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Carbolithiation of *gem*-aryl disubstituted methylenecyclopropanes†

Jin-Wen Huang[a] **and Min Shi***[a,b]
[a] *State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Road, Shanghai, 200032, China*
[b] *East China University of Science and Technology, 130 Mei Long Lu, Shanghai, 200237, China. E-mail: mshi@pub.sioc.ac.cn; Fax: 86-21-64166128*

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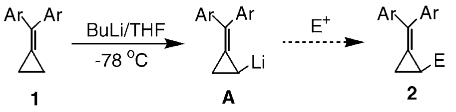
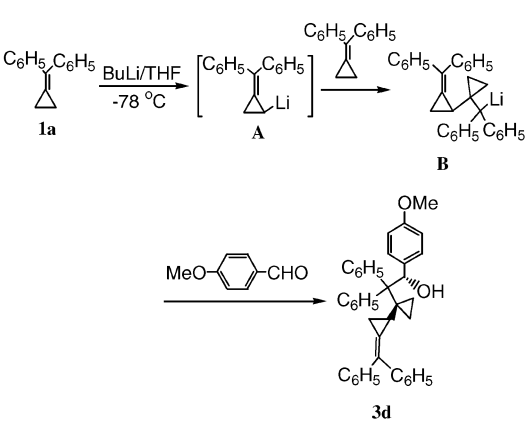
A novel carbolithiation of *gem*-aryl disubstituted methylenecyclopropanes was disclosed by the treatment with BuLi in THF at −78 °C. The corresponding addition products can be obtained in good to high yields by quenching with various electrophiles.

The addition of organometallic reagents to alkenes is of considerable interest, in particular for the construction of stereogenic centers.[1] Alkenes are activated toward carbometalation by the presence of a π-acceptor substituent on the double bond and/or a heteroatom in the allylic position.[2]

In the case of *gem*-aryl disubstituted methylenecyclopropanes (MCPs) **1**,[3] since it is conceivable that lithiation of cyclopropyl ring could easily take place to give the corresponding lithiated intermediate **A** by treatment with BuLi at low temperature and the subsequent quenching with electrophile E^+ would produce product **2** (Scheme 1), we carried out the lithium carbonization (carbolithiation) of MCP **1a** with BuLi (1.17 equiv.) in THF at −78 °C and the subsequent quenching by *p*-anisaldehyde (1.02 equiv.) in a one-pot manner (Scheme 2). However, interestingly we found that compound **3d** was formed exclusively in 99% yield as *anti*-configuration. Its structure was determined by ^{1}H, ^{13}C NMR spectroscopic data, HRMS, and X-ray diffraction (Fig. 1) (also see: Supporting Information†).[4]



Scheme 1 Proposal on the carbolitiation of MCPs **1**.



Scheme 2 Carbolithiation of MCP **1a** with BuLi (1.17 equiv.) and the subsequent quenching with *p*-anisaldehyde (1.02 equiv.).

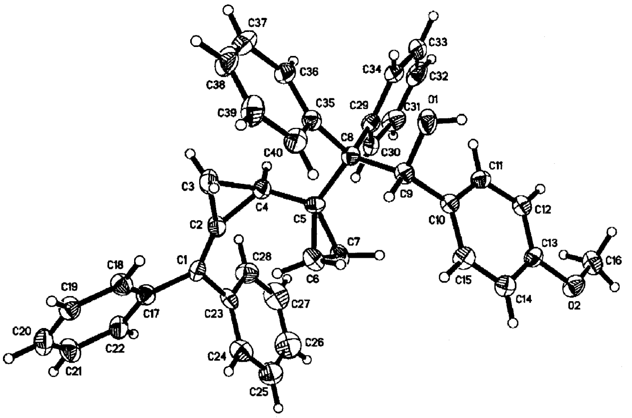


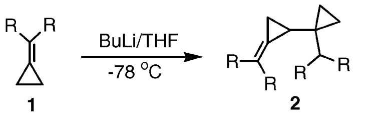
Fig. 1 ORTEP drawing of *anti*-**3d**.

The formation of **3d** can be explained by Scheme 2. The lithiated intermediate **A** undergoes a self-carbolithiation with another molecule of MCP **1a** to furnish the lithiated intermediate **B** which reacts with *p*-anisaldehyde to give **3d**.

In order to clarify the reaction route on the formation of **3d**, the self-carbolithiation of MCPs **1** was performed with BuLi (1.17 equiv.) in THF at −78 °C and the results are summarized in Table 1. As can be seen from Table 1, products **2** derived from the self-carbolithiation of MCPs **1** were obtained in good to high yields (Table 1, entries 1, 3 and 4). For MCP **1b**, since the methyl group on the benzene ring also can be partially lithiated by BuLi, **2b** was obtained in 32% yield (Table 1, entry 2). Aliphatic MCP **1e** indicated that no self-carbolithiation take place but recover the starting materials because the generated corresponding carboanion intermediate **A** is not as stable as MCP **1a** (Table 1, entry 5). It should be emphasized here that the inverse addition of MCP **1a** to excess BuLi gave complicated products.

Ab initio calculations have been performed in order to investigate why the introduction of each trigonal center into a cyclopropane ring results in an increase in strain energy of

Table 1 Intermolecular lithium carbonization between MCPs **1**



Entry[a]	R **1**	Yield (%) **2**
1	C_6H_5 **1a**	**2a**, 99
2	*p*-MeC_6H_4 **1b**	**2b**, 32
3	*p*-ClC_6H_4 **1c**	**2c**, 92
4	*p*-FC_6H_4 **1d**	**2d**, 81
5	C_4H_9 **1e**	**2e**, —[b]

[a] All reactions were carried out for 5 hours. [b] Starting materials recovered.

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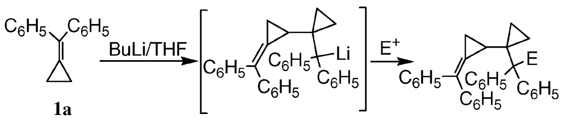
† Electronic supplementary information (ESI) available: ^{13}C NMR and ^{1}H NMR spectral and analytic data for compounds **2** and **3**. See http://www.rsc.org/suppdata/ob/b4/b417139j/

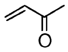
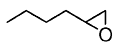
DOI:10.1039/b417139j

Table 2 Reaction of various electrophiles with a carboanion from MCP **1a**



1a

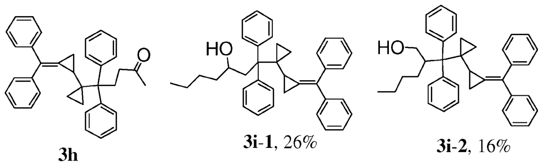
3

Entry	Electrophile E^+	Yield (%)[a] **3**
1	CO_2	**3a**, 96
2	C_6H_5CHO	**3b**, 92[b]
3	*p*-MeC_6H_4CHO	**3c**, 77[b]
4	*p*-$MeOC_6H_4CHO$	**3d**, 99[b]
5	3,4,5-$(MeO)_3C_6H_2HCO$	**3e**, 78[b]
6	*p*-ClC_6H_4CHO	**3f**, 94[b]
7	*p*-FC_6H_4CHO	**3g**, 70[b]
8		**3h**, 95[c]
9		**3i**, 42[d]

[a] Their ^1H and ^{13}C NMR spectroscopic data are summarized in Supporting Information.† [b] The product was formed exclusively as *anti*-configuration. [c] Michael addition product, see Fig. 2. [d] Isolated yield of two products, see Fig. 2.

12–14 kcal mol^{-1}.[5] Johnson and Borden's calculations found that, as is commonly believed, the introduction of a trigonal center into a three-membered ring does create some additional angle strain. However, their computational results showed that the major source of the additional "strain" that results from the introduction of each trigonal center into a cyclopropane is not an increase in angle strain but the loss of a cyclopropane C–C bond.[6] On the basis of this result, we believe that the driving force in this self-carbolithiation of MCPs **1** is the formation of a cyclopropane C–C bond.[6] Namely, the lithiated MCP **1** preferentially undergoes a self-addition to the terminal in the double bond of another molecule of MCP **1** adjacent to the two aromatic groups to give the anionic intermediate **B** because of the energy gain. In addition, this anionic intermediate can also be stabilized by the two aromatic groups. The subsequent addition reaction of anionic intermediate **B** to electrophile exclusively takes place to produce the corresponding adducts.

In order to extend the scope and limitations of this novel self-carbolithiation–addition cascade process, we next examined the reaction of self-carbolithiated MCP **1a** prepared *in situ* by BuLi (1.17 equiv.) with a variety of electrophiles such as carbon dioxide, various arylaldehydes (1.02 equiv.), α,β-unsaturated ketone (1.02 equiv.) and epoxide (1.02 equiv.). The results are summarized in Table 2. As can be seen from Table 2, the corresponding adducts **3** are obtained in good to high yields in most cases (Table 2, entries 1–8). In the reaction with arylaldehydes, the products **3b–3g** are formed exclusively as the *anti*-configuration presumably due to the steric demanding effect. In addition, in the reaction with methyl vinyl ketone, the Michael addition **3h** is formed as the sole product (Table 2, entry 8 and Fig. 2) In the reaction with epoxide, two regioisomers are obtained at the same time (Fig. 2, entry 9).



3h

3i-1, 26%

3i-2, 16%

Fig. 2

Their spectroscopic data have been summarized in Supporting Information.†

In conclusion, we have found a novel carbolithiation of *gem*-aryl disubstituted methylenecyclopropanes with a variety of electrophiles upon treatment with BuLi at −78 °C. This reaction first proceeds through a self-carbolithiation of MCPs **1** and then adds to the various electrophiles, a novel self-carbolithiation–addition cascade process.† Efforts are in progress to elucidate the mechanistic details of this reaction and to disclose its subsequent transformation thereof.

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4 Crystal data for **3d**. Empirical Formula: $C_{40}H_{36}O_2$; Formula Weight: 548.69; Temperature: 293(2) K; Crystal Color, Habit: colorless, prismatic; Crystal Dimensions: 0.398 × 0.217 × 0.071 mm; Crystal System: Orthorhombic; Lattice Type: Primitive; Lattice Parameters: $a = 10.113(2)$ Å, $b = 10.206(2)$ Å, $c = 29.277(7)$ Å, $\alpha = 90°$, $\beta = 90°$, $\gamma = 90°$, $V = 3021.7(12)$ Å^3; Space group: $P2(1)2(1)2(1)$; $Z = 4$; $D_{calc} = 1.206$ g cm^{-3}; $F000 = 1168$; Data/restraints/parameters: 6835/6/413; Diffractometer: Rigaku AFC7R; Residuals: R; R_w: 0.0555, 0.0742; $R_1 = 0.2113$; $R_w = 0.1046$ CCDC reference number 246793. See http://www.rsc.org/suppdata/ob/b4/b417139j/ for crystallographic data in .cif or other electronic format.

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