Electrophilic Addition to 1-Cyclopropylallenes: A Highly Efficient and Stereoselective Method for the Preparation of 6-Substituted-1,3-hexadienes

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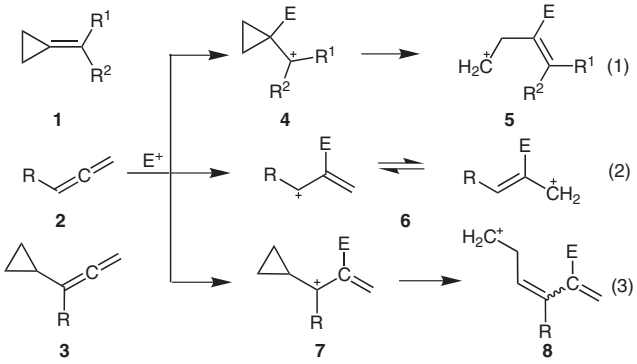
Abstract: Electrophilic additions to 1-cyclopropylallenes were investigated, providing an efficient and stereoselective method for the synthesis of 6-substituted-1,3-hexadienes.

Key words: cyclopropyl, allene, 1,3-hexadiene, electrophilic addition, stereoselective

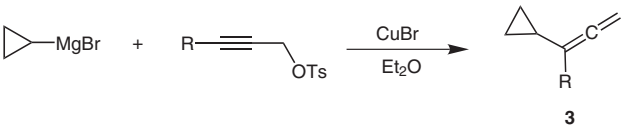
Methylenecyclopropanes **1** (MCP), which are highly strained but readily accessible molecules, are of current interest in synthetic organic chemistry. The relief of their ring strain provides a potent thermodynamic driving force, which facilitates the construction of complex and interesting organic molecules under mild conditions. Recently, the reactions and applications of MCP have been widely investigated.[1] Allenes **2** are also useful building blocks in organic synthesis and have attracted much attention of chemists for a long period. Due to their higher reactivity than noncumulated C–C double bonds, a variety of reactions could take place to produce a series of interesting products. During the last decade, allenes have played very important roles in organic methodology studies.[2]

Previous investigations on MCP have showed that when an electrophile (E^+) reacted with MCP, it first added to the C=C bond to produce an intermediate carbocation **4**. Because of the high strain of the cyclopropyl ring, C–C bond cleavage of **4** takes place and gives the intermediate **5** (Scheme 1, equation 1),[3] which can be transformed to homoallylic compounds in the subsequent reactions. Similarly, when E^+ reacts with allenes, the central carbon of allenes is attacked first to give intermediate **6** (Scheme 1, equation 2),[2c,4] which could be attacked by nucleophiles to produce the corresponding allyl derivatives.

1-Cyclopropylallenes **3**, which contain both a cyclopropyl group and an allene structural unit, could be conveniently prepared by the classical reaction of cyclopropyl Grignard reagent and toluene-4-sulfonic acid prop-2-ynyl ester catalyzed by copper(I) bromide (Scheme 2).[5] Due to the special structure of compound **3**, we assumed that when an electrophile E^+ reacts with **3**, the most probable intermediate would be **7**. The structure of **7** was very similar to that of the intermediate **4**. Therefore, if the same β-scission of C–C bond in the cyclopropyl group takes place, the corresponding 1,3-hexadiene cation **8** might be generated (Scheme 1, equation 3). Subsequent reactions of **8** could produce a compound that contains a conjugate diene structural unit. Conjugate dienes are useful building blocks in organic synthesis.[6] Hence, the investigations on the reactions of 1-cyclopropylallenes and their applications are of value.



Scheme 1



Scheme 2

Recently, we reported the reaction of 1-cyclopropyl-allenes with phenylselenyl bromide (Scheme 3).[7] In that reaction, the phenylselenyl cation first added to compound **3** to produce the intermediate **9**. Due to the large steric hindrance of phenylselenyl group, the cyclopropyl group in **9** should be at the same side with the group R. Hence, **10** was obtained as *E*-isomer selectively in the subsequent reaction. Herein, we wish to report additional findings on the electrophilic additions to 1-cyclopropyl-allenes. As it turned out, the reaction selectivity could be reversed when electrophiles (E^+) with less steric hindrance were employed.

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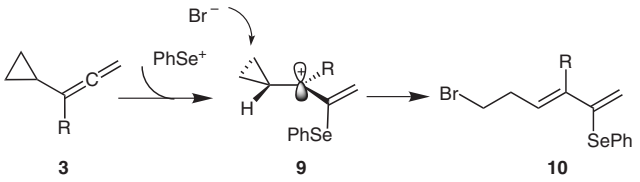
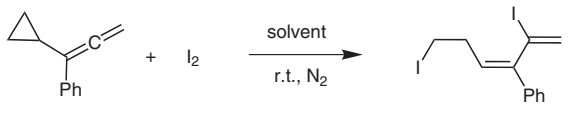


Scheme 3

Table 1 Reaction of 1-Phenyl-1-cyclopropylallene with Iodine under Different Conditions[a]



Entry	Solvent	Time (min)[b]	Yield of **11a** (%)[c]
1	Et_2O	1	72
2	PE	5	66
3	THF	1	78
4	Me_2CO	30	60
5	CH_2Cl_2	1	85
6	$CHCl_3$	1	81

[a] Reaction conditions: iodine (0.3 mmol) was dissolved in solvent (5 mL. The solution was dropped into **1a** (0.3 mmol), which was dissolved in solvent (1 mL) at r.t. under nitrogen atmosphere.
[b] The reaction was monitored by TLC (eluent: PE).
[c] Isolated yields.

Initially, we examined the electrophilic addition of iodine to 1-cyclopropyl allenes (Table 1). When an iodine solution in diethyl ether was dropped to 1-phenyl-1-cyclopropylallene (**3a**), the reaction proceeded rapidly and the color of iodine disappeared immediately. After stirring for one extra minute, the product 2,6-diiodo-3-phenyl-1,3-hexadiene (**11a**) was obtained in 72% yield. Further screening demonstrated that CH_2Cl_2 was a better solvent and in this case, the product yield could be enhanced to 85% (Table 1, entry 5). It was notable that in this reaction, the selectivity was different from our previous investigations and only the *Z*-isomer was obtained. The configuration of the product **11a** was established by the NOESY spectrum studies (Figure 1).

We next examined the application scope of this reaction under the optimized conditions (Table 2) and a series of 2,6-diiodo-1,3-hexadienes were synthesized from the corresponding 1-cyclopropylallenes.[8] In most cases, the *Z*-isomers were obtained as the only product (Table 2, entries 1–5). When R = Bn, a small quantity of the *E*-isomer was also observed from ^{1}H NMR spectrum. This was probably due to the lower steric hindrance of the Bn group (Table 2, entry 6).

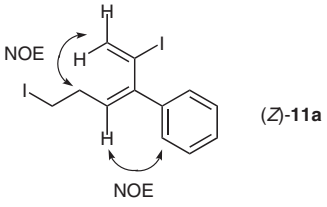
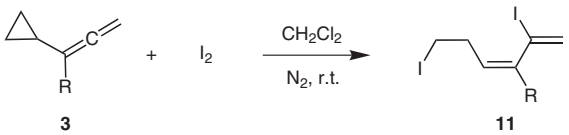


Figure 1

Table 2 Synthesis of 2,6-Diiodo-1,3-hexadienes from 1-Cyclopropylallenes



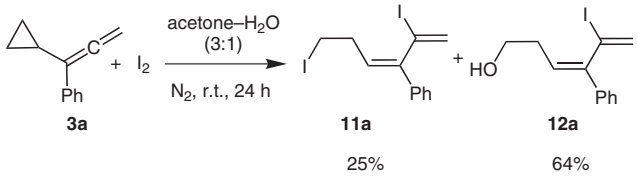
Entry	R	Yield of **11** (%)[a]
1	Ph (**3a**)	85 (*Z*) (**11a**)
2	2-MeC_6H_4 (**3b**)	73 (*Z*) (**11b**)
3	3-MeC_6H_4 (**3c**)	79 (*Z*) (**11c**)
4	4-MeC_6H_4 (**3d**)	88 (*Z*) (**11d**)
5	4-ClC_6H_4 (**3e**)	70 (*Z*) (**11e**)
6	Bn (**3f**)	65 (*Z*/*E* = 84:16) (**11f**)

[a] Isolated yields.

Interestingly, when the reaction was conducted in aqueous acetone, iodohydroxylation product **12a** was obtained in 64% yield as the major product (Scheme 4).[9,10]

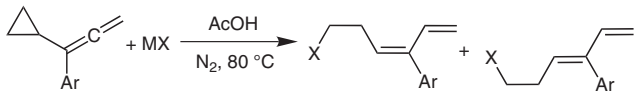
Furthermore, we investigated electrophilic addition of H^+ as electrophile to 1-cyclopropylallenes. When 1-phenyl-1-cyclopropylallene **3a** was heated in AcOH for two hours in the presence of KI, the corresponding electrophilic addition product 3-phenyl-6-iodo-1,3-hexadiene (**13a**) was obtained in 52% yield with poor stereoselectivity (Table 3, entry 1). The stereoselectivity was enhanced when KBr or NaCl was employed (Table 3, entries 2, 3). However, when KF was employed, no HF adduct was found (Table 3, entry 4). Meanwhile, the experimental results showed that the substituent position at the aryl ring would strongly affect the stereoselectivity (Table 3, entries 5–7).[11]

We also examined the Lewis acid assisted addition of EtOH to 1-cyclopropylallenes. However, the stereoselectivity of the reaction was poor. When **3a** was heated in EtOH at 60 °C under nitrogen atmosphere in the presence of $BF_3{\cdot}OEt_2$, the EtOH adduct **14a** was obtained in 78% yield while the ratio of *E*/*Z* was 63:37. Similarly, protonic acid could also be employed in this reaction (Scheme 5).[12]



Scheme 4

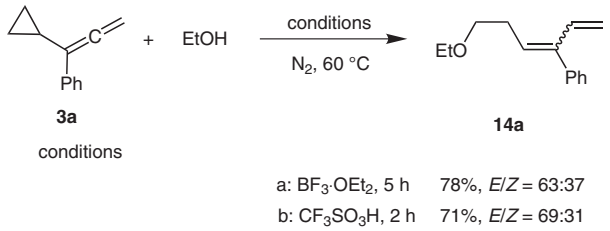
Table 3 Electrophilic Addition of HX to 1-Cyclopropylallenes[a]



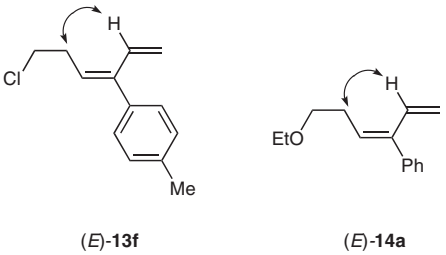
3 (*E*)-**13** (*Z*)-**13**

Entry	Ar	MX	Time (h)[b]	Yield of **13** (%, *E*/*Z*)[c]
1	Ph (**3a**)	KI	2	**13a** 52 (59:41)
2	Ph (**3a**)	KBr	4	**13b** 65 (87:13)
3	Ph (**3a**)	NaCl	4	**13c** 75 (91:9)
4	Ph (**3a**)	KF	24	0[d]
5	2-MeC_6H_4 (**3b**)	NaCl	6	**13d** 60 (68:32)
6	3-MeC_6H_4 (**3c**)	NaCl	6	**13e** 67 (81:19)
7	4-MeC_6H_4 (**3d**)	NaCl	4	**13f** 72 (97:3)

[a] Reaction conditions: **3** (0.3 mmol) and MX (0.6 mmol) were heated in AcOH (1 mL) at 80 °C under a nitrogen atmosphere.
[b] The reaction was monitored by TLC (eluent: PE).
[c] Isolated yields.
[d] Only the cyclopropyl-ring-untouched AcOH adduct was observed.



Scheme 5



(*E*)-**13f** (*E*)-**14a**

Figure 2

The configurations of **13f** and **14a** were also established by NOESY spectroscopic studies (Figure 2).

In conclusion, we reported the electrophilic addition reactions of electrophiles (E^+) to 1-cyclopropylallenes. In most cases, the stereoselectivity of the reaction was good. Hence, it might provide a highly efficient and stereoselective method for the synthesis of 6-sustituted-1,3-hexadienes. Compared with our previous investigations, we have found that the stereoselectivity could be reversed when electrophiles with lower steric hindrance were employed. Further investigations on 1-cyclopropylallenes are being undertaken in our laboratory.

Acknowledgment

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(8) **Preparation of (*Z*)-2,6-Diiodo-3-phenyl-1,3-hexadiene (11a); Typical Procedure**
1-Phenyl-1-cyclopropylallene (**3a**, 0.3mmol) was first dissolved in CH_2Cl_2 (1 mL). Under a nitrogen-atmosphere protection, a solution of I_2 (0.3 mmol) in CH_2Cl_2 (5 mL) was slowly added. The reaction proceeded very rapidly and color of I_2 disappeared immediately. The reaction liquid was stirred for an extra 1 min. Then, the solvent was evaporated under vacuum and residue was separated by preparation TLC (eluent: PE) to give **11a** in 85% yield. The other 2,6-diiodo-1,3-hexadienes were prepared in a similar way.

Selected Spectroscopic Data of 11a

IR (film): 3055, 3024, 2956, 2923, 1602, 1444, 1235, 1171, 1104, 908, 762, 696 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.25–7.45 (m, 5 H), 6.24 (s, 1 H), 6.21 (s, 1 H), 5.83 (t, *J* = 7.2 Hz, 1 H), 3.26 (t, *J* = 7.2 Hz, 2 H), 2.86–2.91 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 3.6, 33.4, 102.6, 126.6, 127.4, 128.1, 128.5, 130.6, 137.4, 145.8. MS (EI, 70 eV): *m/z* (%) = 410 (13) [M^+], 283 (100). HRMS (EI): *m/z* calcd for $C_{12}H_{12}I_2$: 409.9029; found: 409.9038.

(9) **Spectroscopic Data of Compound 12a**

IR (film): 3352, 2924, 2876, 1603, 1444, 1088, 1047, 907, 763, 697cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.26–7.44 (m, 5 H), 6.23 (s, 1 H), 6.21 (s, 1 H), 5.93 (t, *J* = 7.6 Hz, 1 H), 3.79 (t, *J* = 6.4 Hz, 2 H), 2.55–2.60 (m, 2 H), 1.60 (s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 33.4, 61.8, 103.1, 125.3, 126.5, 127.9, 128.4, 130.6, 137.6, 146.2. MS (EI, 70 eV): *m/z* (%) = 300 (10) [M^+], 173 (44), 141 (100). HRMS (EI): *m/z* calcd for $C_{12}H_{13}OI$: 300.0011; found: 300.0019.

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(11) **Preparation of (*E*)-3-Phenyl-6-chloro-1,3-hexadiene (13c); Typical Procedure**

Under a nitrogen-atmosphere protection, 1-phenyl-1-cyclopropylallene (**3a**, 0.3 mmol) and NaCl (0.6 mmol) were dissolved in AcOH (1 mL). The mixture was stirred at 80 °C for 4 h. Then, the solvent was evaporated under vacuum and residue was separated by preparation TLC (eluent: PE) to give **13c** in 75% yield. The other 6-halo-1,3-hexadienes could be prepared in the similar way.

Selected Spectroscopic Data of 13c

IR (film): 3057, 3024, 2959, 1492, 1444, 990, 919, 767, 702 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.24–7.34 (m, 5 H), 6.77–6.82 (m, 1 H), 5.56 (t, *J* = 7.2 Hz, 1 H), 5.32 (d, *J* = 11.2 Hz, 1 H), 5.13 (d, *J* = 17.2 Hz, 1 H), 3.61 (t, *J* = 7.2 Hz, 2 H), 2.76–2.81 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 31.4, 43.9, 118.9, 127.2, 128.0, 128.7, 129.4, 132.7, 140.9, 142.4. MS (EI, 70 eV): *m/z* (%) = 192 (32) [M^+], 143 (80), 128 (100). HRMS (EI): *m/z* calcd for $C_{12}H_{13}Cl$: 192.0706; found: 192.0712.

(12) **Spectroscopic Data of Compound 14a**

E-Isomer: ^1H NMR (400 MHz, $CDCl_3$): δ = 7.13–7.39 (m, 5 H), 6.83–6.90 (m, 1 H), 5.59 (t, *J* = 7.2 Hz, 1 H), 5.28 (d, *J* = 11.2 Hz, 1 H), 5.10 (d, *J* = 17.2 Hz, 1 H), 3.50–3.59 (m, 4 H), 2.59–2.65 (m, 2 H), 1.24 (t, *J* = 7.2 Hz, 3 H).

Z-Isomer: ^1H NMR (400 MHz, $CDCl_3$): δ = 7.13–7.39 (m, 5 H), 6.54–6.61 (m, 1 H), 5.77 (t, *J* = 7.6 Hz, 1 H), 5.01 (d, *J* = 10.8 Hz, 1 H), 4.70 (d, *J* = 17.2 Hz, 1 H), 3.36–3.45 (m, 4 H), 2.21–2.26 (m, 2 H), 1.16 (t, *J* = 7.2 Hz, 3 H).

Mixture of *Z*- and *E*-isomers: IR (film): 2974, 2863, 1491, 1443, 1377, 1112, 911, 768, 703 cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 202 (10) [M^+], 201 (17), 156 (96), 129 (100). HRMS (EI): *m/z* calcd for $C_{14}H_{18}O$: 202.1358; found: 202.1356.