Bromine-Radical-Mediated Site-Selective Allylation of C(sp³)–H Bonds

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Abstract The C(sp³)–H allylation of alkanes is investigated by using allyl bromides under radical reaction conditions. In many cases, methine C–H allylation preceded methylene and methyl C–H allylation with complete or a high degree of site selectivity. The C–H allylation of allylic compounds, such as allylbenezene, gives 1,5-dienes with the SH2 reactions of the allyl radicals occurring at the less hindered carbon.

Key words C(sp³)–H allylation, bromine radicals, SH2 reaction, site selectivity

Site-selective alkyl C–H functionalization has become a growing area of research, and useful catalytic methods have appeared in recent years. S$_2$H$_2$-type hydrogen abstraction has excellent potential for allyl C–H functionalization, and we and the Pavia group have jointly been engaged in the development of C–H functionalization methods using the decatungstate anion as a photocatalyst. Interestingly, we found that both the polar and steric effects in the S$_2$H$_2$ transition states strongly affect the site selectivity in C–H functionalization of compounds possessing a polar functionality, such as ketones, esters, nitriles, and pyridylalkanes. Radical bromination of saturated alkanes by molecular bromine has a long history, representing a textbook radical reaction (Scheme 1, eq 1). The site selectivity is in the order of methine C–H, methylene C–H, and methyl C–H, which is regarded as a reflection of the bond-dissociation energy of C–H bonds. We recently reported the results of DFT calculations with respect to the transition states derived from the hydrogen abstraction of C–H bonds by bromine radical, which are illustrated in Scheme 1. In 1941, Kharasch and co-workers reported methine selective C–H bromination of 2-methylpropane (Scheme 1). Similarly complete site selectivity was observed for the methine C–H bond in the bromination of isooctane (Scheme 1). Russell and Brown reported that methine selectivity with 2-methylpentane drops to a level of 90% (Scheme 1) and it was reasoned that this decrease was due to the increased number of methylene C–H bonds competing in the process.

Although allylic bromides are found to act as useful allylating reagents in a bromine-radical-mediated chain process, the site-selective C–H allylation of saturated alkanes has yet to be investigated. In this paper, we report our results on the C–H allylation of a variety of saturated alkanes by allyl bromides under radical chain reaction conditions.

In the first investigation, we carried out the allylation of isooctane (1a) with ethyl 2-(bromomethyl)acrylate (2a) using di-tert-butyl peroxide (DTBPO) as a radical initiator and potassium carbonate as a HBr scavenger. When the reaction mixture was heated at 130 °C for 24 hours, we were pleased...
to find that the envisaged methine-selective C–H allylation of 1a proceeded to give the expected product, ethyl 4,4,6,6-tetramethyl-2-methyleneheptanoate (3aa) (Scheme 2). In this case, the yield of 3aa was moderate due to the isomerization of the initially formed 3aa into the internal olefin product 4aa. A shorter reaction time of 8 hours suppressed the isomerization and improved the isolated yield of 3aa to 55%. The use of excess amounts of alkane 1a was crucial to obtain good yields of allylated products.11

Encouraged by this result, we next examined the generality of the allylation of several structurally diverse alkanes 1 with allyl bromides 2 (Table 1). The reactions of isooctane (1a) with [(3-bromoprop-1-en-2-yl)sulfonyl]benzene (2b) and 2-(bromomethyl)acrylonitrile (2c) proceeded with complete site selectivity to give the corresponding allylated products 3ab and 3ac (Table 1, entries 1 and 2). The reaction of 1a with (3-bromoprop-1-en-2-yl)benzene (2d) was sluggish, giving product 3ad in a low yield via methine C–H functionalization (entry 3). The C–H allylation of 3-methylpentane (1b) with 2a gave a mixture of methine and methylene C–H allylated products 3ba and 5ba in a 92:8 ratio (entry 4). The drop in the methine selectivity is due to the increased number of methylene C–H bonds. The reactions of 1b with 2b and 2c gave similar sets of products (entries 5 and 6). Interestingly the C–H allylation of 2,3-dimethylbutane (1c) with 2a gave a 62:38 mixture of 5ca and 3ca in 31% total yield (entry 7). The low methine site selectivity is due to the sterically congested methine C–H bonds, which hamper access by the bromine radical.

We then examined four cycloalkanes, 1d, 1e, 1f, and 1g. The reactions of cyclohexane (1d) with 2a and 2c took place to afford the corresponding products 3da and 3dc in 59% and 57% yields, respectively (Table 1, entries 8 and 9). The reaction of cyclopentane (1e) with 2a gave allylated cyclopentane 3ea in 41% yield (entry 10). The C–H allylation of methylcyclohexane (1f) with 2a proceeds with a high degree of site selectivity to give a mixture of methine C–H allylated product 3fa and other regioisomers in an 84:16 ratio (entry 11). The reaction of 1g with 2a gave an 86:14 mixture of 3ga and other isomers in a 37% yield (entry 12).

The proposed reaction mechanism for the present bromine-radical-mediated site-selective C–H allylation of alkanes is illustrated in Scheme 3 using the reaction of isooctane (1a) with 2a: (i) a tBuO radical is generated from DTBPO by homolysis under heating, (ii) the tBuO radical abstracts a hydrogen from alkane 1a to produce tertiary alkyl radical A, (iii) the radical A adds to allylic bromide 2a to form the radical intermediate B, which undergoes β-fission to give the allylated alkane 3aa and a bromine radical, and (iv) the liberated bromine radical abstracts a hydrogen site selectively from another molecule of 1a to produce the carbon radical A, thereby sustaining the radical chain.

Biographical Sketches

Ilhyong Ryu received his Ph.D. from Osaka University, Japan, in 1978. He was appointed as assistant professor at Osaka University in 1988 and promoted to associate professor in 1995. In 2000 he moved to Osaka Prefecture University as a full professor. Since 2016, he has held a chair professorship at National Chiao Tung University in Taiwan. He has been the recipient of many awards which include the Chemical Society of Japan Award for Creative Work (2004) and the Society Award for Synthetic Organic Chemistry, Japan (2014). His current research interests include new methodologies based on radical reactions and green catalytic approaches.
Table 1  Site Selectivity in the Br⁺ Induced C–H Allylation

<table>
<thead>
<tr>
<th>Entry</th>
<th>1</th>
<th>2</th>
<th>Products</th>
<th>Yield (%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="1a" alt="" /></td>
<td>2b</td>
<td>3ab</td>
<td>57</td>
</tr>
<tr>
<td>2</td>
<td>1a</td>
<td>2c</td>
<td>3ac</td>
<td>64</td>
</tr>
<tr>
<td>3</td>
<td>1a</td>
<td>2d</td>
<td>3ad</td>
<td>37</td>
</tr>
<tr>
<td>4</td>
<td><img src="1b" alt="" /></td>
<td>2a</td>
<td>3ba + 5ba</td>
<td>66 (92:8)&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>5</td>
<td><img src="1b" alt="" /></td>
<td>2b</td>
<td>3bb + 5bb</td>
<td>48 (83:17)&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>6</td>
<td><img src="1b" alt="" /></td>
<td>2c</td>
<td>3bc + 5bc</td>
<td>28 (91:9)&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>7</td>
<td><img src="1c" alt="" /></td>
<td>2a</td>
<td>3ca + 5ca</td>
<td>31&lt;sup&gt;d&lt;/sup&gt; (38:62)&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>8</td>
<td><img src="1d" alt="" /></td>
<td>2a</td>
<td>3da</td>
<td>59</td>
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<tr>
<td>9</td>
<td><img src="1d" alt="" /></td>
<td>2c</td>
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</tr>
<tr>
<td>10</td>
<td><img src="1e" alt="" /></td>
<td>2a</td>
<td>3ea</td>
<td>41</td>
</tr>
</tbody>
</table>

R–H + EWG → EWG + R\(\equiv\)C–CO₂Et

EWG:
- 2a: CO₂Et
- 2b: SO₂Ph
- 2c: CN
- 2d: Ph

Reagents:
- (t-BuO)₂ (20 mol%)
- K₂CO₃ (0.5 mmol)

Conditions:
- 130 °C, 8 h
- 1 (5 mL)
- 2 (0.5 mmol)
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The bromine radical smoothly abstracts a hydrogen from the allylic C–H bond of terminal alkenes, as we recently reported. We thought that the formation of allyl radicals by bromine-radical-induced C–H bond cleavage would be followed by allylation with allylic bromides at the least substituted site to give 1,5-dienes. As summarized in Scheme 4, both allylbenzene (1h) and p-allylanisole (1i) undergo the envisaged hydrogen abstraction and SH2'+ reaction at their termini to give the corresponding dienes 3ha and 3ia in acceptable yields. In these reactions, 1,2-epoxybutane was added as a HBr trap to significantly increase the yield. 1-Hexen-3-ol (1j) also participated in the allyl radical formation/allylation sequence. In the case of 1j, we obtained the δ,ε-unsaturated ketone 3ja via enol–keto tautomerization.

In summary, the C–H allylation of saturated alkanes with allyl bromides proceeds with good to excellent preference for the methine C–H bonds over methylene and methyl C–H bonds. These results are in good accordance with previously investigated C–H brominations of alkanes. The degree of the methine C–H preference is affected by both increased numbers of competing C–H bonds and steric congestion of the targeted methine C–H bond. In the case of allylic compounds, C–C bond formation took place at the less hindered site of the resulting allyl radical, which led to the formation of 1,5-dienes.

Thin-layer chromatography (TLC) was performed on Merck precoated plates (silica gel 60 F254, Art 5715, 0.25 mm). The products were purified by flash chromatography on silica gel (Kanto Chem. Co. Silica Gel 60N (spherical, neutral, 40–50 μm)); if necessary, they were further purified using recycling preparative HPLC (Japan Analytical Industry Co. Ltd., LC-918) equipped with GPC columns (JAIGEL-1H + JAIGEL-2H) with CHCl3 as the eluent. Infrared spectra were recorded on a JASCO FT/IR-4100 spectrophotometer and are reported as wavenumbers (cm–1). 1H NMR spectra were recorded using JEOL ECS400 (400 MHz), JEOL ECP500 (500 MHz) and Varian MR400 (400 MHz) spectrometers and referenced to the solvent peak at 7.26 ppm for CHCl3. 13C NMR spectra were recorded using JEOL JNM-ECS400 (100 MHz) and Varian MR400 (100 MHz) spectrometers and referenced to the solvent peak at 77.16 ppm for CHCl3. Splitting patterns are indicated as follows: br, broad; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. High-resolution mass spectrometry (HRMS) was performed using a JEOL MS700 spectrometer and ESI-QTOF (compact-NPC, Bruker). Analytical data for compounds 3ca, 3da, 3ea, and 5ca have already been reported.

Ethyl 4,4,6,6-Tetramethyl-2-methyleneheptanoate (3aa); Typical Procedure

Isooctane (1a) (5 mL, 30 mmol), ethyl 2-(bromomethyl)acrylate (2a) (96.5 mg, 0.5 mmol), potassium carbonate (69.1 mg, 0.5 mmol), and di-tert-butyl peroxide (120 °C, 10 h) were added to the mixture of 1h and 1i. The reaction mixture was stirred at 77.16 ppm for CHCl3. Splitting patterns are indicated as follows: br, broad; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. High-resolution mass spectrometry (HRMS) was performed using a JEOL MS700 spectrometer and ESI-QTOF (compact-NPC, Bruker). Analytical data for compounds 3ca, 3da, 3ea, and 5ca have already been reported.

Ethyl 4,4,6,6-Tetramethyl-2-methyleneheptanoate (3aa); Typical Procedure

Isooctane (1a) (5 mL, 30 mmol), ethyl 2-(bromomethyl)acrylate (2a) (96.5 mg, 0.5 mmol), potassium carbonate (69.1 mg, 0.5 mmol), and di-tert-butyl peroxide (DBTPO) (14.6 mg, 0.1 mmol) were added to a mixture of 1h and 1i. The reaction mixture was stirred at 77.16 ppm for CHCl3. Splitting patterns are indicated as follows: br, broad; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. High-resolution mass spectrometry (HRMS) was performed using a JEOL MS700 spectrometer and ESI-QTOF (compact-NPC, Bruker). Analytical data for compounds 3ca, 3da, 3ea, and 5ca have already been reported.
Ethyl (2Z)-2,4,4,6,6-Pentamethylhept-2-en-2-ynoate (4aa)

Yield: 82.5 mg (57%); yellow oil; \( R_f = 0.33 \) (hexane/\( \text{EtOAc} \), 20:1).

IR (neat): 2925, 2851, 1719, 1178 cm\(^{-1}\).

HRMS (ESI): \([M + Na]^+\) calcd for \( \text{C}_{14}\text{H}_{22}\text{O}_{2}\text{Na} \): 256.1294; found: 256.1293.

Ethyl 4-Ethyl-4-methyl-2-methylenehexanenitrile (3bc)

Yield: 21.2 mg (28%); colorless oil; \( R_f = 0.50 \) (hexane/\( \text{EtOAc} \), 10:1).

IR (neat): 2924, 2852, 1719, 1178 cm\(^{-1}\).

HRMS (ESI): \([M + Na]^+\) calcd for \( \text{C}_{10}\text{H}_{15}\text{NNa} \): 172.1097; found: 172.1102.

[(4-Ethyl-4-methylhex-1-en-2-yl)sulfonyl]benzene (3bb)

Yield: 65.2 mg (62%); colorless oil; \( R_f = 0.40 \) (hexane/\( \text{EtOAc} \), 20:1).

IR (neat): 2925, 2851, 1719, 1175 cm\(^{-1}\).

HRMS (ESI): \([M + Na]^+\) calcd for \( \text{C}_{10}\text{H}_{15}\text{NNa} \): 172.1097; found: 172.1102.

Ethyl 2-[(1-Methylcyclohexyl)methyl]acrylate (3fa)

Yield: 65.2 mg (62%); colorless oil; \( R_f = 0.40 \) (hexane/\( \text{EtOAc} \), 20:1).

IR (neat): 2925, 2851, 1719, 1153 cm\(^{-1}\).
Ethyl 2-[(1-Methylcyclopentyl)methyl]acrylate (3ga)
Yield: 36.3 mg (37%); colorless oil; Rf = 0.25 (hexane/EtOAc, 20:1).
IR (neat): 2954, 2871, 1719, 1161 cm⁻¹.
1H NMR (400 MHz, CDCl₃): δ = 0.82 (s, 3 H), 1.23–1.25 (m, 4 H), 1.28 (t, J = 7.6 Hz, 3 H), 1.39–1.50 (m, 6 H), 2.31 (s, 2 H), 4.17 (q, J = 7.2 Hz, 2 H), 5.43 (d, J = 1.2 Hz, 1 H), 6.16 (d, J = 1.6 Hz, 1 H).
13C NMR (100 MHz, CDCl₃): δ = 13.43 (C), 24.78, 26.27, 33.51, 34.15, 41.47, 57.21, 60.76, 127.05, 143.76, 148.62, 149.52 cm⁻¹.
EIMS: m/z (%) = 211 [M⁺ + H] + calcd for C₁₃H₂₃O₂: 211.1693; found: 211.1613.

Ethyl 2-(Methylene-6-phenylhex-5-enolate (3ha); Typical Procedure
Allylbenezene (1h) (1181.8 mg, 10.0 mmol), ethyl 2-(bromomethyl)acrylate (2a) (193.0 mg, 1.0 mmol), 1,2-epoxybutane (144.2 mg, 1.5 mmol), di-t-butyl peroxide (DBTPO) (29.2 mg, 0.2 mmol) were added to a 5 mL screw-capped test tube; this test tube was then purged with argon and sealed. The mixture was stirred at 120 °C for 16 h and then concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexane/EtOAc, 100:1) and by preparative HPLC (chloroform) to give product 3ha.
Yield: 126.7 mg (55%); colorless oil; Rf = 0.50 (hexane/EtOAc, 20:1).
IR (neat): 1725, 1182 cm⁻¹.
1H NMR (400 MHz, CDCl₃): δ = 1.30 (t, J = 7.2 Hz, 3 H), 2.40 (q, J = 6.8 Hz, 2 H), 2.49 (t, J = 7.6 Hz, 2 H), 4.21 (q, J = 6.8 Hz, 2 H), 5.56 (s, 1 H), 6.8–6.25 (m, 2 H), 6.42 (d, J = 15.6 Hz, 1 H), 7.16–7.33 (m, 5 H).
13C NMR (100 MHz, CDCl₃): δ = 14.12, 31.79 (two overlapping signals), 55.14, 60.53, 113.78, 124.83, 126.96, 127.26, 129.78, 130.35, 140.09, 158.63, 167.08 cm⁻¹.
IR (neat): 2933, 1714, 1607, 1509, 1176, 1138 cm⁻¹.

Ethyl 2-[(4-Methoxyphenyl)-2-Methylenehex-5-enoate (3ja)
Yield: 76.4 mg (36%); colorless oil; Rf = 0.25 (hexane/EtOAc, 20:1).
IR (neat): 2874, 1715, 1462 cm⁻¹.
1H NMR (400 MHz, CDCl₃): δ = 0.89–0.93 (t, J = 7.2 Hz, 3 H), 1.28 (t, J = 7.6 Hz, 3 H), 1.58–1.64 (m, 2 H), 1.76 (q, J = 7.6 Hz, 2 H), 2.30 (t, J = 8.0 Hz, 2 H), 2.36–2.44 (m, 4 H), 4.20 (q, J = 6.8 Hz, 2 H), 5.54 (s, 1 H), 6.16 (s, 1 H).
13C NMR (100 MHz, CDCl₃): δ = 13.42, 21.18, 64.94, 22.06, 30.92, 39.33, 43.48, 60.35, 124.70, 139.88, 166.77, 210.64.
EIMS: m/z (%) = 212 [M⁺] (2), 167 (35), 166 (54), 138 (59), 123 (65), 99 (53), 95 (78), 71 (100).

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Supporting Information
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References


(11) In the reaction shown in Scheme 2 a, decrease of the amount of isooctane from 5 mL to 2.5 mL resulted in a decrease of the yields of products 3aa (39%) and 4aa (6%).


