792 mg, 0.40 mmol) and 1-adamantanecarboxylic acid (2; 216 mg, 1.20 mmol) for 48 h. After aqueous workup, purification by column chromatography on silica gel (n-pentane/Et2O 20:1) afforded 3m; yield: 56.1 mg (169 μmol, 42%); white solid; mp 135–136 °C.

IR (ATR): 2906, 2849, 1561, 1452, 1264, 1044, 801, 739, 704 cm–1.

HRMS (ESI): m/z (%) = 332 ([M + Na]+, 2); 310 ([M + H]+, 100%); 79Br. HRMS (ESI): m/z calcld for C17H20NO+ Br+ [M + Br]+: 310.2165; found: 310.2168.
The general procedure was followed using benzoxazole 1p (87.7 mg, 0.40 mmol) and 1-adamantanecarboxylic acid (72.0 mg, 0.40 mmol) for 48 h. After aqueous workup, purification by column chromatography on silica gel (n-pentane/Et2O 1:1) afforded 3q; yield: 80.0 mg (244 μmol, 61%); white solid; mp 185–187 °C.

IR (ATR): 2904, 1710, 1291, 1268, 1244, 1154, 1044, 943, 777 cm⁻¹.

\[ \text{HRMS (ESI): m/z} = 329.1969; \text{found:} 329.2018. \]

\[ \text{MS (EI): m/z} = 288.1153. \]

The analytical data are in accordance with those reported in the literature.\textsuperscript{21}

\[ 8-[[3R,5R,7R]-Adamantan-1-yl]-7-[2-(methoxymethoxy)propyl]-1,3-dimethyl-3,7-dihydro-1H-purine-2,6-dione (3s) \]

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.

\[ \text{IR (ATR): 2890, 1165, 1536, 1426, 1382, 1137, 1105, 1035, 743 cm}^{-1}. \]

\[ \text{HRMS (ESI): m/z} = 439 ([M + Na]⁺, 100), 417 ([M + H]⁺, 99). \]

\[ \text{HRMS (ESI): m/z} = 439.2316; \text{found:} 439.2319. \]

\[ \text{IR (ATR): 2895, 1700, 1660, 1539, 1426, 1361, 1223, 982, 743 cm}^{-1}. \]

\[ \text{HRMS (ESI): m/z} = 329 ([M + H]⁺, 100). \]

\[ \text{HRMS (ESI): m/z} = 329.1972; \text{found:} 329.1969. \]
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Supporting Information

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