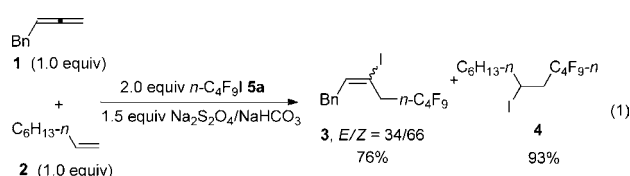


Formal Alkylation of Allenes through Highly Selective Radical Cyclizations of Allene-enes**

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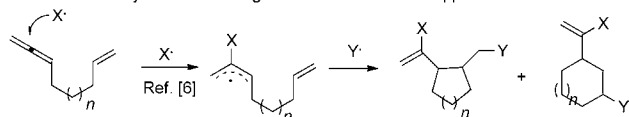
In the last few decades, radical-based transformations have become one of the most powerful ways to form carbon–carbon bonds in organic synthesis.^[1] However, the radical reactions of allenenes are largely unknown.^[2,3] Particularly, in contrast to the radical cyclization reactions of dienes^[4] and enynes,^[4k–m,5] the inter- and intramolecular tandem radical addition/cyclization reactions of allene-enes^[6] has not been extensively explored. All the reported reactions proceed in an “allene-to-alkene” fashion,^[6] which is consistent with the traditional notion that allenenes are more reactive than alkenes towards radicals (Scheme 1). Herein, we report a reaction

a 1:1 mixture of 4-phenylbuta-1,2-diene (**1**) and 1-octene (**2**) afforded a mixture of both addition products, namely the alkenyl iodide **3** and (perfluoroalkyl)alkyl iodide **4**, in 76% and 93% yields, respectively, thus demonstrating a poor selectivity [Eq. (1)].



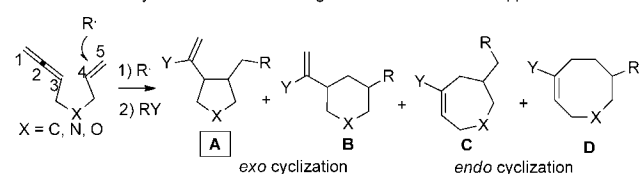
Known protocols:

Radical addition/cyclizations through an “allene-to-alkene” approach



This report:

Radical addition/cyclization with RY through an “alkene-to-allene” approach

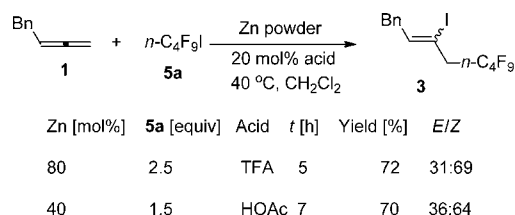


Scheme 1. Radical cyclizations of allene-enes.

that proceeds in an “alkene-to-allene” fashion, starting with the alkene moiety to afford products of type **A** exclusively.

It has been shown that a stoichiometric amount of $\text{Na}_2\text{S}_2\text{O}_4$ may promote the radical addition reaction of olefins and allenenes with perfluoroalkyl iodides in the presence of NaHCO_3 .^[7] It is interesting to observe that the corresponding radical addition reaction of perfluorobutyl iodide (**5a**) with

To avoid using a large amount of $\text{Na}_2\text{S}_2\text{O}_4$ and NaHCO_3 , we started to explore a general catalytic or subcatalytic radical initiation system for the reaction of a simple allene, that is, 4-phenylbuta-1,2-diene (**1**) with **5a** to possibly obtain a better selectivity. The investigation on the reaction of **1** with **5a** was conducted under the known reaction conditions for the radical addition of alkenes:^[8] 1.0 equivalent of **1** and 1.5 equivalents of **5a** reacted in the presence of 20 mol % trifluoroacetic acid (TFA) when using 10 mol % zinc powder as the catalyst at room temperature. Unfortunately, less than 5% product was formed with the recovery of **1** being 92% (see Table S1, entry 1 in the Supporting Information). After some optimization, we were happy to observe that the radical addition reaction may be conducted with 40 mol % of zinc in the presence of 20 mol % of HOAc (Scheme 2; for details see Table S1).



Scheme 2. Zinc-initiated radical addition reactions of allene **1** with **5a**. Reported yield is for the isolated product. Bn = benzyl.

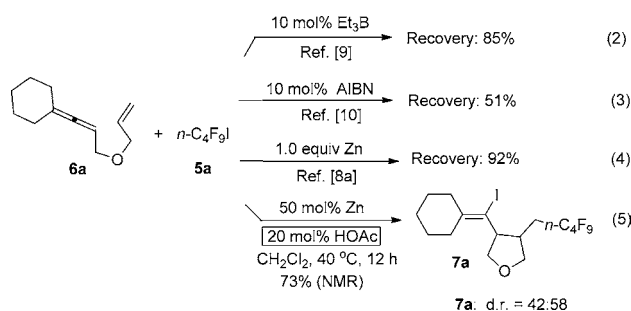
We started to study the radical cyclization by using the allene-ene **6a** as a model substrate. Disappointingly, some typical radical initiators such as Et_3B ,^[9] AIBN,^[10] and zinc powder^[8] failed to catalyze the cyclization reaction of the allene-ene **6a** with **5a** [Eqs. (3)–(5)]. Gladly, we found that the radical addition reaction of the allene-ene **6a** with **5a** was

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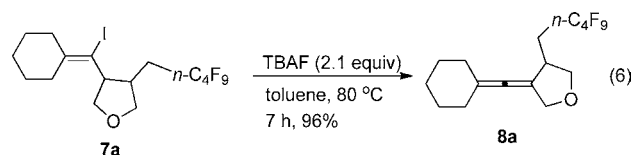
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Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/ange.201107747>.

indeed be promoted by 50 mol% of zinc powder in the presence of 20 mol% HOAc at 40 °C, thus forming two products exclusively. Upon analyzing the spectroscopic data, including ^1H , ^{13}C , and ^{19}F NMR spectra, as well as IR, MS, and HRMS data, for the two products, we found that both the allene and alkene moieties in allene-ene **6a** had been converted: **5a** was incorporated into the product with the R_f group linked to a methylene group; there were no olefinic protons present in the product. Thus, by comparing the data with the possible radical cyclization products of allene-enes shown in Scheme 1, we reasoned that the two compounds should be a pair of diastereomers arising from an **A**-type cyclization to give the product **7a**, which must be formed highly chemoselectively through the alkene-to-allene addition and *exo* cyclization. This result indicates a favored selectivity towards the alkene over the allene [compare with the results shown in Eqs. (1) and (2–5)], which is different from what has been previously reported.^[6] Thus, **7a** was formed in 73 % yield as determined by NMR spectroscopy and 56 % yield upon isolation [Eq. (5)]. With 40 mol % of zinc, **6a** was recovered (8 %). These reaction conditions had shown obvious advantages as compared to the reported ones for allenes:^[7] 1) the reaction proceeds under mild reaction conditions and is very practical; 2) both the zinc powder and HOAc are cheap, nontoxic, user-friendly, and readily available.



Inspired by this observation, we proposed to develop a base-promoted elimination of HI from the two diastereomers to regenerate the allene moiety,^[11] a reaction that would additionally confirm that the two isomers are indeed a pair of diastereomers. After some experimentation, we were happy to observe that the dehydroiodination of **7a** with 2.1 equivalents of TBAF·3H₂O in toluene at 80 °C afforded **8a** in 96 % yield [Eq. (6), for details see Table S2 in the Supporting Information]. Thus, these reaction conditions were defined as the standard reaction conditions.



We then studied the scope of the radical addition/cyclization reaction and the subsequent dehydroiodination reaction of allene-enes with perfluoroalkyl iodides. Some of

the typical results are summarized in Table 1. Differently substituted allene-enes (**6a,b** and **6d–g**) were successfully applied in the radical addition/cyclization reaction to afford the corresponding products **7a–d** and **7g–7n** in moderate to good yields. The products were directly converted into the formal alkylation products of the allene moiety, that is, 3-(1-alkenylidene)tetrahydrofurans **8a–d** and **8g–n**, in good to excellent yields by using the dehydroiodination approach. The substituents R^1 and R^2 could be either different alkyl groups or a carbon chain forming a ring (Table 1). Compared with the other substrates, when $\text{R}^1 = \text{R}^2 = \text{Me}$, the reaction afforded the lowest yield (Table 1, entries 5 and 6). Furthermore, the reactions of substrates in which R^3 was a methyl group (Table 1, entries 11 and 12) gave even better results than those obtained when $\text{R}^3 = \text{H}$ (Table 1, entries 3 and 4). The different perfluoroalkyl iodides, such as *n*-C₄F₉I or *n*-C₆F₁₃I, could be used in the reactions with the similar results.

Table 1: The scope of the radical addition/cyclization and elimination reaction of allene-enes.

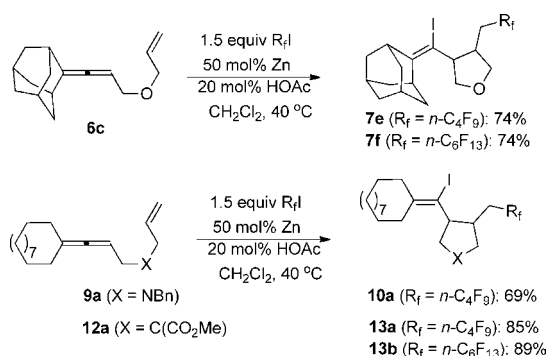
Reaction scheme showing the synthesis of compound **8** from compound **6** and R_fI (1.5 equiv) using 50 mol% Zn, 20 mol% HOAc, and CH_2Cl_2 at 40–45 °C overnight, followed by 2.1 equiv TBAF in toluene at 80 °C.

Entry	6 R^1	R^2	R^3	R_f	Yield [%] ^[a] 7 ^[b]	8
1	–(CH ₂) ₅ –	H (6a)	<i>n</i> -C ₄ F ₉	56 (7a)	92 (8a)	
2	–(CH ₂) ₅ –	H (6a)	<i>n</i> -C ₆ F ₁₃	60 (7b)	95 (8b)	
3	–(CH ₂) ₁₁ –	H (6b)	<i>n</i> -C ₄ F ₉	77 (7c)	93 (8c)	
4	–(CH ₂) ₁₁ –	H (6b)	<i>n</i> -C ₆ F ₁₃	60 (7d)	98 (8d)	
5	Me	Me	H (6d)	<i>n</i> -C ₄ F ₉	59 (7g)	83 (8g)
6	Me	Me	H (6d)	<i>n</i> -C ₆ F ₁₃	53 (7h)	83 (8h)
7	Bn	Bn	H (6e)	<i>n</i> -C ₄ F ₉	86 (7i)	96 (8i)
8	Bn	Bn	H (6e)	<i>n</i> -C ₆ F ₁₃	80 (7j)	88 (8j)
9	Me	<i>i</i> Bu	H (6f)	<i>n</i> -C ₄ F ₉	57 (7k)	83 (8k) ^[c]
10	Me	<i>i</i> Bu	H (6f)	<i>n</i> -C ₆ F ₁₃	74 (7l)	90 (8l) ^[c]
11	–(CH ₂) ₁₁ –	Me (6g)	<i>n</i> -C ₄ F ₉	79 (7m)	97 (8m)	
12	–(CH ₂) ₁₁ –	Me (6g)	<i>n</i> -C ₆ F ₁₃	80 (7n)	99 (8n) ^[d]	

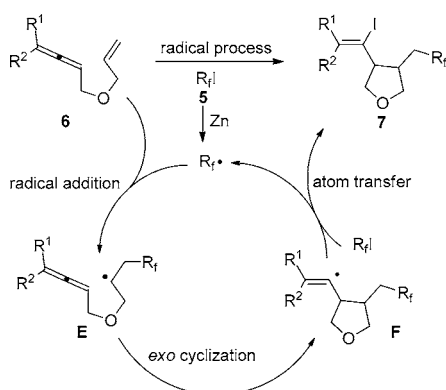
[a] Yield of isolated product. [b] All the products were mixtures of diastereomers. [c] 2.5 equiv of TBAF·3H₂O were used. [d] 2.9 equiv of TBAF·3H₂O were used.

Moreover, the allene-ene **6c** having an adamantanyl group as a terminal substituent on the allene yielded the *exo*-cyclization product **7e–f** in moderate yield. The allene-ene **9a** having NBn and the allene-ene **12a** having C-(COOMe)₂ as tethers instead of the oxygen atom yielded the *exo*-cyclization product **10a** and **13a,b**, respectively, in moderate to good yields (Scheme 3).

Thus, a possible mechanism of the radical addition/cyclization was proposed in Scheme 4: 1) the initiation of the reaction with Zn forms the perfluoroalkyl radical; 2) the formed perfluoroalkyl radical attacks the alkene moiety of allene-ene **6** to form the radical intermediate **E**; 3) an intramolecular radical *exo*-cyclization process yields the intermediate **F**; 4) atom transfer releases the product **7** and regenerates the perfluoroalkyl radical.



Scheme 3. Radical addition/cyclizations of allene-enes **6c**, **9a**, and **12a**.



Scheme 4. The mechanism.

In conclusion, we have developed the first example of radical addition/cyclization reactions of allene-enes in an alkene-to-allene fashion using zinc powder as a cheap, readily available, efficient, and mild initiator to afford the highly selective formation of *exo*-cyclization products in moderate to good yields. Utilizing TBAF-promoted dehydroiodination reactions we converted the inseparable product diastereomers into 3-(1-enylidene)heterocyclopentanes. As a result of the regeneration of the allenic structure, the final products can be additionally manipulated, thus showing the potential of this method in organic synthesis. Additional studies in this area are being carried out in our laboratory.

Experimental Section

Typical procedure: Zinc powder (48.0 mg, 0.74 mmol), **6a** (264.7 mg, 1.49 mmol), CH_2Cl_2 (1 mL), perfluorobutyl iodide (0.39 mL, $d = 2.01$, 0.7839 g, 2.3 mmol), HOAc (18.9 mg, 0.32 mmol), and CH_2Cl_2 (1 mL) were added sequentially under a nitrogen atmosphere at room temperature to a dried Schlenk tube equipped with a Teflon-coated magnetic stirring bar. The tube was then submerged in an oil bath that was preheated to 40 °C. After 12 h, the reaction was complete as monitored by GC. The crude reaction mixture was filtered through a short column of silica gel and evaporation of the solvent afforded a residue, which was purified by column chromatography on silica gel (eluent: 30–60 °C petroleum ether/diethyl ether = 80:1 → 40:1) to afford **7a** (437.4 mg, 56%) as a liquid. Because of the presence of two diastereomers, the ^1H and ^{19}F NMR spectra are very complicated

(see the Supporting Information). The product **7a** was used in next step without further characterization.

TBAF·3H₂O (130.3 mg, 0.42 mmol), **7a** (104.0 mg, 0.2 mmol), and toluene (2.0 mL) were added to a dried Schlenk tube equipped with a Teflon-coated magnetic stirring bar. The tube was then submerged in an oil bath that was preheated to 80 °C. After 7 h, the reaction was complete as monitored by TLC. The crude reaction mixture was filtered through a short column of silica gel and evaporation afforded a residue, which was purified by flash column chromatography on silica gel (eluent: 30–60 °C petroleum ether/diethyl ether = 80:1) to afford **8a** (72.2 mg, 92%) as a liquid. ^1H NMR (300 MHz, CDCl_3): δ = 4.37 (dd, $J_1 = 11.7$ Hz, $J_2 = 1.2$ Hz, 1H, one proton of CH_2O), 4.30–4.16 (m, 2H, 2 × (one proton of CH_2O)), 3.50 (t, $J = 8.6$ Hz, 1H, one proton of CH_2O), 3.18–3.04 (m, 1H, CH), 2.50–2.24 (m, 1H, one proton of CH_2R_f), 2.22–1.93 (m, 5H, one proton of CH_2R_f and 2 × CH_2), 1.75–1.44 ppm (m, 6H, 3 × CH_2); ^{13}C NMR (75 MHz, CDCl_3): δ = 188.1, 110.3, 102.1, 74.0 (d, $J = 4.3$ Hz), 68.5, 35.9 (d, $J = 2.6$ Hz), 33.1 (t, $J = 21.6$ Hz), 32.1, 31.5, 27.9, 27.7, 26.0 ppm; ^{19}F NMR (282 MHz, CDCl_3): δ = −81.0 ≈ (−81.1) (m, 3F), −111.9 (dm, $J = 276$ Hz, 1F), −114.5 (dm, $J = 276$ Hz, 1F), −124.5 ≈ (−124.7) (m, 2F), −125.9 ≈ (−126.2) ppm (m, 2F); IR (neat): $\tilde{\nu}$ = 2932, 2856, 1970, 1449, 1433, 1352, 1235, 1134, 1066, 1020 cm^{-1} ; MS (EI, 70 eV) m/z (%) 396 [M^+ , 100]; HRMS calcd for $\text{C}_{16}\text{H}_{17}\text{OF}_9$ [M^+]: 396.1136. Found: 396.1144.

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