



Difunctional additions to 1-cyclopropylallenes: an efficient and stereospecific method for the synthesis of 2,6-difunctional-1,3-hexadienes

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ABSTRACT

The difunctional additions of electrophiles and nucleophiles to 1-cyclopropylallenes were investigated. Two different functional groups were introduced at the same time to give 2,6-difunctional-1,3-hexadienes stereoselectively in good yields.

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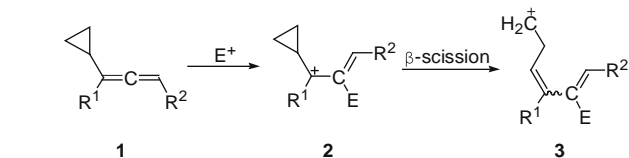
1-Cyclopropylallenes **1**, which contain both a cyclopropyl group and an allene structural unit, are a kind of useful building blocks in organic synthesis.¹ The special molecule structure of 1-cyclopropylallenes makes them act like allenes² and sometimes methylenecyclopropanes³ in organic reactions. Recently, we have investigated the electrophilic additions of 1-cyclopropylallenes.⁴ In these reactions, the electrophilic group was first added to the center carbon of allene group of 1-cyclopropylallenes to give the intermediate carbon cation **2**. The following β -scission of **2** gave the homoallylic carbon cation **3**, which could be transformed to the corresponding homoallylic derivatives (Scheme 1). It is notable that, in these reactions, the stereoselectivities are generally good and one even two multisubstituted C=C double bonds could be generated stereoselectively in the final product. Hence, this would give an efficient and stereospecific method for the synthesis of multisubstituted olefins.

Being able to introduce two different functional groups at the same time, difunctional reactions are important in organic synthesis.⁵ On the basis of our previous investigations on electrophilic additions of 1-cyclopropylallenes, here, we wish to report our recent investigation results on difunctional reactions of 1-cyclopropylallenes. Specially, two changeable functional groups were

introduced simultaneously by one molecule of electrophile and another molecule of nucleophile, which would provide an efficient and stereoselective tool for the synthesis of 2,6-difunctional-1,3-hexadienes.

We initially examined the difunctional reaction of 1-cyclopropylallene **1a** with NIS–MBr system. When **1a**, NIS and KBr were stirred in DCM at room temperature for 15 h, the desired difunctional adduct **4a** could be obtained in 43% yield (Table 1, entry 1). Further screening demonstrated that employing THF as solvent would enhance the yield of **4a** (Table 1, entry 4) and NaBr should be a better bromo source (Table 1, entry 7).

With the optimized reaction conditions in hand, we next examined the application scope of this reaction. The experimental results were listed in Table 2. It is obvious that Cl, Br, or I group could be conveniently introduced to the 2- or 6-position of the product as wish (Table 2, entries 1–6). The yields of **4** were gener-



Scheme 1. Electrophilic addition of 1-cyclopropylallenes to generate homoallylic derivatives.

Table 1
The reaction of **1a** with NIS–MBr system^a

Entry	MBr	Solvent	Time ^b (h)	Yield of 4a ^c (%)
1	KBr	DCM	15	43
2	KBr	DMF	6	27
3	KBr	MeCN	8	48
4	KBr	THF	15	52
5	Bu ₄ NBr	THF	10	31
6	LiBr	THF	3	59
7	NaBr	THF	0.5	77

^a 0.3 mmol of **1a**, NIS and MBr, and 2 mL of solvent were employed.

^b The reaction was monitored by TLC (eluent: petroleum ether).

^c Isolated yields.

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Table 2
Dihalogenation of 1-cyclopropylallenes (**1**)^a

Entry	R	X	MY	Yield of 4 ^b (%)
1	Ph (1a)	I	NaBr	77 (4a)
2	1a	I	NaCl	61 (4b)
3	1a	I	NaI	87 (4c)
4	1a	Br	NaCl	67 (4d)
5	1a	Br	NaBr	74 (4e)
6	1a	Cl	NaCl	69 (4f)
7	<i>p</i> -CH ₃ C ₆ H ₄ (1b)	I	NaBr	85 (4g)
8	<i>p</i> -ClC ₆ H ₄ (1c)	I	NaBr	79 (4h)
9	Bn (1d)	I	NaBr	54 (4i) (Z/E = 81:19) ^c

^a 0.3 mmol of **1**, NIS and MY, and 2 mL of THF were employed.

^b Isolated yields.

^c The ratio of isomers was calculated from ¹H NMR spectrum.

ally good and only *Z*-isomers were obtained except in entry 9, when R was Bn, which had a lower steric hindrance. The configurations of **4c** and **4h** were determined by the NOESY spectrum study (Fig. 1).

When distally substituted 1-cyclopropylallenes were employed, two multisubstituted C=C double bonds could be generated in the product to give the 1*Z*, 3*Z* isomer as the major product (Table 3). The configurations of **4k**, **4m**, and **4o** were established on the NOESY spectrum studies (Fig. 2).

Furthermore, the application scope of this reaction was not limited only to the synthesis of 2,6-dihalo-1,3-hexadienes. The corresponding difunctional adducts could be smoothly obtained when

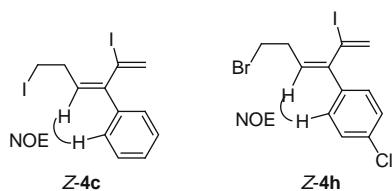


Figure 1. Configurations of *Z*-**4c**, **4h**.

Table 3
Dihalogenation of 1,3-disubstituted-1-cyclopropylallenes^a

Entry	R ¹ , R ²	X	Y	Yield of 4 (%) (A/B/C/D) ^b
1	C ₆ H ₅ , <i>p</i> -BrC ₆ H ₄ (1e)	I	Br	76 (86/14/0/0) (4j)
2	<i>o</i> -CH ₃ C ₆ H ₄ , <i>p</i> -BrC ₆ H ₄ (1f)	I	Br	68 (89/11/0/0) (4k)
3	<i>m</i> -CH ₃ C ₆ H ₄ , <i>p</i> -BrC ₆ H ₄ (1g)	I	Br	71 (85/15/0/0) (4l)
4	<i>p</i> -ClC ₆ H ₄ , <i>p</i> -BrC ₆ H ₄ (1h)	I	Br	81(89/11/0/0) (4m)
5	C ₆ H ₅ , C ₂ H ₅ (1i)	I	Br	58 (60/40/0/0) (4n) ^c
6	C ₆ H ₅ , <i>p</i> -BrC ₆ H ₄ (1e)	I	Cl	69(91/9/0/0) (4o)
7	C ₆ H ₅ , C ₆ H ₅ (1j)	Br	Cl	61(66/34/0/0) (4p)

^a 0.3 mmol of **1**, NXS and NaY, and 2 mL of THF were employed.

^b Isolated yields.

^c The ratio of isomers was calculated from ¹H NMR spectrum.

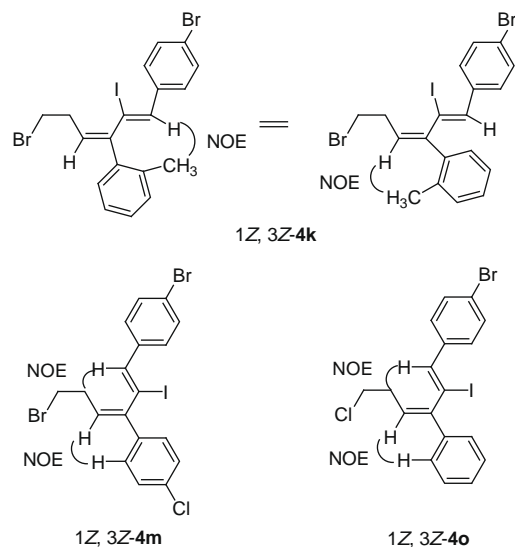


Figure 2. Configurations of 1*Z*, 3*Z*-**4k**, **4m**, **4o**.

other nucleophiles were employed. These include alcohol, carboxylic acid, amide, and NaNCS (Table 4, entries 1–5). Similarly, PhSe⁺, generated by *N*-phenylselenophthalimide (NPSP), could also be employed as electrophile to produce the corresponding 2,6-difunctional adducts (Table 4, entries 6 and 7). It is notable that all these reactions underwent with excellent stereoselectivity. The configurations of **5b** and **5g** were established on the NOESY spectrum studies (Fig. 3).

A possible mechanism of this reaction was shown in Scheme 2. Electrophilic addition of electrophiles to **1** would give the intermediate allylic carbon cation **5**, which could be **5(A)** and **5(B)** in resonance.⁴ In **5(A)**, R² was inclined to be at the same side with E due to the steric hindrance factor while in **5(B)**, R¹ was inclined to be at the same side with the hydrogen atom. These determined the configuration of the 1-position and 3-position C=C double bonds in product **4**.⁶ Further reaction of **5(B)** with nucleophiles would give the final product **4** in 1*Z*, 3*Z* configuration as the overwhelming major product (Table 3). When R¹ = alkyl group, the carbon cation in **5(B)** could not be well stabilized. Thus, the yield of **4** declined (Table 2, entry 9). Meanwhile, when R¹ or R² were lower steric hindrance groups, the selectivity on the 3-position or 1-position C=C double bonds declined, respectively (Table 2, entry 9 and Table 3, entry 5).

Table 4
Difunctional additions of **1a** with other electrophiles and nucleophiles

Entry	Electrophile	Nucleophile	Yield of 5 ^c (%)
1 ^a	NIS	EtOH	82 (5a)
2 ^a	NIS	(CH ₃) ₂ CHOH	76 (5b)
3 ^b	NIS	NaOAc	87 (5c)
4 ^b	NIS	NaNCS	69 (5d)
5 ^c	NBS	PhCONH ₂	21 (5e)
6 ^d	NPSP	EtOH	76 (5f)
7 ^d	NPSP	NaBr	65 (5g)

^a 0.3 mmol of **1a**, NIS, and 2 mL of nucleophile were employed.

^b 0.3 mmol of **1a**, NIS, nucleophile, and 2 mL of THF were employed.

^c 0.3 mmol of **1a**, NBS, PhCONH₂, and 2 mL of EtOAc were employed.

^d 0.3 mmol of **1a**, NPSP, nucleophile, and 2 mL of THF were employed.

^e Isolated yields.

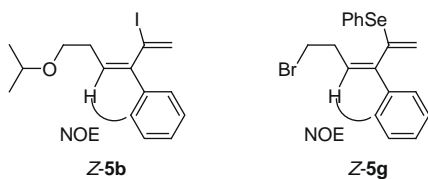
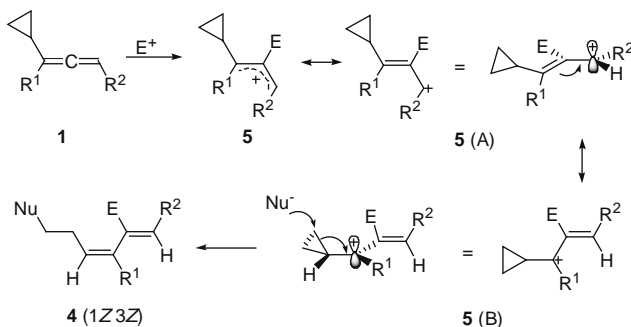
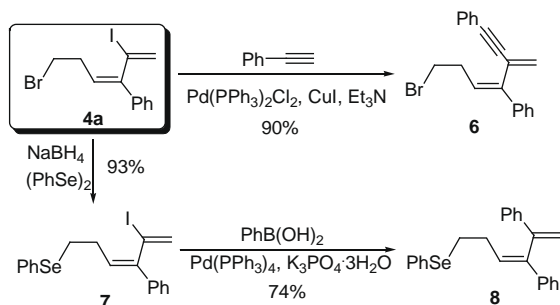


Figure 3. Configurations of Z-5b, 5g.



Scheme 2. Proposed mechanism for the reaction.



Scheme 3. The synthetic utilities of Z-4a.

Containing both a conjugated diene structural unit and a homoallylic structural unit, **4** might be of potential value in organic synthesis.^{7,8} Moreover, the functional groups on 2- or 6-position of **4** allowed it to be easily transformed to some other useful skeletons (Scheme 3). For example, the Sonogashira coupling⁹ of **4a** with alkyne would give the alkynyl-substituted conjugated diene **6** in good yield. Compound **7** was generated through nucleophilic substitution of **4a** in the presence of NaBH₄ and (PhSe)₂, and could further occur Suzuki coupling to give **8** in 74% yield. All of these analogs are important organic compounds in part due to their applications in Diels–Alder reactions and exploration of materials for electronic and photonic applications,¹⁰ and in part due to their existence in many chromophores as a substructure.¹¹

In conclusion, we reported the difunctional additions of 1-cyclopropylallenes. The selectivity of this reaction was good and two different functional groups could be introduced at the same time. This would provide an efficient and stereospecific method for the synthesis of 2,6-difunctional-1,3-hexadienes.¹² Further investigations on 1-cyclopropylallenes are being undertaken in our laboratory.

Acknowledgments

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Research Program of China (973 Program, 2009CB825300), and CAS Academician Foundation of Zhejiang Province for financial support.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.02.055.

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- Typical procedure of Synthesis of 2,6-dihalo-1,3-hexadienes 4*: In a Schlenk tube, 0.3 mmol of **1** was dissolved in 2 mL of THF under nitrogen atmosphere. Then, 0.3 mmol of NXS and MY (metal halides) were added. The mixture was stirred at room temperature and the reaction was monitored by TLC (eluent: petroleum ether). When the reaction terminated, the solvent was evaporated under vacuum, and the residue was isolated by preparation TLC (eluent: petroleum ether) to give the corresponding product **4**. *Selected spectroscopic data of compound 4a*: Oil. IR (film): 3023, 2959, 1603, 1445, 1105, 965, 761, 694 cm⁻¹. ¹H NMR (400 MHz, CDCl₃, TMS): δ 7.41 (d, J = 6.8 Hz, 2H), 7.30–7.35 (m, 3H), 6.22 (s, 1H), 6.19 (s, 1H), 5.87 (t, J = 7.2 Hz, 1H), 3.47 (t, J = 6.8 Hz, 2H), 2.84 (q, J = 6.8 Hz, 2H). ¹³C NMR (100 MHz, CDCl₃): δ 31.3, 32.8, 102.6, 125.5, 126.6, 128.1, 128.4, 130.7, 137.3, 146.3. MS (EI, 70 eV): m/z (%) 362 (25) [M⁺], 156 (100). HRMS (EI): m/z calcd for C₁₂H₁₂BrI: 361.9167; found: 361.9165. *Selected spectroscopic data of compound 5a*: Oil. IR (film): 2973, 2864, 1604, 1446, 1375, 1109, 907, 763 cm⁻¹. ¹H NMR (400 MHz, CDCl₃, TMS): δ 7.44–7.45 (m, 2H), 7.31–7.38 (m, 3H), 6.25 (s, 1H), 6.22 (s, 1H), 5.96 (t, J = 7.2 Hz, 1H), 3.51–3.59 (m, 4H), 2.59 (t, J = 7.2 Hz, 2H), 1.24 (t, J = 7.2 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 15.2, 30.6, 66.2, 69.3, 103.2, 125.9, 126.6, 127.8, 128.3, 130.5, 137.8, 145.3. MS (EI, 70 eV): m/z (%) 328 (7) [M⁺], 115 (100). HRMS (EI):

m/z calcd for C₁₄H₁₇O: 328.0324; found: 328.0316. *Selected spectroscopic data of compound 6*: Oil. IR (film): 2922, 1724, 1490, 1241, 1172, 913, 756 cm⁻¹. ¹H NMR (400 MHz, CDCl₃, TMS): δ 7.48–7.50 (m, 2H), 7.34–7.37 (m, 4H), 7.26–7.32 (m, 4H), 5.88–5.91 (m, 2H), 5.46 (s, 1H), 3.28 (t, *J* = 7.2 Hz, 2H), 2.99 (q, *J* = 7.2 Hz, 2H). ¹³C NMR (100 MHz, CDCl₃): δ 5.0, 33.5, 89.3, 89.9, 122.9, 126.7, 127.1, 127.6, 128.2, 128.3, 128.3, 128.5, 129.0, 131.6, 140.0, 141.6. MS (EI, 70 eV): *m/z* (%) 336 (20) [M⁺], 105 (100). HRMS (EI): *m/z* calcd for C₂₀H₁₇Br: 336.0514; found: 336.0508. *Spectroscopic data of Compound 7*: Oil. IR (film): 2936, 1598, 1411, 1207, 985, 764 cm⁻¹. ¹H NMR (400 MHz, CDCl₃, TMS): δ 7.58–7.61 (m, 2H), 7.30–7.45 (m, 8H), 6.19 (s, 1H), 6.18 (s, 1H), 5.95 (t, *J* = 7.6 Hz, 1H), 3.08 (t, *J* = 7.2 Hz, 2H), 2.76 (q, *J* = 7.2 Hz, 2H). ¹³C NMR (100 MHz, CDCl₃): δ 26.2, 30.3, 102.9, 126.5, 126.8, 127.6, 127.8, 128.3, 129.0,

130.0, 130.4, 132.7, 137.5, 145.0. MS (EI, 70 eV): *m/z* (%) 440 (2) [M⁺], 313 (100). HRMS (EI): *m/z* calcd for C₁₈H₁₇Se: 439.9540; found: 439.9544. *Spectroscopic data of Compound 8*: Oil. IR (film): 2963, 1588, 1432, 1311, 1125, 1094, 887, 775 cm⁻¹. ¹H NMR (400 MHz, CDCl₃, TMS): δ 7.49–7.51 (m, 2H), 7.44–7.46 (m, 2H), 7.29–7.34 (m, 5H), 7.26–7.28 (m, 3H), 7.22–7.23 (m, 3H), 5.86 (t, *J* = 7.2 Hz, 1H), 5.52 (s, 1H), 5.38 (s, 1H), 2.84 (t, *J* = 7.6 Hz, 2H), 2.61 (q, *J* = 7.2 Hz, 2H). ¹³C NMR (100 MHz, CDCl₃): δ 27.1, 30.6, 117.9, 126.6, 126.8, 127.5, 128.1, 128.2, 128.5, 129.0, 129.1, 129.2, 130.2, 132.6, 136.6, 139.0, 140.0, 141.7. MS (EI, 70 eV): *m/z* (%) 390 (12) [M⁺], 235 (100). HRMS (EI): *m/z* calcd for C₂₄H₂₂Se: 390.0887; found: 390.0882. Spectroscopic data of the other compounds please see the [Supplementary data file](#).