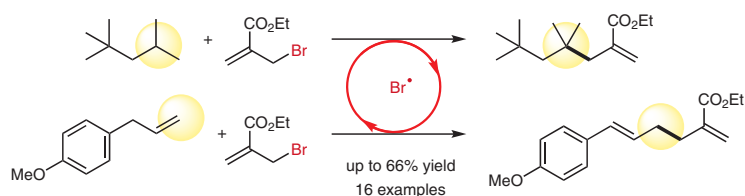


Bromine-Radical-Mediated Site-Selective Allylation of C(sp³)-H Bonds

Mitsuhiro Ueda^aAyami Maeda^aKanako Hamaoka^aMika Sasano^aTakahide Fukuyama^aIlhyong Ryu^{*a,b} 

^a Department of Chemistry, Graduate School of Science, Osaka Prefecture University, Sakai, Osaka, 599-8531, Japan

^b Department of Applied Chemistry, National Chiao Tung University, Hsinchu 30010, Taiwan
ryu@c.s.osakafu-u.ac.jp

Published as part of the 50 Years SYNTHESIS – Golden Anniversary Issue

Received: 12.10.2018

Accepted after revision: 26.11.2018

Published online: 07.01.2019

DOI: 10.1055/s-0037-1610413; Art ID: ss-2018-z0686-fa

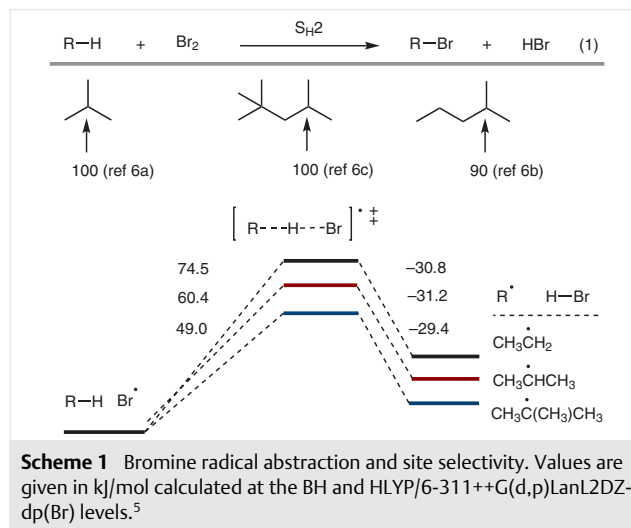
License terms:

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 allylbenzene, gives 1,5-dienes with the S_H2' reactions of the allyl radicals occurring at the less hindered carbon.

Key words C(sp³)-H allylation, bromine radicals, S_H2 reaction, S_H2' reaction, site selectivity

Site-selective alkyl C-H functionalization has become a growing area of research,¹ and useful catalytic methods have appeared in recent years.² S_H2-type hydrogen abstraction has excellent potential for alkyl 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_H2 transition states strongly affect the site selectivity in C-H functionalization of compounds possessing a polar functionality, such as ketones, esters, nitriles, and pyridylalkanes.^{3,4} 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 1.⁵ In 1941, Kharasch and co-workers reported methine selective C-H bromination of 2-methylpropane (Scheme 1).^{6a} Similarly

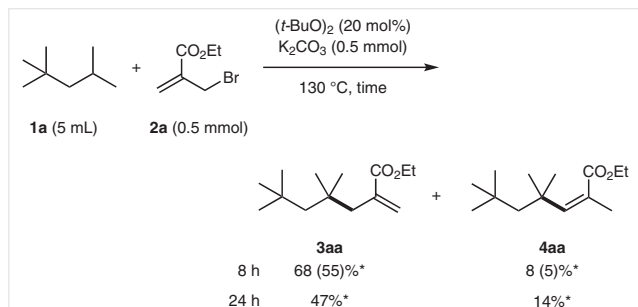
complete site selectivity was observed for the methine C-H bond in the bromination of isooctane (Scheme 1).^{6b} Russell and Brown reported that methine selectivity with 2-methylpentane drops to a level of 90% (Scheme 1),^{6c} and it was reasoned that this decrease was due to the increased number of methylene C-H bonds competing in the process.^{6d}



Although allylic bromides are found to act as useful allylating reagents in a bromine-radical-mediated chain process,^{7,8} the site-selective C-H allylation of saturated alkanes has yet to be investigated.^{9,10} 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



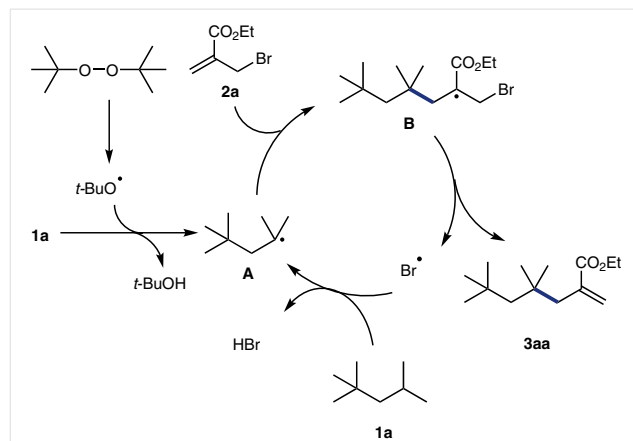
Scheme 2 Site-selective C–H allylation of isooctane. * NMR yields. Isolated yields are in parentheses.

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 *t*BuO radical is generated from DTBPO by homolysis under heating, (ii) the *t*BuO 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.



Scheme 3 Proposed radical chain mechanism

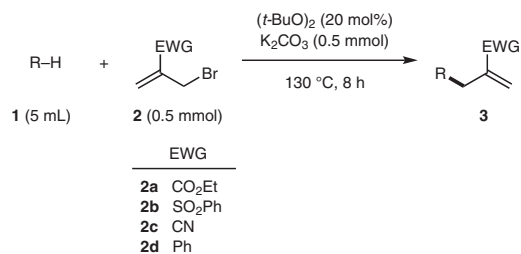
Biographical Sketches



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 Pre-

fecture 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^a

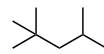
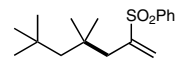
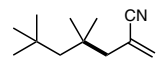
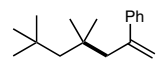
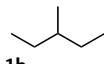
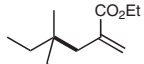
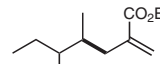
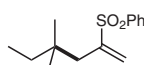
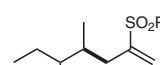
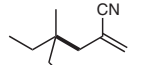
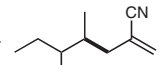
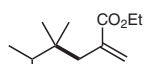
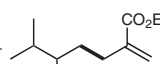

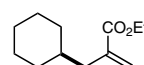

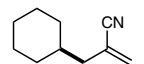

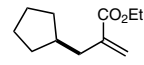

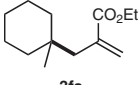

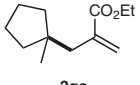
Entry	1	2	Products	Yield (%) ^b
1	 1a	2b	 3ab	57
2	1a	2c	 3ac	64
3	1a	2d	 3ad	37
4	 1b	2a	 3ba	66 (92:8) ^c
5	1b	2b	 5ba	
6	1b	2c	 3bb	48 (83:17) ^c
7	1b	2d	 5bb	
8	1b	2c	 3bc	28 (91:9) ^c
9	1b	2d	 5bc	
10	1b	2a	 3ca	31 ^d (38:62) ^c
11	1b	2b	 5ca	
12	 1c	2a	 3da	59
13	 1d	2c	 3dc	57
14	 1e	2a	 3ea	41

Table 1 (continued)

Entry	1	2	Products	Yield (%) ^b
11	 1f	2a	 3fa + regioisomers	62 (84:16) ^c
12	 1g	2a	 3ga + regioisomers	37 (86:14) ^c

^a Reaction conditions: **1** (5 mL), **2** (0.5 mmol), DTBPO (20 mol%), K₂CO₃ (0.5 mmol), 130 °C, 8 h.

^b Yield of isolated products.

^c Determined by ¹H NMR analysis of the crude reaction mixture.

^d Total yield of a mixture of **3ca** and **5ca**.

The bromine radical smoothly abstracts a hydrogen from the allylic C–H bond of terminal alkenes, as we recently reported.¹² 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 S_H2' 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 is (**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.

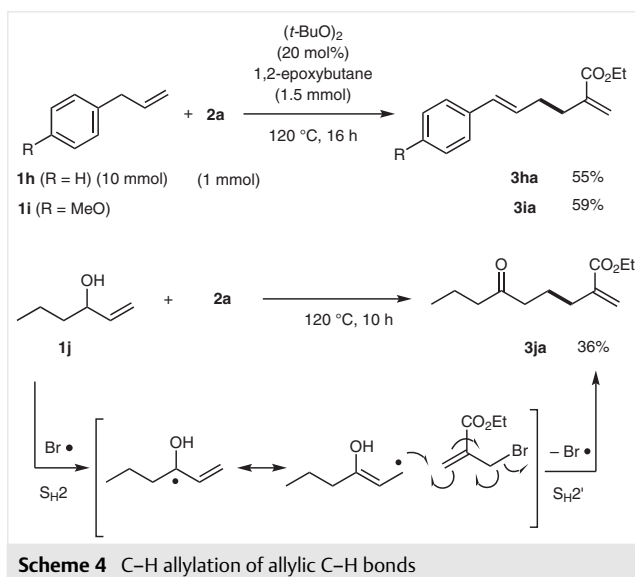
In summary, the C–H allylation of saturated alkanes with allyl bromides proceeds with good to excellent preference for the methine C–H bonds over methylene and meth-

yl 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 nm). The products were purified by flash chromatography on silica gel [Kanto Chem. Co. Silica Gel 60N (spherical, neutral, 40–50 μ m)]; 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**,¹³ **3da**,¹⁴ **3ea**,¹⁵ and **5ca**¹⁶ 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 (DTBPO) (14.6 mg, 0.1 mmol) were added to a 50 mL screw-capped pressure-resistant test tube; this test tube was then purged with argon and sealed. The mixture was stirred at 130 °C for 8 h and then filtered with Et₂O through a short plug of Celite. The filtrate was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel (hexane/EtOAc, 100:1) and by preparative HPLC (chloroform) to give product **3aa**. A small amount of isomerized product **4aa** was also obtained.



Yield: 58.5 mg (55%); yellow oil; R_f = 0.33 (hexane/EtOAc, 20:1).

IR (neat): 2953, 1720, 1626 cm^{-1} .

^1H NMR (400 MHz, CDCl_3): δ = 0.93 (s, 6 H), 0.99 (s, 9 H), 1.28–1.32 (m, 5 H), 2.35 (s, 2 H), 4.20 (q, J = 7.2 Hz, 2 H), 5.43 (s, 1 H), 6.16 (d, J = 2.0 Hz, 1 H).

^{13}C NMR (100 MHz, CDCl_3): δ = 14.42, 27.87, 32.22, 32.43, 36.01, 45.56, 55.40, 60.63, 127.17, 139.17, 168.59.

EIMS: m/z (%) = 226 [M^+] (2), 181 [$\text{M}^+ - \text{OEt}$] (7), 155 (29), 114 (100), 113 (28), 109 (28), 86 (21), 57 (97).

HRMS (EI): m/z [$\text{M} - \text{OEt}$] $^+$ calcd for $\text{C}_{12}\text{H}_{21}\text{O}$: 181.1587; found: 181.1589.

Ethyl (Z)-2,4,4,6,6-Pentamethylhept-2-enoate (4aa)

Yield: 5.66 mg (5%); yellow oil; R_f = 0.33 (hexane/EtOAc, 20:1).

IR (neat): 2955, 2903, 1710, 1247 cm^{-1} .

^1H NMR (400 MHz, CDCl_3): δ = 0.95 (s, 9 H), 1.22 (s, 6 H), 1.28 (t, J = 7.5 Hz, 3 H), 1.53 (s, 2 H), 1.95 (s, 3 H), 4.18 (q, J = 7.5 Hz, 2 H), 6.86 (s, 1 H).

^{13}C NMR (100 MHz, CDCl_3): δ = 13.37, 14.43, 30.62, 31.83, 32.28, 37.95, 56.70, 60.64, 125.11, 151.90, 169.54.

HRMS (ESI): m/z [$\text{M} + \text{Na}$] $^+$ calcd for $\text{C}_{14}\text{H}_{26}\text{O}_2\text{Na}$: 249.1825; found: 249.1825.

[(4,4,6,6-Tetramethylhept-1-en-2-yl)sulfonyl]benzene (3ab)

Yield: 83.9 mg (57%); yellow oil; R_f = 0.15 (hexane/EtOAc, 30:1).

IR (neat): 2956, 1446, 1365, 1151 cm^{-1} .

^1H NMR (400 MHz, CDCl_3): δ = 0.93 (s, 9 H), 0.99 (s, 6 H), 1.25 (s, 2 H), 2.28 (s, 2 H), 5.90 (s, 1 H), 6.49 (s, 1 H), 7.52 (t, J = 7.2 Hz, 2 H), 7.60 (t, J = 7.2 Hz, 1 H), 7.88 (d, J = 7.2 Hz, 2 H).

^{13}C NMR (100 MHz, CDCl_3): δ = 28.70, 32.07, 32.33, 36.23, 42.44, 55.03, 126.76, 128.50, 129.22, 133.42, 139.51, 148.98.

HRMS (ESI): m/z [$\text{M} + \text{Na}$] $^+$ calcd for $\text{C}_{17}\text{H}_{26}\text{O}_2\text{NaS}$: 317.1546; found: 317.1554.

4,4,6,6-Tetramethyl-2-methyleneheptanenitrile (3ac)

Yield: 57.4 mg (64%); yellow oil; R_f = 0.45 (hexane/EtOAc, 30:1).

IR (neat): 2953, 2902, 2221, 1473, 1367 cm^{-1} .

^1H NMR (400 MHz, CDCl_3): δ = 1.01 (s, 9 H), 1.07 (s, 6 H), 1.33 (s, 2 H), 2.21 (s, 2 H), 5.67 (s, 1 H), 5.98 (s, 1 H).

^{13}C NMR (100 MHz, CDCl_3): δ = 28.24, 32.15, 32.45, 36.12, 49.58, 54.69, 120.30, 120.59, 134.28.

EIMS: m/z (%) = 180 [M^+] (32), 124 (31), 113 [$\text{M}^+ - \text{C}_4\text{H}_4\text{N}$] (20), 127 (29), 57 (100).

HRMS (EI): m/z [$\text{M} + \text{H}$] $^+$ calcd for $\text{C}_{12}\text{H}_{22}\text{N}$: 180.1747; found: 180.1744.

(4,4,6,6-Tetramethylhept-1-en-2-yl)benzene (3ad)

Yield: 42.6 mg (37%); colorless oil; R_f = 0.75 (hexane).

IR (neat): 2951, 2871, 1471, 1365 cm^{-1} .

^1H NMR (400 MHz, CDCl_3): δ = 0.83 (s, 6 H), 0.95 (s, 9 H), 1.25 (s, 2 H), 2.53 (s, 2 H), 5.01 (s, 1 H), 5.23 (s, 1 H), 7.21 (t, J = 7.6 Hz, 1 H), 7.29 (t, J = 7.6 Hz, 2 H), 7.35 (d, J = 8.0 Hz, 2 H).

^{13}C NMR (100 MHz, CDCl_3): δ = 29.02, 32.26, 32.44, 36.40, 50.11, 56.02, 117.10, 126.75, 126.99, 128.22, 144.34, 147.72.

HRMS (ESI): m/z [$\text{M} + \text{Na}$] $^+$ calcd for $\text{C}_{17}\text{H}_{26}\text{Na}$: 253.1927; found: 253.0922.

Ethyl 4-Ethyl-4-methyl-2-methylenehexanoate (3ba)

Yield: 65.4 mg (66%); colorless oil; R_f = 0.40 (hexane/EtOAc, 20:1).

IR (neat): 2965, 2938, 1720, 1176 cm^{-1} .

^1H NMR (500 MHz, CDCl_3): δ = 0.73 (s, 3 H), 0.80 (t, J = 7.5 Hz, 6 H), 1.22 (m, 4 H), 1.29 (t, J = 8.5 Hz, 3 H), 2.28 (s, 2 H), 4.19 (q, J = 7.0 Hz, 2 H), 5.42 (s, 1 H), 6.15 (s, 1 H).

^{13}C NMR (100 MHz, CDCl_3): δ = 8.10, 14.30, 23.46, 30.49, 36.51, 39.84, 60.75, 126.79, 139.25, 168.67.

HRMS (ESI): m/z [$\text{M} + \text{Na}$] $^+$ calcd for $\text{C}_{12}\text{H}_{22}\text{O}_2\text{Na}$: 221.1512; found: 221.1513.

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

Yield: 63.9 mg (48%); orange oil; R_f = 0.20 (hexane/EtOAc, 20:1).

IR (neat): 2965, 2938, 1305, 1148 cm^{-1} .

^1H NMR (400 MHz, CDCl_3): δ = 0.74 (t, J = 6.4 Hz, 6 H), 0.78 (s, 3 H), 1.23 (q, J = 7.2 Hz, 4 H), 2.17 (s, 2 H), 5.85 (s, 1 H), 6.49 (s, 1 H), 7.54 (t, J = 7.2 Hz, 2 H), 7.62 (t, J = 8.0 Hz, 1 H), 7.87 (d, J = 8.4 Hz, 2 H).

^{13}C NMR (100 MHz, CDCl_3): δ = 8.03, 24.02, 30.82, 36.54, 36.83, 126.23, 128.49, 129.21, 133.42, 139.40, 148.73.

EIMS: m/z (%) = 237 [$\text{M}^+ - \text{C}_2\text{H}_5$] (5), 182 (100), 142 (26), 125 [$\text{M}^+ - \text{SO}_2\text{Ph}$] (61), 95 (29), 85 (41), 83 (23), 78 (21), 77 (23).

HRMS (EI): m/z [$\text{M} - \text{C}_2\text{H}_5$] $^+$ calcd for $\text{C}_{13}\text{H}_{17}\text{O}_2\text{S}$: 237.0944; found: 237.0946.

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

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

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

^1H NMR (400 MHz, CDCl_3): δ = 0.83 (t, J = 6.0 Hz, 6 H), 0.89 (s, 3 H), 1.28–1.33 (m, 4 H), 2.15 (s, 2 H), 5.67 (d, J = 1.0 Hz, 1 H), 5.96 (d, J = 1.0 Hz, 1 H).

^{13}C NMR (100 MHz, CDCl_3): δ = 7.99, 23.71, 30.60, 36.66, 43.45, 120.09, 120.49, 133.93.

EIMS: m/z (%) = 152 [$\text{M}^+ + \text{H}$] (43), 149 (19), 121 (11), 118 (23), 85 (96), 83 (100), 57 (51).

HRMS (ESI): m/z [$\text{M} + \text{Na}$] $^+$ calcd for $\text{C}_{10}\text{H}_{17}\text{NNa}$: 174.1253; found: 174.1254.

2-(Cyclohexylmethyl)acrylonitrile (3dc)

Yield: 42.5 mg (57%); yellow oil; R_f = 0.40 (hexane/EtOAc, 20:1).

IR (neat): 2924, 2852, 2222, 1449, 940 cm^{-1} .

^1H NMR (400 MHz, CDCl_3): δ = 0.86–0.96 (m, 2 H), 1.08–1.34 (m, 4 H), 1.51–1.78 (m, 5 H), 2.14 (d, J = 9.0 Hz, 2 H), 5.66 (d, J = 1.5 Hz, 1 H), 5.86 (s, 1 H).

^{13}C NMR (100 MHz, CDCl_3): δ = 26.07, 26.36, 32.72, 36.14, 42.61, 119.07, 131.32.

HRMS (ESI): m/z [$\text{M} + \text{Na}$] $^+$ calcd for $\text{C}_{10}\text{H}_{15}\text{NNa}$: 172.1097; found: 172.1095.

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

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

IR (neat): 2925, 2851, 1719, 1153 cm^{-1} .

^1H NMR (400 MHz, CDCl_3): 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).

^{13}C NMR (100 MHz, CDCl_3): δ = 14.33, 22.18, 24.27, 26.50, 34.01, 37.56, 43.49, 60.76, 127.05, 138.76, 168.62.

EIMS: m/z (%) = 211 [M^+ + H] (59), 182 (100), 169 (59), 116 (24), 115 (67), 101 (30), 97 (100), 55 (51).

HRMS (EI): m/z [$\text{M} + \text{H}$] $^+$ calcd for $\text{C}_{13}\text{H}_{23}\text{O}_2$: 211.1693; found: 211.1613.

Ethyl 2-[(1-Methylcyclopentyl)methyl]acrylate (3ga)

Yield: 36.3 mg (37%); colorless oil; R_f = 0.50 (hexane/EtOAc, 10:1).

IR (neat): 2954, 2871, 1719, 1161 cm^{-1} .

^1H NMR (500 MHz, CDCl_3): δ = 0.89 (s, 3 H), 1.24–1.32 (m, 5 H), 1.38–1.45 (m, 2 H), 1.61–1.65 (m, 4 H), 2.38 (s, 2 H), 4.20 (q, J = 7.0 Hz, 2 H), 5.51 (s, 1 H), 6.15 (d, J = 1.5 Hz, 1 H).

^{13}C NMR (100 MHz, CDCl_3): δ = 14.33, 23.97, 25.62, 38.87, 42.31, 43.10, 60.78, 126.72, 139.65, 168.54.

HRMS (ESI): m/z [$\text{M} + \text{Na}$] $^+$ calcd for $\text{C}_{12}\text{H}_{20}\text{O}_2\text{Na}$: 219.1356; found: 219.1356.

Ethyl (E)-2-Methylene-6-phenylhex-5-enoate (3ha); Typical Procedure

Allylbenzene (**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), and di-*tert*-butyl peroxide (DTBPO) (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; R_f = 0.50 (hexane/EtOAc, 20:1).

IR (neat): 1725, 1182 cm^{-1} .

^1H NMR (400 MHz, CDCl_3): 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), 6.18–6.25 (m, 2 H), 6.42 (d, J = 15.6 Hz, 1 H), 7.16–7.33 (m, 5 H).

^{13}C NMR (100 MHz, CDCl_3): δ = 14.13, 31.83, 31.98, 60.75, 125.11, 126.07, 127.05, 128.57, 129.65, 130.63, 137.72, 140.20, 167.25.

EIMS: m/z (%) = 230 [M^+] (3), 155 (28), 140 (53), 117 (75), 111 (48), 91 (100).

HRMS (EI): m/z [M] $^+$ calcd for $\text{C}_{15}\text{H}_{18}\text{O}_2$: 230.1307; found: 230.1307.

Ethyl (E)-6-(4-Methoxyphenyl)-2-methylenehex-5-enoate (3ia)

Yield: 153.6 mg (59%); colorless oil; R_f = 0.50 (hexane/EtOAc, 20:1).

^1H NMR (400 MHz, CDCl_3): δ = 1.30 (t, J = 7.2 Hz, 3 H), 2.37 (q, J = 6.8 Hz, 2 H), 2.48 (t, J = 7.6 Hz, 2 H), 3.80 (s, 3 H), 4.21 (q, J = 6.8 Hz, 2 H), 5.56 (s, 1 H), 6.04–6.07 (m, 1 H), 6.18 (s, 1 H), 6.34 (d, J = 15.6 Hz, 1 H), 6.82–6.84 (m, 2 H), 7.20–7.27 (m, 2 H).

^{13}C NMR (100 MHz, CDCl_3): 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.

IR (neat): 2933, 1714, 1607, 1509, 1176, 1138 cm^{-1} .

EIMS: m/z (%) = 260 [M^+] (9), 148 (11), 147 (100), 121 (10), 115 (12), 91 (21).

HRMS (EI): m/z [M] $^+$ calcd for $\text{C}_{16}\text{H}_{20}\text{O}_3$: 260.1412; found: 260.1411.

Ethyl 2-Methylene-6-oxononanoate (3ja)

Yield: 76.4 mg (36%); colorless oil; R_f = 0.25 (hexane/EtOAc, 20:1).

IR (neat): 2874, 1715, 1462 cm^{-1} .

^1H NMR (400 MHz, CDCl_3): 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).

^{13}C NMR (100 MHz, CDCl_3): δ = 13.42, 13.88, 16.94, 22.06, 30.57, 39.33, 44.38, 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).

HRMS (EI): m/z [M] $^+$ calcd for $\text{C}_{12}\text{H}_{20}\text{O}_3$: 212.1412; found: 212.1415.

Funding Information

This work was supported by Grants-in-Aid for Scientific Research (A) (no. 26248031) from JSPS and Scientific Research on Innovative Areas 2707 Middle Molecular Strategy (no. 15H05850) from MEXT.

Acknowledgment

We thank Kazuya Kamikawa for collecting additional spectral data.

Supporting Information

Supporting information for this article is available online at <https://doi.org/10.1055/s-0037-1610413>.

References

- (1) For reviews on site-selective $\text{C}(\text{sp}^3)\text{--H}$ functionalization, see: (a) Zhou, M.; Crabtree, R. H. *Chem. Soc. Rev.* **2011**, *40*, 1875. (b) Che, C.-M.; Lo, V. K.-Y.; Zhou, C.-Y.; Huang, J.-S. *Chem. Soc. Rev.* **2011**, *40*, 1950. (c) Brückl, T.; Baxter, R. D.; Ishihara, Y.; Baran, P. S. *Acc. Chem. Res.* **2012**, *45*, 826. (d) Liu, W.; Groves, J. T. *Acc. Chem. Res.* **2015**, *48*, 1727. (e) Hartwig, J. F.; Larsen, M. A. *ACS. Cent. Sci.* **2016**, *2*, 281. (f) *C–H Activation*, In *Topics in Current Chemistry*; Yu, J.-Q.; Shi, Z., Ed.; Springer-Verlag: Berlin, **2010**. (g) Milan, M.; Salamone, M.; Costas, M.; Bietti, M. *Acc. Chem. Res.* **2018**, *51*, 1984. (h) White, M. C.; Zhao, J. J. *Am. Chem. Soc.* **2018**, *140*, 13988.
- (2) For selected recent papers on site-selective $\text{C}(\text{sp}^3)\text{--H}$ functionalization, see: (a) Adams, A. M.; Du Bois, J.; Malik, H. A. *Org. Lett.* **2015**, *17*, 6066. (b) Cuthbertson, J. D.; MacMillan, D. W. C. *Nature* **2015**, *519*, 74. (c) Lee, M.; Sanford, M. S. *J. Am. Chem. Soc.* **2015**, *137*, 12796. (d) Miao, J.; Yang, K.; Kurek, M.; Ge, H. *Org. Lett.* **2015**, *17*, 3738. (e) Huang, X.; Groves, J. T. *ACS Catal.* **2016**, *6*, 751. (f) Chu, J. C. K.; Rovis, T. *Nature* **2016**, *539*, 272. (g) Kawamata, Y.; Yan, M.; Liu, Z.; Bao, D.-H.; Chen, J.; Starr, J. T.; Baran, P. S. *J. Am. Chem. Soc.* **2017**, *139*, 7448. (h) Mbofana, C. T.; Chong, E.; Lawniczak, J.; Sanford, M. S. *Org. Lett.* **2016**, *18*, 4258. (i) Liu, Y.; Ge, H. *Nat. Chem.* **2017**, *9*, 26. (j) Nanjo, T.; de Lucca, E. C. Jr.; White, M. C. *J. Am. Chem. Soc.* **2017**, *139*, 14586. (k) Liao, K.; Pickel, T. C.; Boyarskikh, V.; Bacsa, J.; Musaev, D. G.; Davies, H. M. L. *Nature* **2017**, *551*, 609.
- (3) (a) Okada, M.; Fukuyama, T.; Yamada, K.; Ryu, I.; Ravelli, D.; Fagnoni, M. *Chem. Sci.* **2014**, *5*, 2893. (b) Okada, M.; Yamada, K.; Fukuyama, T.; Ravelli, D.; Fagnoni, M.; Ryu, I. *J. Org. Chem.* **2015**,

- 80, 9365. (c) Yamada, K.; Okada, M.; Fukuyama, T.; Ravelli, D.; Fagnoni, M.; Ryu, I. *Org. Lett.* **2015**, *17*, 1292. (d) Yamada, K.; Fukuyama, T.; Fujii, S.; Ravelli, D.; Fagnoni, M.; Ryu, I. *Chem. Eur. J.* **2017**, *23*, 8615. (e) Quattrini, M. C.; Fujii, S.; Yamada, K.; Fukuyama, T.; Ravelli, D.; Fagnoni, M.; Ryu, I. *Chem. Commun.* **2017**, *53*, 2335. (f) Fukuyama, T.; Nishikawa, T.; Yamada, K.; Ravelli, D.; Fagnoni, M.; Ryu, I. *Org. Lett.* **2017**, *19*, 6436. (g) Fukuyama, T.; Yamada, K.; Nishikawa, T.; Ravelli, D.; Fagnoni, M.; Ryu, I. *Chem. Lett.* **2018**, *47*, 207.
- (4) For a perspective, see: Ravelli, D.; Fagnoni, M.; Fukuyama, T.; Nishikawa, T.; Ryu, I. *ACS Catal.* **2018**, *8*, 701.
- (5) Manabe, Y.; Fukase, K.; Matsubara, H.; Hino, Y.; Fukuyama, T.; Ryu, I. *Chem. Eur. J.* **2014**, *20*, 12750.
- (6) For site-selective radical C–H bromination, see: (a) Kharasch, M. S.; Hered, W.; Mayo, F. R. *J. Org. Chem.* **1941**, *6*, 818. (b) Jiang, X.; Shen, M.; Tang, Y.; Li, C. *Tetrahedron Lett.* **2005**, *46*, 487. (c) Russell, G. A.; Brown, H. C. *J. Am. Chem. Soc.* **1955**, *77*, 4025. (d) Schmidt, V. A.; Quinn, R. K.; Brusoe, A. T.; Alexanian, E. J. *J. Am. Chem. Soc.* **2014**, *136*, 14389.
- (7) (a) Tanko, J. M.; Sadeghipour, M. *Angew. Chem. Int. Ed.* **1999**, *38*, 159. (b) Struss, J. A.; Sadeghipour, M.; Tanko, J. M. *Tetrahedron Lett.* **2009**, *50*, 2119.
- (8) (a) Kippo, T.; Fukuyama, T.; Ryu, I. *Org. Lett.* **2010**, *12*, 4006. (b) Kippo, T.; Fukuyama, T.; Ryu, I. *Org. Lett.* **2011**, *13*, 3864. (c) Kippo, T.; Hamaoka, K.; Ryu, I. *J. Am. Chem. Soc.* **2013**, *135*, 632. (d) Kippo, T.; Ryu, I. *Chem. Commun.* **2014**, *50*, 5993. (e) Kippo, T.; Kimura, Y.; Maeda, A.; Matsubara, H.; Fukuyama, T.; Ryu, I. *Org. Chem. Front.* **2014**, *1*, 755. (f) Kippo, T.; Hamaoka, K.; Ueda, M.; Fukuyama, T.; Ryu, I. *Tetrahedron* **2016**, *72*, 7866. (g) Kippo, T.; Kimura, Y.; Ueda, M.; Ryu, I. *Synlett* **2017**, *28*, 1733. (h) Kippo, T.; Hamaoka, K.; Ueda, M.; Fukuyama, T.; Ryu, I. *Org. Lett.* **2017**, *19*, 5198.
- (9) For radical allylations of alkane C(sp³)–H bonds, see: (a) Xiang, J.; Evarts, J.; Rivkin, A.; Curran, D. P.; Fuchs, P. L. *Tetrahedron Lett.* **1998**, *39*, 4163. (b) Kamijo, S.; Kamijo, K.; Maruoka, K.; Murafuji, T. *Org. Lett.* **2016**, *18*, 6516. (c) Zhang, J.; Li, Y.; Zhang, F.; Hu, C.; Chen, Y. *Angew. Chem. Int. Ed.* **2016**, *55*, 1872.
- (10) For radical allylations of benzylic C(sp³)–H bonds and α -C(sp³)–H bonds of heteroatoms (N, O), see: (a) Patil, S.; Chen, L.; Tanko, J. M. *Eur. J. Org. Chem.* **2014**, 502. (b) Xuan, J.; Zeng, T.-T.; Feng, Z.-J.; Deng, Q.-H.; Chen, J.-R.; Lu, L.-Q.; Xiao, W.-J.; Alper, H. *Angew. Chem. Int. Ed.* **2015**, *54*, 1625. (c) Li, Y.; Zhang, J.; Li, D.; Chen, Y. *Org. Lett.* **2018**, *20*, 3296; and reference 7 cited therein.
- (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%).
- (12) Sumino, S.; Fusano, A.; Ryu, I. *Org. Lett.* **2013**, *15*, 2826.
- (13) Lüthy, M.; Darmency, V.; Renaud, P. *Eur. J. Org. Chem.* **2011**, 547.
- (14) Lévêque, C.; Chénneberg, L.; Corcé, V.; Ollivier, C.; Fensterbank, L. *Chem. Commun.* **2016**, *52*, 9877.
- (15) Corcé, V.; Chamoreau, L.-M.; Derat, E.; Goddard, J.-P.; Ollivier, C.; Fensterbank, L. *Angew. Chem. Int. Ed.* **2015**, *54*, 11414.
- (16) Reichle, M. A.; Breit, B. *Angew. Chem. Int. Ed.* **2012**, *51*, 5730.