Tetrahedron Letters 50 (2009) 1947-1950

Contents lists available at ScienceDirect

**Tetrahedron Letters** 

journal homepage: www.elsevier.com/locate/tetlet



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

Bo Meng<sup>a</sup>, Lei Yu<sup>b</sup>, Xian Huang<sup>a,c,\*</sup>

<sup>a</sup> Department of Chemistry, Zhejiang University (Xixi Campus), Hangzhou 310028, People's Republic of China <sup>b</sup> School of Chemistry and Chemical Engineering, Yangzhou University, Yangzhou 225002, People's Republic of China <sup>c</sup> State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, People's Republic of China

#### ARTICLE INFO

Article history: Received 23 November 2008 Revised 4 February 2009 Accepted 6 February 2009 Available online 13 February 2009

#### 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.

© 2009 Elsevier Ltd. All rights reserved.

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 allenes<sup>2</sup> and sometimes methylenecyclopropanes<sup>3</sup> in organic reactions. Recently, we have investigated the electrophilic additions of 1-cyclopropylallenes.<sup>4</sup> 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  $\beta$ -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.<sup>5</sup> 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



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

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-1,3hexadienes.

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-

# Table 1 The reaction of 1a with NIS-MBr system<sup>a</sup>

	$\begin{array}{c} & \\ & \\ & \\ Ph \end{array} = C = + NIS + MBr \xrightarrow{solvent}_{N_2, temp} Br \xrightarrow{I}_{Ph} \end{array}$					
	1a		4a			
Entry	MBr	Solvent	Time <sup>b</sup> (h)	Yield of <b>4a</b> <sup>c</sup> (%)		
1	KBr	DCM	15	43		
2	KBr	DMF	6	27		
3	KBr	MeCN	8	48		
4	KBr	THF	15	52		
5	Bu4NBr	THF	10	31		
6	LiBr	THF	3	59		
7	NaBr	THF	0.5	77		

<sup>a</sup> 0.3 mmol of **1a**, NIS and MBr, and 2 mL of solvent were employed.

<sup>b</sup> The reaction was monitored by TLC (eluent: petroleum ether).

<sup>c</sup> Isolated yields.

<sup>\*</sup> Corresponding author. Tel.: +86 571 88807077; fax: +86 571 88807077. *E-mail address:* huangx@mail.hz.zj.cn (X. Huang).

<sup>0040-4039/\$ -</sup> see front matter @ 2009 Elsevier Ltd. All rights reserved. doi:10.1016/j.tetlet.2009.02.055

#### Table 2

1

3

4

5

7

9

Dihalogenation of 1-cyclopropylallenes (1)<sup>a</sup>



<sup>a</sup> 0.3 mmol of **1**, NIS and MY, and 2 mL of THF were employed.

<sup>b</sup> Isolated yields.

<sup>c</sup> The ratio of isomers was calculated from <sup>1</sup>H 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 1Z, 3Z 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



				isomers of 4
Entry	R <sup>1</sup> , R <sup>2</sup>	Х	Y	Yield of <b>4</b> (%) (A/B/C/D) <sup>b</sup>
1	$C_6H_5$ , <i>p</i> -Br $C_6H_4$ ( <b>1e</b> )	Ι	Br	76 (86/14/0/0) ( <b>4j</b> )
2	o-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> , p-BrC <sub>6</sub> H <sub>4</sub> ( <b>1f</b> )	Ι	Br	68 (89/11/0/0) ( <b>4k</b> )
3	m-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> , $p$ -BrC <sub>6</sub> H <sub>4</sub> ( <b>1g</b> )	Ι	Br	71 (85/15/0/0) ( <b>4l</b> )
4	p-ClC <sub>6</sub> H <sub>4</sub> , $p$ -BrC <sub>6</sub> H <sub>4</sub> ( <b>1h</b> )	Ι	Br	81(89/11/0/0) ( <b>4m</b> )
5	$C_6H_5$ , $C_2H_5$ ( <b>1i</b> )	Ι	Br	58 (60/40/0/0) ( <b>4n</b> ) <sup>c</sup>
6	$C_6H_5$ , p-Br $C_6H_4$ ( <b>1e</b> )	Ι	Cl	69(91/9/0/0) ( <b>40</b> )
7	$C_6H_5, C_6H_5$ ( <b>1j</b> )	Br	Cl	61(66/34/0/0) (4p)

<sup>a</sup> 0.3 mmol of **1**, NXS and NaY, and 2 mL of THF were employed.

<sup>b</sup> Isolated yields.

<sup>c</sup> The ratio of isomers was calculated from <sup>1</sup>H NMR spectrum.



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

other nucleophiles were employed. These include alcohol, carboxylic acid, amide, and NaNCS (Table 4, entries 1-5). Similarly, PhSe<sup>+</sup>, 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.<sup>4</sup> In 5(A),  $R^2$  was inclined to be at the same side with E due to the steric hindrance factor while in 5(B),  $R^1$  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**.<sup>6</sup> 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  $R^1$  = 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 R<sup>1</sup> or R<sup>2</sup> 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 $5^{e}$ (%)
1 <sup>a</sup>	NIS	EtOH	82 ( <b>5a</b> )
2 <sup>a</sup>	NIS	(CH <sub>3</sub> ) <sub>2</sub> CHOH	76 ( <b>5b</b> )
3 <sup>b</sup>	NIS	NaOAc	87 ( <b>5c</b> )
4 <sup>b</sup>	NIS	NaNCS	69 ( <b>5d</b> )
5 <sup>c</sup>	NBS	PhCONH <sub>2</sub>	21 ( <b>5e</b> )
6 <sup>d</sup>	NPSP	EtOH	76 ( <b>5f</b> )
7 <sup>d</sup>	NPSP	NaBr	65 ( <b>5g</b> )

<sup>a</sup> 0.3 mmol of **1a**, NIS, and 2 mL of nucleophile were employed.

<sup>b</sup> 0.3 mmol of **1a**, NIS, nucleophile, and 2 mL of THF were employed.

<sup>c</sup> 0.3 mmol of **1a**, NBS, PhCONH<sub>2</sub>, and 2 ml of EtOAc were employed.

<sup>d</sup> 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.<sup>7,8</sup> 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 coupling<sup>9</sup> 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 NaBH<sub>4</sub> and (PhSe)<sub>2</sub>, 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,<sup>10</sup> and in part due to their existence in many chromophores as a substructure.<sup>11</sup>

In conclusion, we reported the difunctional additions of 1cyclopropylallenes. 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.<sup>12</sup> Further investigations on 1-cyclopropylallenes are being undertaken in our laboratory.

#### Acknowledgments

We are grateful to the National Natural Science Foundation of China (Project Nos. 20732005 and 20872127), National Basic 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.

## **References and notes**

- 1. 1-Cyclopropylallenes could be conveniently prepared by the classical reaction of cyclopropyl Grignard reagent with toluene-4-sulfonic acid prop-2-ynyl ester catalyzed by copper (I) bromide. For details see: Brandsma, L; Verkruijsse, H. D. Synthesis of Acetylenes, Allenes and Cumlenes; Elsevier: Netherlands, 1981.
- For recent reviews and accounts of allenes see: (a) Yamamoto, Y.; Radhakrishnan, U. Chem. Soc. Rev. 1999, 28, 199; (b) Ma, S. Acc. Chem. Res. 2003, 36, 701; (c) Larock, R. C. J. Organomet. Chem. 1999, 576, 111; (d) Grigg, R.; Sridharan, V. J. Organomet. Chem. 1999, 576, 65; (e) Zimmer, R.; Dinesh, C. U.; Nandanan, E.; Khan, F. A. Chem. Rev. 2000, 100, 3067; (f) Hashmi, A. S. K. Angew. Chem. 2000, 112, 3737; Hashmi, A. S. K. Angew. Chem., Int. Ed. 2000, 39, 3590; (g) Ma, S.; Li, L. Synlett 2001, 1206; (h) Reissing, H. U.; Schade, W.; Amombo, M. O.; Pulz, R.; Hausherr, A. Pure Appl. Chem. 2002, 175; (i) Ma, S. Carbopalladation of Allenes. In Handbook of Organopalladium Chemistry for Organic Synthesis; Negishi, E., Ed.; Wiley-Interscience: NewYork, 2002; p 1491.
- Selected reviews on methylenecyclopropanes: (a) Brandi, A.; Goti, A. Chem. Rev. 1998, 98, 589; (b) Brandi, A.; Cicchi, S.; Cordero, F. M.; Goti, A. Chem. Rev. 2003, 103, 1213; (c) Nakamura, I.; Yamamoto, Y. Adv. Synth. Catal. 2002, 344, 111.
   (a) Yu, L.; Meng, B.; Huang, X. Synlett 2007, 2919; (b) Yu, L.; Meng, B.; Huang, X.
- (a) Yu, L; Meng, B.; Huang, X. Synlett 2007, 2919; (b) Yu, L.; Meng, B.; Huang, X. Synlett 2008, 1331; (c) Yu, L.; Meng, B.; Huang, X. J. Org. Chem. 2008, 73, 6895.
   Select recent article about difunctional reactions: (a) Morgan, J. B.; Miller, S. P.;
- S. Select recent and the about unfunctional reactions. (a) Morgan, J. B., Minler, S. F., Morken, J. P. J. Am. Chem. Soc. 2003, 125, 8702; (b) Rauhut, C. B.; Melzig, L.; Knochel, P. Org. Lett. 2008, 10, 3891; (c) Shi, M.; Jiang, M.; Liu, L-P. Org. Biomol. Chem. 2007, 5, 438.
- Siriwardana, A. I.; Nakamura, I.; Yamamoto, I. *Tetrahedron Lett.* 2003, 44, 985.
   Selected recent articles about conjugated dienes: (a) Zhou, C.; Fu, C. L.; Ma, S. M. *Tetrahedron* 2007, 63, 7612; (b) Shi, M.; Wang, B. Y.; Huang, J. W. J. Org. Chem. 2005, 70, 5606; (c) Wong, K.; Hung, Y. *Tetrahedron Lett.* 2003, 44, 8033; (d) Taylor, D. K.; Avery, T. D.; Greatrex, B. W.; Tiekink, E. R. T.; Macreadie, I. G.; Macreadie, P. I.; Humphries, A. D.; Kalkanidis, M.; Fox, E. N.; Klonis, N.; Tilley, L. J. Med. Chem. 2004, 47, 1833.
- Selected recent articles about homoallylic compounds: (a) Shi, M.; Xu, B. Org. Lett. 2002, 4, 2145; (b) Xu, B.; Shi, M. Org. Lett. 2003, 5, 1415; (c) Liu, L. P.; Shi, M. J. Org. Chem. 2004, 69, 2805; (d) Huang, J. W.; Shi, M. Tetrahedron 2004, 60, 2057; (e) Huang, X.; Yu, L. Synlett 2005, 2953; (f) Chen, Y.; Shi, M. J. Org. Chem. 2004, 69, 426; (g) Huang, J. W.; Shi, M. Tetrahedron Lett. 2003, 44, 9343; (h) Shao, L. X.; Huang, J. W.; Shi, M. Tetrahedron 2004, 60, 11895; (i) Zhou, H. W.; Huang, X.; Chen, W. L. Synlett 2003, 2080.
- 9. Negishi, E.; de Meijere, A., et al *Organopalladium Chemistry for Organic Synthesis*; Wiley: New York, 2002. pp 493–529, and references cited therein.
- (a) Hopf, H.; Jager, H.; Ernst, L. Liebigs Ann. 1996, 815; (b) Kros, A.; Nolte, R. J. M.; Sommerdijk, N. A. J. M. Adv. Mater. 2002, 14, 1779; (c) Carroll, R. L.; Gorman, C. B. Angew. Chem., Int. Ed. 2002, 41, 4378; (d) McQuade, D. T.; Pullen, A. E.; Swager, T. M. Chem. Rev. 2000, 100, 2537; (e) Tour, J. M. Acc. Chem. Res. 2000, 33, 791; (f) Liphardt, M.; Goonesekera, A.; Jones, B. E.; Ducharme, S.; Takacs, J. M.; Zhang, L. Science 1994, 263, 367; (g) Miller, J. S. Adv. Mater. 1993, 5, 671; (h) Greenham, N. C.; Moratti, S. C.; Bradley, D. D. C.; Friend, R. H.; Holmes, A. B. Nature 1993, 365, 628; (i) Nalwa, H. S. Adv. Mater. 1993, 5, 341; (j) Buckley, A. Adv. Mater. 1992, 4, 153.
- 11. (a) Michinobu, T.; Boudon, C.; Gisselbrecht, J. P.; Seiler, P.; Frank, B.; Moonen, N. N. P.; Gross, M.; Diederich, F. *Chem. Eur. J.* **2006**, *12*, 1889; (b) Pahadi, N. K.; Camacho, D. H.; Nakamura, I.; Yamamoto, Y. *J. Org. Chem.* **2006**, *71*, 1152; (c) Michinobu, T.; May, J. C.; Lim, J. H.; Boudon, C.; Gisselbrecht, J. P.; Seiler, P.; Gross, M.; Biaggio, I.; Diederich, F. *Chem. Commun.* **2005**, 737.
- Typical procedure of Synthesis of 2,6-dihalo-1,3-hexadienes 4: In a Schlenk tube, 12. 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<sup>-1</sup>. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 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). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  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<sup>+</sup>], 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<sup>-1</sup>. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 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). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): 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<sup>+</sup>], 115 (100). HRMS (EI):

*m*/*z* calcd for C<sub>14</sub>H<sub>17</sub>IO: 328.0324; found: 328.0316. Selected spectroscopic data of compound **6**: Oil. IR (film): 2922, 1724, 1490, 1241, 1172, 913, 756 cm<sup>-1</sup>. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 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). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): 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<sup>+</sup>], 105 (100). HRMS (EI): *m/z* calcd for C<sub>20</sub>H<sub>17</sub>Br: 336.0514; found: 336.0508. Spectroscopic data of Compound **7**: Oil. IR (film): 2936, 1598, 1411, 1207, 985, 764 cm<sup>-1</sup>. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 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). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): 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<sup>+</sup>], 313 (100). HRMS (EI): m/z calcd for  $C_{18}H_{17}$ ISe: 439.9540; found: 439.9544. *Spectroscopic data of Compound* **8**: Oil. IR (film): 2963, 1588, 1432, 1311, 1125, 1094, 887, 775 cm<sup>-1</sup>. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, TMS):  $\delta$  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). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  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<sup>+</sup>], 235 (100). HRMS (EI): m/z calcd for  $C_{24}H_{22}$ Se: 390.0887; found: 390.0882. Spectroscopic data of the other compounds please see the Supplementary data file.