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Evaluation of cyclopentyl methyl ether (CPME) as a solvent for radical reactions

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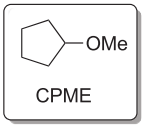
ABSTRACT

We have explored the potential of cyclopentyl methyl ether (CPME) as a solvent for radical reactions. Hydrostannation, hydrosilylation, hydrothiolation, and tributyltin hydride mediated reductions were successfully carried out in CPME. GC–MS analysis indicated that CPME degraded into methyl pentanoate, cyclopentanone, 2-cyclopenten-1-ol, and cyclopentanol under thermal radical conditions, albeit only slightly. We also achieved radical-containing one-pot reactions in CPME as a demonstration of its applicability to multi-step reactions.

1. Introduction

Cyclopentyl methyl ether (CPME), a new hydrophobic ethereal solvent developed by us, has some advantageous features that can compensate for the weaknesses of conventional ethereal solvents.[1] In particular, its less explosive nature as demonstrated by sluggish peroxide formation and a narrow explosion range is a major advantage over the most commonly used laboratory solvents, THF, and Et_2O (Fig. 1). High hydrophobicity and low vaporization energy enable easy recovery and reuse of CPME by the usual extractive workup and distillation methods. According to GlaxoSmithKline's solvent selection guide, CPME surpasses other ethereal solvents in terms of environmental, health, and safety aspects.[2] For these reasons, CPME has increasingly been used in both bench scale experiments and, importantly, process development for the synthesis of active pharmaceutical ingredients (API).



bp: 106 °C
mp: <–140 °C
vaporization energy (bp): 69.2 kcal/kg
solubility in water: 1.1 g/100 g (23 °C)
flash point: –1 °C
ignition point: 180 °C
explosion range: 1.1–9.9 vol%

Fig. 1. Selected physical properties of CPME.

In recent years, a broad range of organic reactions has successfully been performed in CPME, individually reported by various researchers.[3] However, systematic studies that focus on CPME itself are rather limited.[4] Additionally, to the best of our knowledge, the application of CPME to radical reactions and multi-step processes remains unaddressed. As radical reactions are generally performed at high temperatures in benzene, toluene, or other aromatic hydrocarbons,[5] the relatively high boiling point of CPME (bp 106 °C) makes it an appropriate solvent in which to execute these reactions. Furthermore, the bond dissociation energy of the α-CH bond adjacent to the ether oxygen in CPME is calculated to be 393.3 kJ/mol, which is larger by 2–3 kJ/mol than those of diisopropyl ether and THF.[6] This suggests that CPME would be resistant to hydrogen abstraction by radical species. In this study, we demonstrate that CPME is a suitable alternative to conventional solvents in radical additions and tributyltin hydride mediated reductions. We also characterize the CPME-derived degraded products under radical conditions and propose their degradation pathway. Furthermore, radical-containing one-pot processes in CPME are investigated.

2. Results and discussion

2.1. Radical additions in CPME

Initially, we explored radical additions of alkyl metal hydrides to terminal alkynes with 4-pentyn-1-ol (**1a**) and its TBS ether **1b** as

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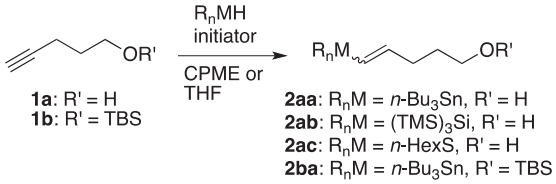
Table 1
Radical additions of *n*-Bu_3SnH, $(TMS)_3SiH$, or *n*-HexSH with **1a** and **1b**



1a: R' = H
1b: R' = TBS

2aa: R_nM = *n*-Bu_3Sn, R' = H
2ab: R_nM = $(TMS)_3Si$, R' = H
2ac: R_nM = *n*-HexS, R' = H
2ba: R_nM = *n*-Bu_3Sn, R' = TBS

Entry	Substrate	R_nMH	Initiator	Solvent	Temp/°C	Time/h	Yield[a]/%	*E*/*Z*[b]
1	**1a**	*n*-Bu_3SnH	V-65	CPME	70	3	93	84/16
2	**1a**	*n*-Bu_3SnH	V-65	THF	70	3	98	86/14
3	**1a**	$(TMS)_3SiH$	V-65	CPME	70	4	94	12/88
4	**1a**	$(TMS)_3SiH$	V-65	THF	70	4	95	11/89
5	**1a**	*n*-HexSH	AIBN	CPME	90	2	78	48/52
6	**1a**	*n*-HexSH	V-65	THF	70	3	83	48/52
7	**1b**	*n*-Bu_3SnH	AIBN	CPME	90	2	88	80/20
8	**1b**	*n*-Bu_3SnH	V-65	THF	70	3	91	95/5
9	**1b**	*n*-Bu_3SnH	Et_3B/O_2	CPME	rt	1	87	76/24

Abbreviations: V-65, [2,2′-azobis(2,4-dimethylvaleronitrile)]; AIBN, [2,2′-azobis(isobutyronitrile)].
[a] Isolated yield after silica gel chromatography.
[b] Determined by NMR analysis of the crude mixture.

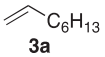
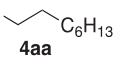
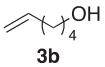
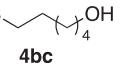
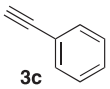
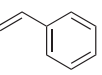
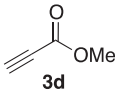
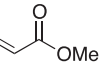
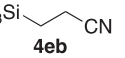
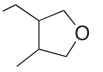
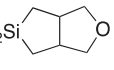
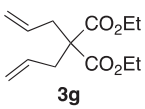
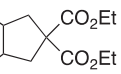
representative substrates (Table 1). All reactions were carried out in both CPME and THF to evaluate the performance of ethereal solvents. The results clearly showed that hydrostannation, hydrosilylation, and hydrothiolation were all effective in both CPME (78–94% yields) and THF (83–98% yields). The *E*/*Z* ratios were mostly independent of the solvent used. Et_3B/O_2 could also be applied as the radical initiator (entry 9).[7]

As CPME was found to be effective for these representative radical additions, we then explored the generality of the reaction by varying the substrates (Table 2). Notably, both intermolecular and intramolecular reactions took place efficiently in CPME to provide adducts **4aa**–**gc** in moderate to good yields, comparable to those with conventional solvents.[8] Successful examples of intramolecular reactions as shown in entries 8–11 indicated that direct hydrogen abstraction from the solvent by the initially generated secondary radicals was not significant. Tin, silicon, and thiyl radicals were all acceptable for these reactions.[9]

2.2. Radical deoxygenation and reduction in CPME

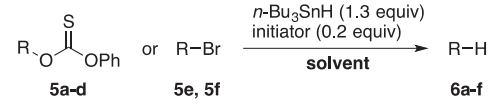
After identifying the adaptability of CPME to radical addition reactions, we then carried out Barton–McCombie radical deoxygenation as a second example (Table 3).[10] The representative primary and secondary thiocarbonates **5a**–**d** were prepared from the corresponding alcohols by treatment with phenyl chlorothionoformate and pyridine[10c] in 82–100% yields. Since we encountered difficulty in supplying tertiary thiocarbonates by the above method, alkyl bromides, generally prepared by bromination of the parent alcohols with HBr,[11] were alternatively submitted to reduction instead of tertiary thiocarbonates. Deoxygenation and reduction were carried out as follows. To a heated solution of thiocarbonates **5a**–**d** or bromides **5e**, **5f** in CPME was added dropwise a solution of *n*-Bu_3SnH and AIBN in CPME with a syringe pump over 30 min. After disappearance of the starting material as monitored by TLC, the reaction mixture was concentrated in vacuo and

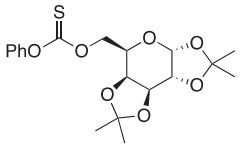
Table 2
Generality of radical additions in CPME[a]

Entry	Substrate	R_nMH	Product	Yield[b]/%
1	 **3a**	*n*-Bu_3SnH	*n*-Bu_3Sn  **4aa**	85
2	 **3b**	*n*-HexSH	*n*-HexS  **4bc**	89
3	 **3c**	$(TMS)_3SiH$	R_nM  **4cb**: R_nM = $(TMS)_3Si$ **4cc**: R_nM = *n*-HexS	**4cb**: 77 (*E*/*Z*=17/83)
4		*n*-HexSH		**4cc**: 76 (*E*/*Z*=83/17)
5	 **3d**	*n*-Bu_3SnH	R_nM  **4da**: R_nM = *n*-Bu_3Sn **4db**: R_nM = $(TMS)_3Si$	**4da**: 58 (*E*/*Z*=56/44)
6		$(TMS)_3SiH$		**4db**: 55 (*E*/*Z* <1/20)
7	 **3e**	$(TMS)_3SiH$	$(TMS)_3Si$  **4eb**	63
8	 **3f**	$(TMS)_3SiH$	R_nM  $(TMS)_2Si$  **4fb**: R_nM = $(TMS)_3Si$ **4fb'** **4fc**: R_nM = *n*-HexS	**4fb**: 48 (dr=68/32), **4fb′**: 39
9		*n*-HexSH		**4fc**: 42 (dr=61/39)
10	 **3g**	*n*-Bu_3SnH	R_nM  **4ga**: R_nM = *n*-Bu_3Sn **4gc**: R_nM = *n*-HexS	**4ga**: 95 (dr=67/33)
11		*n*-HexSH		**4gc**: 96 (dr=85/15)

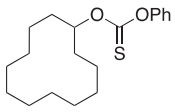
[a] General procedure: to a solution of alkene or alkyne (1 mmol) in CPME (2 mL for intermolecular reactions and 10 mL for intramolecular reactions) was added dropwise a solution of reductant (1.3 mmol) and AIBN (0.2 mmol) in CPME (2 mL) with a syringe pump over 30 min at 90 °C. The resulting mixture was stirred at 90 °C for 3–4 h before concentration and purification by flash column chromatography.
[b] Isolated yield after silica gel chromatography. The isomeric ratios were determined by NMR analyses of the crude mixture.

Table 3
Radical deoxygenation and reduction[a]

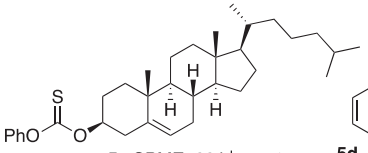




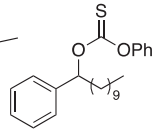
5a CPME, 2 h[b]: 76% (9%)[c]
toluene, 2 h[b]: 76% (13%)[c]
THF, 5 h: 61% (7%)[c]



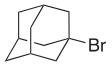
5b CPME, 2 h: 74%
toluene, 3 h: 85%
THF, 3 h: 96%



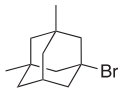
5c CPME, 22 h[b]: 75%
toluene, 24 h[b]: 70%
THF, 22 h: 62%



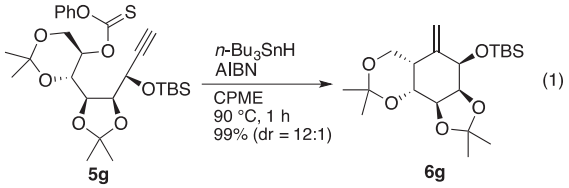
5d CPME, 1 h: 100%
toluene, 1 h: 79%[d]
THF, 1 h: 100%



5e CPME, 5 h: 51%
toluene, 5 h: 35%
THF, 5 h: 79%



5f CPME, 1 h: 100%
toluene, 1 h: 100%
THF, 1 h: 100%



[a] For reactions in CPME and toluene, AIBN was used as the initiator and the temperature was maintained at 90 °C, while in THF, V-65 was used as the initiator and the reaction was carried out at 70 °C.

[b] Reaction performed at reflux.

[c] Yields in parentheses refer to the recovery of the starting material.

[d] (*E*)-1-Phenyl-1-undecene was formed in 21% yield.

purified directly by 10% w/w K_2CO_3-silica gel column chromatography[12] to remove excess reagents, thiocarbonate-derived degraded products (i.e., phenol and carbonyl sulfide), and tin-derived byproducts. While not all examples listed in Table 3 were satisfactory, it was evident that CPME was generally acceptable and yields were comparable to those in toluene and THF. The only matter of concern was the boiling point of CPME, which hampered isolation of the sublimation product adamantane (**6e**) by the usual evaporation technique. Of special interest is that deoxygenation of the benzyl alcohol derivative **5d** in the ethereal solvents (CPME and THF) produced the reduction product **6d** quantitatively, while the corresponding reaction in toluene generated a significant amount of the β-elimination product [i.e., (*E*)-1-phenyl-1-undecene] as the minor component. Moreover, it should be noted that deoxygenative radical cyclization of the sugar-derived thiocarbonate **5g**[13] in CPME gave rise to the oxygenated methylenecyclohexane **6g** in quantitative yield with high diastereoselectivity (Eq. 1), which again suggested that hydrogen abstraction from CPME by the intermediary secondary radical did not compete with cyclization.

2.3. Degradation pathway of CPME under radical conditions

After evaluating the performance of CPME in general radical reactions, we turned our attention to the recycling of CPME, along with inspection of its integrity after the radical reaction. Thus, CPME used in the radical addition reaction between **1a** and *n*-Bu_3SnH was recovered by distillation and recycled four times before analysis by GC–MS. The yields of **2aa** and *E*/*Z* ratios were invariable with the conditions examined, while the purity of CPME slightly decreased (99.9%→99.4%) (Table 4). GC–MS analysis after four recycles revealed more than ten kinds of products in trace amounts, such as methyl pentanoate (**B**), cyclopentanone (**F**), cyclopentanol (**I**), and 2-cyclopenten-1-ol (**J**), which were assigned as the degradation products of CPME (Fig. 2).

On the basis of the GC–MS analysis, we deduced a possible degradation pathway for CPME under radical addition conditions. Initially, hydrogen abstraction at the tertiary position by a stannyl radical takes place to provide tertiary carbon radical (**i**), which reacts with dissolved oxygen to afford the peroxy radical (**ii**) (Scheme 1).

Table 4
Radical addition experiments between **1a** and *n*-Bu_3SnH with the recycled solvent[a]

Run	Yield of **2aa**[b]/% (*E*/*Z*)[c]	Recovery of CPME[d]/%	Purity of CPME[e]/%
1	95 (87/13)	95	99.9
2	94 (86/14)	91	ND[f]
3	95 (81/19)	92	ND[f]
4	94 (85/15)	83	99.4

[a] Each reaction was carried out in CPME by treating **1a** (1.0 equiv), *n*-Bu_3SnH (1.3 equiv), and AIBN (0.2 equiv) for 2 h at 90 °C.
[b] Isolated yield after 10% w/w K_2CO_3-silica gel column chromatography.
[c] Determined by ^1H NMR analysis of the crude mixture.
[d] CPME was recovered by distillation under reduced pressure at room temperature.
[e] Determined by GC.
[f] ND=not determined.

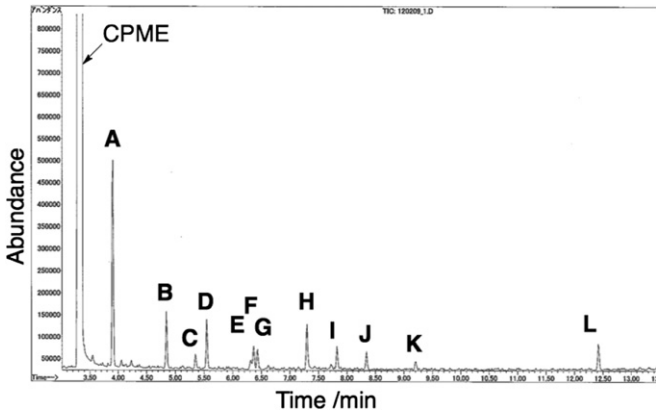
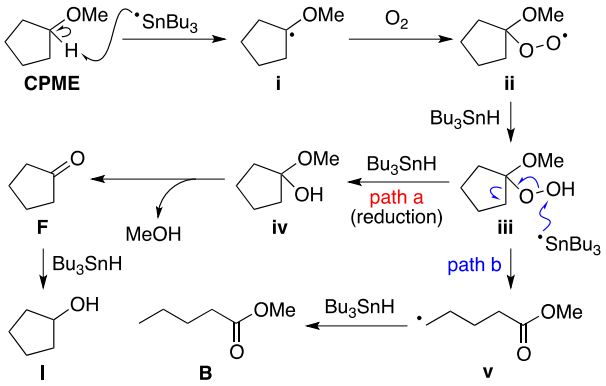


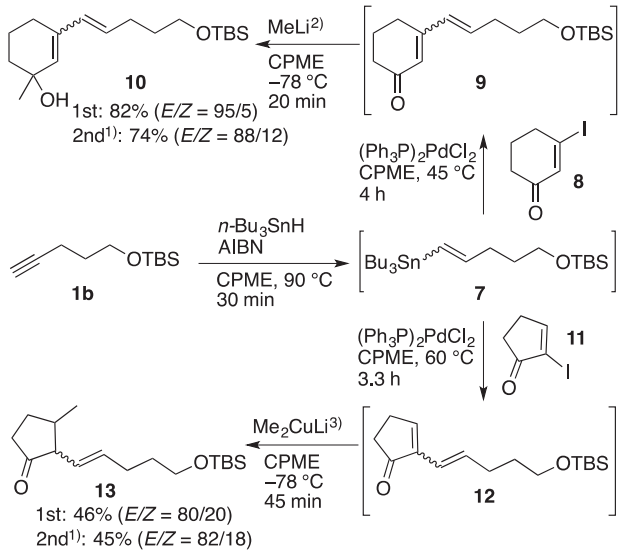
Fig. 2. GC–MS chromatogram of CPME after four recycles. Peak identifications were made by comparing the mass spectra with those in the reference library (Wiley Registry of Mass Spectral Database, Seventh Edition). **A**=Me_2CHCN; **B**=methyl pentanoate; **C**=$Me_2C{=}N{-}N{=}CMe_2$; **D**=*n*-butanol; **F**=cyclopentanone; **I**=cyclopentanol; **J**=2-cyclopenten-1-ol; **L**=AIBN; **E**, **G**, **H**, **K**=unidentifiable.



Scheme 1. Possible degradation pathway of CPME under radical addition conditions.

Upon hydrogen abstraction, the generated peroxide (**iii**) undergoes facile reduction to provide hemiacetal (**iv**) (path a), which degrades into cyclopentanone (**F**) with the exclusion of methanol. Further reduction by *n*-Bu_3SnH gives rise to cyclopentanol (**I**), although this process is sluggish.[14] Conversely, tributyltin radical-promoted degradation of the peroxide intermediate (**iii**) provokes C–C bond cleavage, which results in the formation of methyl pentanoate (**B**) through the primary radical (**v**) (path b). Although the mechanism for the formation of 2-cyclopenten-1-ol (**J**) remains to be determined, it can be assumed that it also originates from hydrogen abstraction at the tertiary carbon center.

Finally, we investigated radical-containing one-pot reactions in CPME to evaluate its potential contributions to process research. By taking advantage of the wide liquid state range of CPME, and in consideration of the diversity of the reaction, we designed a three-component one-pot reaction with an alkenyl iodide, a terminal alkyne, and an alkylating agent. Thus, radical addition of alkyne **1b** with *n*-Bu_3SnH/AIBN in CPME was followed by Stille coupling reaction[8c] with 3-iodocyclohex-2-enone (**8**)[15] in the presence of $(Ph_3P)_2PdCl_2$ to afford dienone **9**, which was methylated without isolation to provide allylic alcohol **10** in 82% overall yield from **1b** (Scheme 2). Similarly, the intermediate vinyl stannane **7** was coupled with 2-iodocyclopent-2-enone (**11**)[16] to generate dienone **12**, which was submitted to conjugate addition by Gilman reagent to provide 2,3-disubstituted cyclopentanone **13**, which possessed a skeleton analogous to prostaglandins, in 46% overall yield. The high hydrophobicity of CPME enabled easy recovery and reuse of the solvent by the general extraction method, which realized the second batch reactions with the recycled solvents, affording **10** and **13** in comparable yields. It is noteworthy that three types of reactions including a radical addition, a Pd-catalyzed coupling, and an organometallic addition were achieved in CPME, in a highly efficient one-pot process with the reaction temperature ranging from −78 °C to 90 °C.



1) Recycled solvent was used.
2) 1.0 M diethyl ether solution was used.
3) Prepared as an 1:1 solution of CPME and diethyl ether.

Scheme 2. Radical-containing one-pot reactions in CPME.

3. Conclusion

In summary, we have demonstrated that CPME was an effective solvent for radical additions and reductions. Low vaporization energy and water-immiscibility of CPME allowed for easy recycling of the solvent by the usual extractive workup. GC–MS analysis revealed that CPME was essentially stable to tributyltin radical-mediated conditions, but degraded slightly into cyclopentanone, methyl pentanoate, cyclopentanol, and 2-cyclopenten-1-ol. It was thought that the degradation arose from hydrogen abstraction at the tertiary position adjacent to the ether oxygen. Furthermore, we succeeded in one-pot reactions consisting of a radical addition, a Pd-catalyzed coupling, and an organometallic addition with CPME as the reaction solvent. We believe that the present investigation will be useful for process chemists who are engaged in developing environmentally benign synthetic methods that

minimize waste, toxicities, and hazards. Further applications of CPME to radical-containing reactions and multi-step reactions are being studied in our laboratory.

4. Experimental section

4.1. General remarks

All reactions were carried out under an atmosphere of argon, unless otherwise stated. Commercially available dry solvent was used for THF. CPME and toluene were reagent grade and stored over molecular sieves 4 Å. *n*-Bu_3SnH was distilled under reduced pressure. Other commercially available reagents were used without further purification, unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm silica gel plates (60-F_{254}) that were analyzed by fluorescence upon 254 nm irradiation or by staining with *p*-anisaldeyde/AcOH/H_2SO_4/EtOH, $12MoO_3 \cdot H_3PO_4$/EtOH, or $(NH_4)_6Mo_7O_{24} \cdot 4H_2O$/$H_2SO_4$. The products were purified by flash chromatography on silica gel (spherical, neutral, 40–50 μm) and, if necessary, were further purified by HPLC equipped with a pre-packed column using hexane/EtOAc as the eluent. NMR spectra were recorded with a 300 MHz (^{1}H: 300 MHz, ^{13}C: 75 MHz) spectrometer and referenced to the solvent peak at 7.26 ppm (^{1}H) and 77.16 ppm (^{13}C) for $CDCl_3$. Splitting patterns are indicated as follows: br, broad; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Infrared spectra were recorded with a FT/IR spectrometer and reported as wavenumber (cm^{-1}). Low- and high-resolution EI and FAB mass spectra were recorded with a double-focusing magnetic sector mass spectrometer in positive ion mode.

4.2. General procedure for the radical addition with terminal alkyne 1

In a typical experiment (Table 1, entry 1), a solution of 4-pentyn-1-ol (**1a**) (84.4 mg, 1.00 mmol), V-65 (51.1 mg, 0.200 mmol), and *n*-Bu_3SnH (384 mg, 1.32 mmol) in CPME (3.3 mL) was stirred at 70 °C for 3 h. After the reaction mixture was concentrated, the residue was purified by flash chromatography on silica gel (hexane/EtOAc=30/1 containing 2% Et_3N) to give vinyl stannane **1a** (336 mg, 0.931 mmol, 93%) as an inseparable 84:16 *E*/*Z* mixture.

*4.2.1. 5-(Tributylstannyl)pent-4-en-1-ol (**2aa**, E/Z=84/16).*[17] Pale yellow oil; the following NMR data were selected from the spectra obtained by a *E*/*Z* mixture. The selected NMR data for *E*-isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.95 (m, 2H), 3.66 (td, 2H, *J*=6.5, 5.6 Hz), 2.26–2.19 (m, 2H), 1.74–1.64 (m, 2H), 1.52–1.43 (m, 6H), 1.36–1.24 (m, 6H), 0.93–0.83 (m, 15H). The selected NMR data for *Z*-isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.53 (dt, 1H, *J*=12.5, 7.0 Hz), 5.83 (dt, 1H, *J*=12.5, 1.1 Hz), 3.67 (td, 2H, *J*=6.5, 5.6 Hz), 2.15–2.07 (m, 2H), 1.73–1.62 (m, 2H), 1.60–1.42 (m, 6H), 1.38–1.23 (m, 6H), 0.98–0.79 (m, 15H).

*4.2.2. 5-(1,1,1,3,3,3-Hexamethyl-2-(trimethylsilyl)trisilan-2-yl)pent-4-en-1-ol (**2ab**, E/Z=12/88).* Colorless oil; the following NMR data were selected from the spectra obtained by a *E*/*Z* mixture. The selected NMR data for *Z*-isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.38 (dt, 1H, *J*=13, 7.0 Hz), 5.53 (dt, 1H, *J*=13, 1.5 Hz), 3.67 (td, 2H, *J*=6.7, 5.4 Hz), 2.19–2.11 (m, 2H), 1.72–1.62 (m, 2H), 1.54 (t, 1H, *J*=5.4 Hz), 0.17 (s, 27H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.3, 121.0, 62.8, 32.9, 31.8, 1.2. The selected NMR data for *E*-isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.99 (dt, 1H, *J*=18, 6.4 Hz), 5.55 (dt, 1H, *J*=18, 1.4 Hz), 3.70–3.60 (m, 2H), 2.78–2.70 (m, 2H), 1.72–1.62 (m, 2H), 1.16 (t, 1H, *J*=7.3 Hz), 0.15 (s, 27H). FT-IR (ZnSe) 3338, 2948, 2893, 1597, 1441, 1396, 1245, 1060 cm^{-1}; HRMS (FAB): *m*/*z* calcd for $C_{14}H_{37}OSi_4$ $[M+H]^+$ 333.1921, found 333.1892.

*4.2.3. 5-(Hexylthio)pent-4-en-1-ol (**2ac**, E/Z=48/52).* Since the *E*-isomer was prone to cyclize into *O*,*S*-acetal (i.e., 2-(hexylthio)tetrahydro-2*H*-pyran) under the chromatographic conditions, it was unable to obtain the spectroscopic data of *E*-isomer in pure form. Data for *Z*-isomer: colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.96 (dt, 1H, *J*=15.0, 1.2 Hz), 5.60 (dt, 1H, *J*=15.0, 6.9 Hz), 3.65 (t, 2H, *J*=6.6 Hz), 2.63 (t, 2H, *J*=7.2 Hz), 2.24–2.13 (m, 2H), 1.70–1.56 (m, 4H), 1.43–1.25 (m, 6H), 0.88 (t, 3H, *J*=7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 129.3, 123.8, 77.2, 76.7, 62.2, 32.3, 31.5, 29.5, 28.5, 22.6, 14.1; HRMS (FAB): *m*/*z* calcd for $C_{11}H_{23}OS$ $[M+H]^+$ 203.1470, found 203.1452.

*4.2.4. tert-Butyldimethyl((5-(tributylstannyl)pent-4-en-1-yl)oxy)silane (**2ba**, E/Z=95/5).* Colorless oil; the following NMR data were selected from the spectra obtained by a *E*/*Z* mixture. Data for *E*-isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.95–5.91 (m, 2H), 3.61 (t, 2H, *J*=6.6 Hz), 2.21–2.14 (m, 2H), 1.70–1.58 (m, 2H), 1.55–1.24 (m, 12H), 0.95–0.83 (m, 15H), 0.90 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.2, 127.7, 62.8, 34.1, 32.1, 29.3, 27.5, 27.4, 26.1, 13.9, 9.5, −5.1; data for *Z*-isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.52 (dt, 1H, *J*=13.0, 7.2 Hz), 5.79 (br d, 1H, *J*=13.0 Hz), 3.62 (t, 2H, *J*=6.3 Hz), 2.13–2.03 (m, 2H), 1.70–1.58 (m, 2H), 1.55–1.24 (m, 12H), 0.95–0.83 (m, 15H), 0.89 (s, 9H), 0.05 (s, 6H); HRMS (FAB): *m*/*z* calcd for $C_{19}H_{41}OSiSn$ $[M-Bu]^+$ 433.1949, found 433.1915.

4.3. General procedure for the radical addition with unsaturated compound 3

In a typical experiment (Table 2, entry 11), to a solution of diene **3g** (249 mg, 1.04 mmol) in CPME (10 mL) was added dropwise a solution of 1-hexanethiol (154 mg, 1.30 mmol) and AIBN (32.8 mg, 0.200 mmol) in CPME (2 mL) with a syringe pump over 30 min at 90 °C. The resulting mixture was stirred at 90 °C for 1.5 h before concentration. The residue was purified by flash chromatography on silica gel (hexane/EtOAc=10/1) to give the cyclized product **4gc** (358 mg, 0.998 mmol, 96%) as an inseparable 85:15 diastereomeric mixture.

*4.3.1. Tributyl(octyl)stannane (**4aa**).* Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.52–1.44 (m, 8H), 1.36–1.24 (m, 8H), 1.05–0.86 (m, 28H); FT-IR (ZnSe) 2956, 2925, 2871, 2854, 1463, 1416, 1376, 1339, 1292, 1246 cm^{-1}. (CAS: 14775-14-5).

*4.3.2. 6-(Hexylthio)hexan-1-ol (**4bc**).* Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.64 (t, 2H, *J*=6.3 Hz), 2.53–2.47 (m, 4H), 1.62–1.26 (m, 16H), 0.89 (t, 3H, *J*=7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 63.0, 32.7, 32.3, 32.2, 31.6, 29.8, 29.7, 28.8, 28.7, 25.5, 22.7, 14.1; FT-IR (ZnSe) 3369, 3351, 2928, 2857, 1466, 1378, 1303, 1284, 1260, 1240, 1054 cm^{-1}; HRMS (FAB): *m*/*z* calcd for $C_{12}H_{27}OS$ $[M+H]^+$ 219.1783, found 219.1759.

*4.3.3. (E)-1,1,1,3,3,3-Hexamethyl-2-styryl-2-(trimethylsilyl)trisilane (**4cb**, E/Z=17/83).*[8d,18] Colorless oil; the following NMR data were selected from the spectra obtained by a *E*/*Z* mixture. Data for *Z*-isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 (d, 1H, *J*=15 Hz), 7.42–7.19 (m, 5H), 5.89 (d, 1H, *J*=15 Hz), 0.13 (s, 27H, TMS). Data for *E*-isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42–7.19 (m, 5H), 6.89 (d, 1H, *J*=19.0 Hz), 6.44 (d, 1H, *J*=19.0 Hz), 0.22 (s, 27H, TMS).

*4.3.4. Hexyl(styryl)sulfane (**4cc**, E/Z=83/17).* Colorless oil; the following ^{1}H NMR data were selected from the spectra obtained by a *E*/*Z* mixture. Data for *E*-isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48–7.13 (m, 5H), 6.71 (d, 1H, *J*=15.4 Hz), 6.44 (d, 1H, *J*=15.4 Hz), 2.78 (dd, 2H, *J*=7.5, 7.2 Hz), 1.72–1.62 (m, 2H), 1.46–1.35 (m, 2H, H8), 1.33–1.25 (m, 4H, H7), 0.88 (t, 3H, *J*=6.9 Hz, H9). Data for *Z*-isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21–7.13 (m, 5H), 6.41 (d, 1H,

J=11.1 Hz), 6.23 (d, 1H, J=11.1 Hz), 2.48 (t, 2H, J=7.2 Hz), 1.72–1.62 (m, 2H), 1.47–1.35 (m, 2H), 1.31–1.26 (m, 4H), 0.87 (t, 3H, J=6.9 Hz, H9); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.3, 127.8, 126.9, 126.8, 126.7, 125.6, 125.5, 125.4, 77.6, 77.2, 36.1, 32.8, 31.5, 30.8, 29.5, 28.8, 28.6, 28.4, 28.2, 22.7, 14.1; FT-IR (ZnSe) 3076, 3058, 3022, 2955, 2928, 2870, 2857, 1598, 1571, 1495, 1466, 1446, 1378, 1286, 936 cm^{-1}; HRMS (FAB): m/z calcd for $C_{14}H_{20}S$ $[M+H]^+$ 221.1364, found 221.1373.

*4.3.5. Methyl 3-(tributylstannyl)acrylate (**4da**, E/Z=56/44).* Colorless oil; the following NMR data were selected from the spectra obtained by an E/Z mixture. Data for E-isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (d, 1H, J=19.2 Hz), 6.30 (d, 1H, J=19.5 Hz), 3.75 (s, 3H), 1.56–1.45 (m, 6H), 1.36–1.24 (m, 6H), 0.99–0.94 (m, 6H), 0.89 (t, 9H, J=7.2 Hz). Data for Z-isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17 (d, 1H, J=13.2 Hz), 6.73 (d, 1H, J=12.9 Hz), 3.75 (s, 3H), 1.54–1.44 (m, 6H), 1.35–1.23 (m, 6H), 0.99–0.94 (m, 6H), 0.88 (t, 9H, J=7.5 Hz); FT-IR (ZnSe) 2955, 2922, 2871, 2854, 1210, 1183, 1145, 1072 cm^{-1}; HRMS (FAB): m/z calcd for $C_{12}H_{23}O_2Sn$ $[M-C_4H_9]^+$ 319.0722, found 319.0741.

*4.3.6. (Z)-Methyl 3-(1,1,1,3,3,3-hexamethyl-2-(trimethylsilyl)trisilan-2-yl)acrylate (**4db**, Z-isomer).*[19] Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.74 (d, 1H, J=13.8 Hz), 6.59 (d, 1H, J=13.8 Hz), 3.70 (s, 3H), 0.18 (s, 27H); FT-IR (ZnSe) 3027, 2949, 2894, 1723, 1583, 1435, 1398, 1362, 1244, 1213, 1178, 1007 cm^{-1}; HRMS (FAB): m/z calcd for $C_{12}H_{29}O_2Si_4$ $[M-CH_3]^+$ 317.1245, found 317.1251.

*4.3.7. 3-(1,1,1,3,3,3-Hexamethyl-2-(trimethylsilyl)trisilan-2-yl)propanenitrile (**4eb**).*[8d] Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.37–2.31 (m, 2H), 1.24–1.18 (m, 2H), 0.19 (s, 27H).

*4.3.8. 1,1,1,3,3,3-Hexamethyl-2-((4-methyltetrahydrofuran-3-yl) methyl)-2-(trimethylsilyl)trisilane (**4fb**, dr=68/32).*[8d] Colorless oil; the following NMR data were selected from the spectra obtained by a mixture of diastereomers. Data for the major isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.04 (dd, 1H, J=8.1, 6.9 Hz), 3.99 (dd, 1H, J=8.1, 6.9 Hz), 3.33 (dd, 1H, J=8.1, 5.1 Hz), 3.30 (dd, 1H, J=8.1, 4.8 Hz), 1.86–1.66 (m, 2H), 1.18 (dd, 1H, J=14.4, 3.0 Hz), 1.01 (d, 3H, J=6.6 Hz), 0.64 (dd, 1H, J=14.4, 10.5 Hz), 0.17 (s, 27H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 76.1, 75.1, 47.0, 44.0, 16.0, 10.0, 1.38; data for the minor isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.91 (dd, 1H, J=9.0, 6.0 Hz), 3.89 (dd, 1H, J=8.1, 3.6 Hz), 3.48 (dd, 1H, J=8.1, 4.2 Hz), 3.37 (t, 1H, J=7.5 Hz), 2.31–2.17 (m, 2H), 0.95 (dd, 1H, J=14.4, 4.2 Hz), 0.94 (d, 3H, J=6.9 Hz), 0.68 (dd, 1H, J=14.4, 9.6 Hz), 0.17 (s, 27H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 75.0, 74.3, 42.1, 37.8, 13.0, 4.6, 1.41; FT-IR (ZnSe) 2952, 2894, 1245, 1045 cm^{-1}; HRMS (FAB): m/z calcd for $C_{14}H_{35}OSi_4$ $[M-CH_3]^+$ 331.1765, found 331.1759.

*4.3.9. 5,5-Bis(trimethylsilyl)hexahydro-1H-silolo[3,4-c]furan (**4fb′**).*[20] Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.93 (dd, 2H, J=8.4, 6.9 Hz), 3.42 (dd, 2H, J=8.1, 5.4 Hz), 2.69–2.57 (m, 2H), 1.04 (dd, 2H, J=15.0, 8.1 Hz), 0.76 (dd, 2H, J=15.0, 6.3 Hz), 0.12 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 74.8, 46.4, 10.8, −0.59, −0.76; MS (EI, 70 eV): m/z (%) 272 ([M$^+$], 4), 189 (63), 157 (65), 131 (87), 117 (75), 73 (100); HRMS (EI): m/z calcd for $C_{12}H_{28}OSi_3$ $[M]^+$ 272.1448, found 272.1409.

*4.3.10. 3-((Hexylthio)methyl)-4-methyltetrahydrofuran (**4fc**, dr=61/39).* Colorless oil; the following NMR data were obtained after separation of the diastereomers by HPLC. Data for the major isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.98–3.91 (m, 2H), 3.63–3.58 (m, 1H), 3.47 (dd, 1H, J=8.4, 4.2 Hz), 2.68–2.30 (m, 6H), 1.63–1.41 (m, 2H), 1.44–1.22 (m, 6H), 0.98 (d, 3H, J=6.9 Hz), 0.89 (t, 3H, J=6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 75.2, 72.1, 42.4, 36.1, 32.8, 31.6, 30.8, 29.8, 28.7, 22.7, 14.2, 12.9; data for the minor isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.05–3.97 (m, 2H), 3.56 (dd, 1H, J=9.0, 6.6 Hz), 3.33 (dd, 1H, J=8.4, 7.2 Hz), 2.75–2.66 (m, 1H), 2.55–2.40 (m, 3H), 2.26–1.90 (m, 2H), 2.62–1.53 (m, 2H), 1.42–1.23 (m, 6H), 1.06 (d, 3H, J=6.3 Hz), 0.89 (t, 3H, J=7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 75.4, 73.5, 47.1, 39.9, 35.3, 32.9, 31.6, 29.8, 28.7, 22.7, 17.2, 14.2; FT-IR (ZnSe) 2956, 2928, 2856, 1456, 1436, 1380, 1285, 1240, 1052 cm^{-1}; HRMS (FAB): m/z calcd for $C_{12}H_{24}OS$ $[M+H]^+$ 217.1626, found 217.1600.

*4.3.11. Diethyl 3-methyl-4-((tributylstannyl)methyl)cyclopentane-1,1-dicarboxylate (**4ga**, dr=67/33).* Colorless oil; the following NMR data were obtained after separation of the diastereomers by HPLC. The major isomer was isolated in pure form, while the minor isomer was not completely separated from the major isomer. Data for the major isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.16 (q, 4H, 7.2 Hz), 2.54–2.43 (m, 1H), 2.40–2.30 (m, 2H), 2.24–2.12 (m, 1H), 2.06–1.99 (m, 2H), 1.86 (dd, 1H, J=13.2, 9.9 Hz), 1.77–1.63 (m, 1H), 1.52–1.41 (m, 6H), 1.36–1.21 (m, 12H), 0.98–0.71 (m, 18H); FT-IR (ZnSe) 2954, 2928, 2872, 2854, 1736, 1729, 1464, 1446, 1419, 1376, 1366, 1253, 1184, 1153 cm^{-1}; HRMS (FAB): m/z calcd for $C_{21}H_{39}O_4Sn$ $[M-C_4H_9]^+$ 475.1874, found 475.1850.

*4.3.12. Diethyl 3-((hexylthio)methyl)-4-methylcyclopentane-1,1-dicarboxylate (**4gc**, dr=85/15).* Colorless oil; the following NMR data were selected from the spectra obtained by a mixture of diastereomers. Data for the major isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.17 (q, 4H, J=7.2 Hz), 2.80–1.98 (m, 10H), 1.61–1.51 (m, 2H), 1.42–1.21 (m, 4H), 1.23 (t, 6H, J=7.2 Hz), 0.89 (d, 3H, J=6.9 Hz), 0.88 (t, 3H, J=6.9 Hz); FT-IR (ZnSe) 2957, 2929, 2872, 2858, 1731, 1464, 1447, 1366, 1254, 1180 cm^{-1}; HRMS (FAB): m/z calcd for $C_{19}H_{35}O_4S$ $[M+H]^+$ 359.2256, found 359.2238.

4.4. General procedure for the preparation of thiocarbonates 5a–d

To a solution of cholesterol (863 mg, 2.23 mmol) in CH_2Cl_2 (10 mL) were added pyridine (485 μL, 6.00 mmol) and phenyl chlorothionoformate (277 μL, 2.00 mmol) (For other substrates, CH_3CN was used in place of CH_2Cl_2.). The mixture was stirred at room temperature for 50 min and diluted with EtOAc. The solution was washed with brine and dried over anhydrous $MgSO_4$. After concentration, the residue was purified by flash chromatography on silica gel (hexane→hexane/EtOAc=10/1) to give thiocarbonate **5b** (1.04 g, 1.99 mmol, 100%).

*4.4.1. O-Phenyl O-(((3aR,5R,5aS,8aS,8bR)-2,2,7,7-tetramethyltetrahydro-3aH-bis([1,3]dioxolo)[4,5-b:4′,5′-d]pyran-5-yl)methyl) carbonothioate (**5a**).* This compound was obtained from the corresponding commercially available alcohol in 93% yield. Colorless solid; mp 73–76 °C (hexane/$CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45–7.38 (m, 2H), 7.32–7.26 (m, 1H), 7.13–7.09 (m, 2H), 5.58 (d, 1H, J=5.1 Hz), 4.73 (dd, 1H, J=11.4, 4.8 Hz), 4.68–4.60 (m, 2H), 4.38–4.25 (m, 3H), 1.55 (s, 3H), 1.48 (s, 3H), 1.36 (s, 3H), 1.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.2, 153.6, 129.6, 126.7, 122.0, 109.9, 109.0, 96.4, 72.6, 71.1, 70.9, 70.6, 65.6, 26.2, 26.1, 25.1, 24.6; FT-IR (ZnSe) 2989, 2935, 1591, 1492, 1456, 1383, 1373, 1294, 1207, 1166, 1114, 1071, 1008 cm^{-1}; HRMS (FAB): m/z calcd for $C_{19}H_{25}O_7S$ $[M+H]^+$ 397.1321, found 397.1297.

*4.4.2. O-Cyclododecyl O-phenyl carbonothioate (**5b**).*[10b] This compound was obtained from cyclododecanol in 82% yield. Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44–7.38 (m, 2H), 7.31–7.25 (m, 1H), 7.12–7.08 (m, 2H), 5.55–5.47 (m, 1H), 1.94–1.70 (m, 4H), 1.52–1.32 (m, 18H); HRMS (FAB): m/z calcd for $C_{19}H_{29}O_2S$ $[M+H]^+$ 321.1888, found 321.1856.

*4.4.3. Cholest-5-en-3-ol (3β)-(O-phenyl carbonothioate) (**5c**).*[10b] This compound was obtained from cholesterol in 100%

yield. Colorless solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45–7.38 (m, 2H), 7.31–7.26 (m, 1H), 7.13–7.08 (m, 2H), 5.44 (br d, 1H, J=5.1 Hz), 5.10 (m, 1H), 2.66–2.45 (m, 2H), 2.19–0.80 (m, 26H), 1.06 (s, 3H), 0.92 (d, 3H, J=6.3 Hz), 0.87 (d, 3H, J=6.6 Hz), 0.86 (d, 3H, J=6.6 Hz), 0.68 (s, 3H).

*4.4.4. O-Phenyl O-(1-phenylundecyl) carbonothioate (**5d**).* This compound was obtained from the corresponding alcohol in 83% yield. Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44–7.24 (m, 8H), 7.08–7.05 (m, 2H), 6.19 (t, 1H, J=7.2 Hz), 2.21–2.08 (m, 1H), 1.98–1.85 (m, 1H), 1.38–1.23 (m, 16H), 0.88 (t, 3H, J=7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.0, 153.1, 138.8, 129.1, 128.2, 128.0, 126.7, 126.2, 121.7, 86.4, 35.8, 31.6, 29.3, 29.2, 29.1, 29.02, 28.99, 25.0, 22.4, 13.8; FT-IR (ZnSe) 3065, 3033, 2924, 2854, 1727, 1592, 1490, 1466, 1456, 1276, 1199 cm^{-1}; HRMS (FAB): m/z calcd for $C_{24}H_{33}O_2S$ $[M+H]^+$ 385.2201, found 385.2199.

*4.4.5. O-(3-(1,3-Dioxan-2-yl)-1-phenylpropyl) O-phenyl carbonothioate (**5g**).* This compound was obtained from the corresponding alcohol in 62% yield. Colorless solid; $[\alpha]_D^{27}$ −82.1 (c 1.15, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44–7.40 (m, 2H), 7.32–7.26 (m, 1H), 7.11–7.08 (m, 2H), 5.52 (ddd, 1H, J=8.4, 4.8 Hz), 4.75 (dd, 1H, J=8.4, 2.4 Hz), 4.32–4.25 (m, 3H), 4.19 (dd, 1H, J=12.8, 4.8 Hz), 3.92 (dd, 1H, J=12.8, 4.8 Hz), 2.60 (d, 1H, J=2.4 Hz), 1.55 (s, 3H, acetonide), 1.52 (s, 3H, acetonide), 1.42 (s, 3H, acetonide), 1.41 (s, 3H, acetonide), 0.92 (s, 9H, TBS), 0.25 (s, 3H, TBS), 0.23 (s, 3H, TBS); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.2, 153.4, 129.4, 126.5, 121.8, 110.2, 99.8, 83.2, 79.1, 76.5, 75.6, 75.1, 68.5, 61.8, 61.3, 26.11, 26.07, 25.8, 25.6, 22.0, 18.0, −3.2, −4.3; FT-IR (ZnSe) 3306, 2986, 2955, 2931, 2859, 2119, 1591, 1491, 1471, 1463, 1381, 1368, 1324, 1288, 1259, 1200, 1164, 1133, 1093, 1081, 1050, 1024 cm^{-1}; HRMS (EI): m/z calcd for $C_{26}H_{37}O_7SSi$ $[M-CH_3]^+$ 521.2024, found 521.2029.

4.5. General procedure for the preparation of alkyl bromides 5e and 5f

In a screw cap test tube were placed with 1-adamantanol (316 mg, 2.07 mmol) and aqueous HBr (47%, 10 mL). The mixture was shaken vigorously for 40 min. The solid was collected by filtration and washed several times with water. The crude bromide **5e** (389 mg, 1.81 mmol, 87%) was dried in vacuo and used without further purification. Commercially available bromides **5e** and **5f** were also used for examination.

4.6. General procedure for Barton–McCombie radical reduction of compound 5

To a solution of thiocarbonate **5g** (107 mg, 0.200 mmol) in CPME (0.5 mL) were added dropwise a solution of n-Bu_3SnH (75.7 mg, 0.260 mmol) and AIBN (6.6 mg, 0.040 mmol) in CPME (1.5 mL) with a syringe pump over 30 min at 90 °C. The resultant mixture was stirred at 90 °C for 30 min and concentrated. The residue was purified by 10% w/w K_2CO_3-silica gel flash column chromatography (hexane→hexane/EtOAc=100/1→50/1→20/1) to give the cis-fused cyclized product **6g** (53.6 mg, 0.140 mmol, 70%) and 2.8:1 mixture of cis and trans-fused diastereomers (22.0 mg, 0.0572 mmol, 29%). These isomers were separated by the repeated column chromatography for spectral analysis.

*4.6.1. 1,2,3,4-Di-O-isopropylidene-α-D-fucopyranose (**6a**).*[21] Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.52 (d, 1H, J=5.1 Hz), 4.59 (dd, 1H, J=8.0, 2.3 Hz), 4.29 (dd, 1H, J=5.3, 2.3 Hz), 4.08 (dd, 1H, J=7.8, 1.8 Hz), 3.92 (dq, 1H, J=6.6, 1.9 Hz), 1.53 (s, 3H), 1.47 (s, 3H), 1.36 (s, 3H), 1.33 (s, 3H), 1.26 (d, 3H, J=6.6 Hz). This compound is commercially available (CAS: 4026-27-1).

*4.6.2. Cyclododecane (**6b**).* Colorless waxy solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.34. This compound is commercially available. (CAS: 294-62-2).

*4.6.3. Cholest-5-ene (**6c**).*[22] Colorless solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.29–5.25 (m, 1H), 2.32–2.17 (m, 1H), 2.04–0.90 (m, 29H), 1.00 (s, 3H), 0.92 (d, 3H, J=6.6 Hz), 0.87 (d, 3H, J=6.9 Hz), 0.86 (d, 3H, J=6.6 Hz), 0.68 (s, 3H).

*4.6.4. Undecylbenzene (**6d**).* Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32–7.25 (m, 2H), 7.20–7.14 (m, 3H), 2.60 (dd, 2H, J=8.1, 7.5 Hz), 1.66–1.56 (m, 2H), 1.36–1.20 (m, 16H), 0.89 (t, 3H, J=7.2 Hz). This compound is commercially available (CAS: 6742-54-7).

*4.6.5. Adamantane (**6e**).* Colorless solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.87 (br s, 4H), 1.75 (m, 10H). This compound is commercially available. (CAS: 281-23-2).

*4.6.6. 1,3-Dimethyladamantane (**6f**).* Colorless solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.99–1.94 (m, 2H), 1.56–1.52 (m, 2H), 1.43–1.28 (m, 8H), 1.14 (br s, 2H), 0.77 (s, 6H). This compound is commercially available. (CAS: 702-79-4).

*4.6.7. tert-Butyldimethyl(((3aS,4R,5aS,9aR,9bS)-2,2,8,8-tetramethyl-5-methylenehexahydro-3aH-[1,3]dioxolo[4′,5′:5,6]benzo[1,2-d][1,3]dioxin-4-yl)oxy)silane (**6g**).* Colorless syrup; data for the cis-fused isomer: $[\alpha]_D^{27}$ +162 (c 1.21, $CHCl_3$); ^{1}H NMR (400 MHz, $CHCl_3$) δ 5.46 (br s, 1H), 5.10 (d, 1H, J=0.8 Hz), 5.06 (dd, 1H, J=2.8, 1.6 Hz), 4.41 (dd, 1H, J=7.6, 2.8 Hz), 4.26 (dd, 1H, J=7.6, 2.4), 4.13 (dd, 1H, J=11.6, 3.6 Hz), 4.08 (t, 1H, J=2.8 Hz), 3.90 (dd, 1H, J=11.6, 2.4 Hz), 2.52 (br t, 1H, J=1.6 Hz), 1.43 (s, 3H, acetonide), 1.40 (s, 3H, acetonide), 1.34 (s, 3H, acetonide), 1.32 (s, 3H, acetonide), 0.96 (s, 9H, TBS), 0.17 (s, 3H, TBS), 0.14 (s, 3H, TBS); ^{13}C NMR (75 MHz, $CHCl_3$) δ 145.1, 110.8, 109.3, 98.8, 77.1, 76.0, 70.7, 67.9, 66.0, 35.2, 29.3, 26.4, 26.3, 24.1, 19.1, 18.9, −4.36, −5.02; FT-IR (ZnSe) 2991, 2955, 2930, 2858, 1472, 1465, 1382, 1258, 1232, 1210, 1199, 1167, 1133, 1095, 1075, 1027, 971 cm^{-1}; HRMS (FAB): m/z calcd for $C_{20}H_{37}O_5Si$ $[M-CH_3]^+$ 369.2097, found 369.2069. Data for the trans-fused isomer: colorless syrup; ^{1}H NMR (400 MHz, $CHCl_3$) δ 5.25 (d, 1H, J=0.8 Hz), 4.88 (d, 1H, J=0.8 Hz), 4.32 (d, 1H, J=3.6 Hz), 4.22 (dd, 1H, J=6.4, 4.0 Hz), 4.18 (dd, 1H, J=11.6, 8.0 Hz), 4.09 (dd, 1H, J=8.0, 6.4 Hz), 4.00–3.90 (m, 2H), 2.18–2.09 (m, 1H), 1.52 (s, 3H, acetonide), 1.48 (s, 3H, acetonide), 1.45 (s, 3H, acetonide), 1.35 (s, 3H, acetonide), 0.93 (s, 9H, TBS), 0.11 (s, 3H, TBS), 0.10 (s, 3H, TBS).

4.7. Recycle of CPME in the radical addition reaction with 1a and n-Bu$_3$SnH

In a typical experiment (Table 4, run 1), a solution of 4-pentyn-1-ol (**1a**, 84.6 mg, 1.01 mmol), n-Bu_3SnH (381 mg, 1.31 mmol), and AIBN (33.0 mg, 0.201 mmol) in CPME (3.3 mL) was heated at 90 °C and stirred for 2 h. The reaction mixture was cooled to room temperature and the distillation apparatus was attached to the flask. The volatiles containing CPME were distillated under reduced pressure (bp 40–45 °C/18 kPa) and weighed to determine the yield of recovery. The residual oil was purified by flash chromatography on silica gel (hexane/EtOAc=30/1 containing 2% Et_3N) to give vinyl stannane **2aa** as an inseparable 84:16 E/Z mixture (359 mg, 0.956 mmol, 95%). The recovered CPME was directly used for the next reaction without drying.

4.8. GC–MS analysis of the recovered CPME

Gas-phase chromatography was performed on an HP-6890 instrument using a DB-WAX column (30 m×0.25 mm×0.25 μm film thickness). The oven was heated at 50 °C for 5 min followed by

a temperature gradient of 10 °C/min to 200 °C and, finally, at 200 °C for 5 min. Inlet temperature and pressure were 200 °C and 83 kPa, respectively, with a split ratio of 100:1. Helium was the carrier gas (1.0 mL/min).

4.9. Three-component one-pot reaction with alkyne 1b and iodide 8

To a two-necked round-bottom flask equipped with a reflux condenser were placed with alkyne **1b** (198 mg, 1.00 mmol), *n*-Bu_3SnH (378 mg, 1.30 mmol), AIBN (32.8 mg, 0.200 mmol), and CPME (3.3 mL). The mixture was heated at 90 °C and stirred for 35 min. After disappearance of **1a** as monitored by TLC, the reaction mixture was cooled to 45 °C. A solution of 3-iodocyclohex-2-enone (**8**) (157 mg, 0.709 mmol) in CPME (1.4 mL) and $(Ph_3P)_2PdCl_2$ were successively added and the resulting mixture was stirred at 45 °C for 4 h. After disappearance of **8** as monitored by TLC, the reaction mixture was cooled to −78 °C followed by the addition of MeLi (1.07 M in Et_2O, 2.80 mL, 3.00 mmol). The resulting mixture was stirred at −78 °C for 20 min and quenched by the addition of saturated aqueous NH_4Cl solution. The resultant mixture was extracted with CPME (12.5 mL×2), and the combined organic layer was washed with brine and dried over anhydrous $MgSO_4$. After filtration (washing with 8 mL of CPME), CPME were recovered by vacuum distillation at room temperature (ca. 30 mL of CPME was collected), which was dried over anhydrous $MgSO_4$ before usage for the second reaction. The residual oil was purified by flash chromatography on silica gel (hexane/EtOAc=15/1) to give allylic alcohol **10** (179 mg, 0.576 mmol, 82%) as a 95:5 *E*/*Z* mixture.

*4.9.1. (E)-3-(5-((tert-Butyldimethylsilyl)oxy)pent-1-en-1-yl)-1-methylcyclohex-2-enol ((E)-**10**).* Pale yellow oil; ^1H NMR (300 MHz, C_6D_6) δ 6.08 (br d, 1H, *J*=15.6 Hz), 5.61 (dt, 1H, *J*=15.6, 6.9 Hz), 5.50 (br s, 1H), 3.55 (t, 2H, *J*=6.3 Hz), 2.17 (q, 2H, *J*=7.3 Hz), 2.08 -1.96 (m, 1H), 1.92−1.78 (m, 1H), 1.74−1.37 (m, 6H), 1.25 (s, 3H), 0.98 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (75 MHz, C_6D_6) δ 136.5, 133.9, 133.6, 129.1, 68.2, 62.6, 38.3, 33.1, 29.8, 29.6, 26.2, 25.0, 19.8, 18.5, −5.1; FT-IR (ZnSe) 3368, 3021, 2929, 2858, 1653, 1623, 1471, 1462, 1387, 1362, 1339, 1255, 1190, 1166, 1102 cm^{-1}; HRMS (FAB): *m*/*z* calcd for $C_{18}H_{33}OSi$ $[M-H_2O+H]^+$ 293.2301, found 293.2299.

4.10. Three-component one-pot reaction with alkyne 1b and iodide 11

To a solution of alkyne **1b** (198 mg, 1.00 mmol) in CPME (1.0 mL) was added slowly a solution of *n*-Bu_3SnH (378 mg, 1.30 mmol) and AIBN (32.8 mg, 0.200 mmol) in CPME (2.3 mL) at 90 °C. The mixture was stirred at that temperature for 30 min. After consumption of all the starting material as monitored by TLC, the reaction mixture was kept at 60 °C followed by the addition of iodide **11** (143 mg, 0.687 mmol) in CPME (1.4 mL) and $(Ph_3P)_2PdCl_2$ (49.1 mg, 0.0700 mmol). The reaction mixture was stirred at 60 °C for 3.3 h. In another two-necked round-bottom flask were placed with CuI (571 mg, 3.00 mmol) and CPME (7.5 mL), which was cooled to −78 °C. MeLi (1.07 M solution in Et_2O, 5.6 mL, 6.0 mmol) was added and the mixture was stirred at −78 °C for 10 min. To this flask was added the above reaction mixture containing the coupling product via cannula, and the resulting mixture was stirred at −78 °C for 44 min. The reaction was quenched by the addition of saturated aqueous NH_4Cl solution, which was extracted with CPME (12.5 mL×2). The combined organic layer was washed with brine and dried over anhydrous $MgSO_4$. After filtration (washing with 10 mL of CPME), CPME were recovered by vacuum distillation at room temperature (ca. 31 mL of CPME was collected), which was dried over anhydrous $MgSO_4$ before usage for the second reaction. The residual oil was purified by flash chromatography on silica gel (hexane/EtOAc=30/1) to give ketone **13** (93.6 mg, 1.34 mmol, 46%) as a mixture of three stereoisomers. Further purification by HPLC enabled separation of the *E*/*Z* stereoisomers and determined the diastereomeric ratio with respect to *E*-isomer to be 63:37. The minor *Z*-isomer was detected as a single stereoisomer by ^1H NMR.

*4.10.1. (E)-2-(5-((tert-Butyldimethylsilyl)oxy)pent-1-en-1-yl)-3-methylcyclopentanone ((E)-**13**, dr=63/37).* Pale yellow oil; the following NMR data were selected from the spectra obtained by a mixture of diastereomers. The selected NMR data for the major isomer: ^1H NMR (300 MHz, $CDCl_3$) δ 5.54 (dt, 1H, *J*=15, 7.5 Hz), 5.24 (ddt, 1H, *J*=15, 7.5, 1.5 Hz), 3.60 (t, 2H, *J*=6.3 Hz), 2.43−2.08 (m, 6H), 1.98−1.86 (m, 1H), 1.66−1.55 (m, 2H), 1.50−1.35 (m, 1H), 1.11 (d, 3H, *J*=6.3 Hz), 0.88 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 219.2, 135.1, 125.6, 62.7, 61.1, 38.3, 38.1, 32.5, 29.8, 29.2, 26.1, 19.2, 18.5, −5.15; FT-IR (ZnSe) 2955, 2929, 2858, 1745, 1472, 1463, 1409, 1389, 1361, 1256, 1152, 1103 cm^{-1}; HRMS (FAB): *m*/*z* calcd for $C_{17}H_{32}O_2Si$ $[M+H]^+$ 297.2250, found 297.2248.

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Supplementary data

These data include ^1H and ^{13}C NMR spectra for all new synthetic compounds. Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.tet.2013.01.030.

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