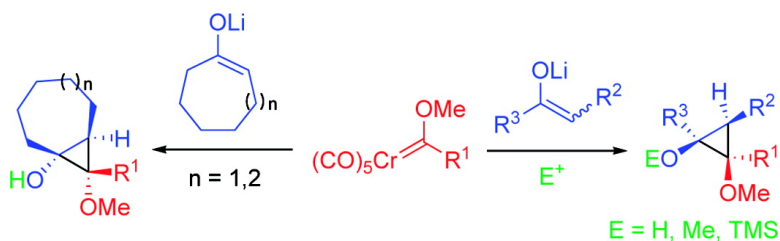


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## Diastereoselective Cyclopropanation of Ketone Enols with Fischer Carbene Complexes

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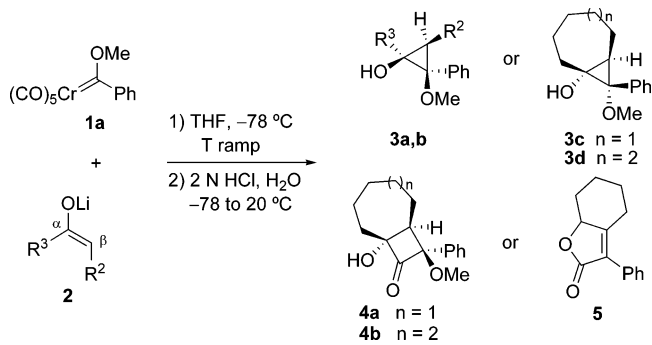
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The addition of metal enolates to the electrophilic carbene carbon atom of group 6 Fischer carbene complexes (FCCs) generates new nucleophilic intermediates:  $\gamma$ -oxo functionalized alkylpentacarbonylmetalate species, which have been showing a high synthetic potential.<sup>1,2</sup> So far, the chemical behavior of these anionic species, which are stable derivatives at low temperature, has been explored in the case of aryl- and alkenylcarbene complexes providing acyclic derivatives in the former case<sup>3,4</sup> and either acyclic<sup>3</sup> or five- and seven-membered carbocycles<sup>5,6</sup> in the later case. A 3-oxoalkylpentacarbonylmetalate derivative has been reported to undergo a CO insertion reaction leading subsequently to the formation of a cyclic anhydride.<sup>7</sup> In general, alkylpentacarbonylmetalate species are prone to undergo insertion of CO to give anionic acyltetracarbonylmetalate intermediates whose further evolution depends on the nature of the reaction partners.<sup>8</sup> On the other hand, the cyclopropanation reaction of electron-rich alkenes with alkoxy FCCs requires thermal conditions and high pressures of CO to avoid the olefin metathesis process.<sup>9</sup> Apart from transfer of the carbene ligand of alkoxy FCCs to the C=C bond of  $\beta$ -unsubstituted enol ethers that occurs at low temperature although giving mixtures of diastereoisomers,<sup>9c</sup> a general method for the cyclopropanation of electron-rich olefins with FCCs in smooth conditions is still required.

Herein, we describe a novel reaction of Fischer carbene complexes of chromium with ketone lithium enolates which allowed the diastereoselective synthesis of highly substituted cyclopropanols and that formally represents the cyclopropanation at low temperature and in the absence of CO of an electron-rich alkene ( $\beta$ -substituted ketone enol) with a heteroatom-stabilized FCC.

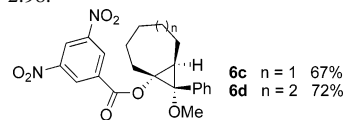
Initially, we observed that the reaction of methoxy(phenyl)-carbene complex **1a** with  $\beta$ -substituted ketone lithium enolates **2a–d** performed under the reaction conditions summarized in Table 1 led, after hydrolysis and decoordination of the metal species by exposure to air and light, to tetrasubstituted cyclopropanols **3a–d**, which were formed in each case as a single diastereoisomer.<sup>10</sup> Lithium enolates **2** can be alternately generated from the corresponding ketone and lithium diisopropylamide (LDA) or the appropriate trimethylsilyl enol ether and BuLi. Two different experimental conditions in the first step can be used with acyclic lithium enolates **2a,b** (method A)  $-78$  to  $-55$  °C, 10 min;  $-55$  °C, 1 h;  $20$  °C, 30 min or (method B)  $-78$  °C, 5 min;  $20$  °C, 45 min; Table 1, entries 1–3). But, the experiments with cyclic lithium enolates **2c,d** need to be conducted under the former slower conditions (method A) in order to get cyclopropanols **3c,d** (Table 1, entries 4, 6). When these reactions were carried out using the later faster conditions (method B), the selective formation of bicyclic hydroxycyclobutanones **4a,b** was observed (Table 1, entries 5, 7). In contrast, the reaction of carbene complex **1a** with cyclohexanone lithium enolate (**2e**), performed under the above-mentioned slower reaction conditions, furnished selectively bicyclic 2-buten-4-olide **5** (Table 1, entry 8). This heterocyclic ring has been generated by the assembly of the

**Table 1.** Coupling of Carbene Complex **1a** and Lithium Enolates **2**<sup>a</sup>



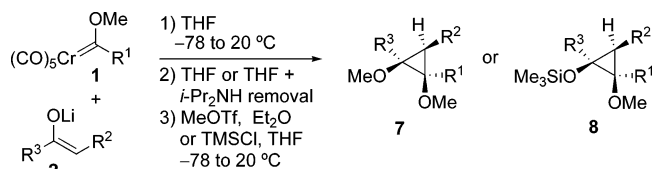
entry	enolate <b>2</b>	R <sup>2</sup>	R <sup>3</sup>	T ramp (°C) <sup>b</sup>	reaction product	yield (%) <sup>c</sup>
1	<b>2a</b> <sup>d,e</sup>	Et	Pr	A: $-55$ , $20$	<b>3a</b>	62
2	<b>2a</b> <sup>e,f</sup>	Et	Pr	B: $20$	<b>3a</b>	77
3	<b>2b</b> <sup>d,g</sup>	Me	Ph	B: $20$	<b>3b</b>	86
4	<b>2c</b> <sup>f</sup>	(CH <sub>2</sub> ) <sub>5</sub>		A: $-55$ , $20$	<b>3c</b>	74
5	<b>2c</b> <sup>f</sup>	(CH <sub>2</sub> ) <sub>5</sub>		B: $20$	<b>4a</b>	75
6	<b>2d</b> <sup>d</sup>	(CH <sub>2</sub> ) <sub>6</sub>		A: $-55$ , $20$	<b>3d</b>	79
7	<b>2d</b> <sup>f</sup>	(CH <sub>2</sub> ) <sub>6</sub>		B: $20$	<b>4b</b>	68
8	<b>2e</b> <sup>f</sup>	(CH <sub>2</sub> ) <sub>4</sub>		A: $-55$ , $20$	<b>5</b>	75

<sup>a</sup> Reaction conditions: 1.2 equiv of enolate **2**. <sup>b</sup> Method A:  $-78$  to  $-55$  °C, 10 min and then  $-55$  °C, 1 h and  $20$  °C, 30 min. Method B:  $-78$  °C, 5 min and then  $20$  °C, 45 min. <sup>c</sup> Yield of isolated, analytically pure product based on carbene complex **1a**. <sup>d</sup> Enolate prepared from the appropriate trimethylsilyl enol ether and BuLi. <sup>e</sup> Enolate geometry *E/Z* = 17:83. <sup>f</sup> Enolate prepared from the corresponding ketone and LDA. <sup>g</sup> Enolate geometry *E/Z* = 2:98.



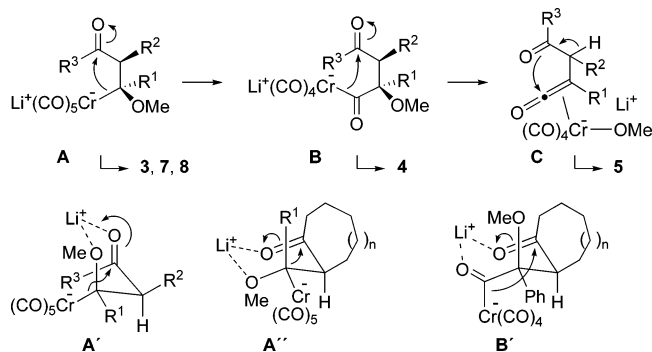
lithium enolate as a three-atom unit and the carbene and a carbonyl ligands both as one-carbon synthons.<sup>11</sup>

Cyclopropanols **3a,b** show a trans disposition of the enolate substituents (R<sup>2</sup>, R<sup>3</sup>) and a cis orientation of the methoxy and hydroxy groups, while bicyclic cyclopropanols **3c,d** hold both a cis ring fusion and a cis arrangement of the oxygenated functional groups. The structure and relative stereochemistry of products **3** and the other new compounds reported here, were ascertained by 1D and 2D NMR spectroscopic experiments.<sup>12</sup> The later studies were carried out with compounds **3b**, **4b**, **5**, and **6d** (Table 1). To establish the relative configuration of bicyclic derivatives **3c,d**, it was necessary to transform these cyclopropyl alcohols into the corresponding benzoate derivatives **6c,d** using 3,5-dinitrobenzoyl chloride [Et<sub>3</sub>N, 4-(dimethylamino)pyridine (DMAP), THF, room temperature]. Furthermore, a single-crystal X-ray analysis of **4a** and **6c,d**<sup>13</sup> confirmed the structural assignment.

**Table 2.** Preparation of 1,2-Dimethoxycyclopropanes **5** and 1-Methoxy-2-trimethylsilyloxycyclopropanes **6**<sup>a</sup>

entry	FCC 1	R <sup>1</sup>	enolate 2, Z/E <sup>b</sup>	R <sup>2</sup>	R <sup>3</sup>	7/8	yield (%) <sup>c</sup>
1	<b>1a</b>	Ph	<b>2a</b> <sup>d</sup> 83:17	Et	Pr	<b>7a</b>	81 <sup>e</sup>
2	<b>1a</b>	Ph	<b>2f</b> <sup>d</sup> 100:0	Me	<i>i</i> -Pr	<b>7b</b>	84
3	<b>1a</b>	Ph	<b>2g</b> <sup>d</sup> – <sup>g</sup>	Me	2-Thi	<b>7c</b>	77
4	<b>1b</b>	2-Naph	<b>2a</b> <sup>d</sup> 83:17	Et	Pr	<b>7d</b>	81 <sup>e</sup>
5	<b>1c</b>	<i>p</i> C <sub>10</sub> H <sub>4</sub>	<b>2b</b> <sup>d</sup> 98:2	Me	Ph	<b>7e</b>	73
6	<b>1a</b>	Ph	<b>2h</b> <sup>d</sup> 30:70	Me	Et	<b>8a</b>	80
7	<b>1a</b>	Ph	<b>2b</b> <sup>d</sup> 98:2	Me	Ph	<b>8b</b>	84
8	<b>1d</b>	3-Thi	<b>2a</b> <sup>d</sup> 83:17	Et	Pr	<b>8c</b>	72

<sup>a</sup> Reaction conditions: (1) **2** (1.2 equiv), –78 °C, 5 min and then 20 °C, 45 min; (2) removal of THF, addition of Et<sub>2</sub>O or removal of THF and *i*-Pr<sub>2</sub>NH, addition of THF; (3) MeOTf (2 equiv) or TMSiCl (1.5 equiv), –78 °C, 5 min and then 20 °C, 30 min. 2-Naph = 2-naphthyl; 2-Thi = 2-thienyl; 3-Thi = 3-thienyl. <sup>b</sup> Enolate geometry. <sup>c</sup> Yield of isolated, analytically pure product **7** or **8** based on carbene complex **1**. <sup>d</sup> Enolate prepared from the corresponding trimethylsilyl enol ether and BuLi. <sup>e</sup> In this experiment the reaction conditions in the first step were (1) **2** (1.2 equiv), –78 to –55 °C, 10 min and then –55 °C, 1 h and 20 °C, 30 min. <sup>f</sup> Enolate prepared from the corresponding ketone and LDA. <sup>g</sup> Not determined.

**Scheme 1.** Proposed Mechanism

To gain insight into the scope of this new cyclopropanation reaction we next tested the behavior of other FCCs and other  $\beta$ -substituted ketone lithium enolates. Given that cyclopropanols **3** are somewhat unstable compounds,<sup>14</sup> we decided to quench the reaction with methyl triflate or trimethylsilyl chloride as a means to facilitate the characterization of the final products. Accordingly, stable and diastereomerically pure 1,2-dimethoxycyclopropanes **7a–e** (Table 2, entries 1–5) or 1-methoxy-2-trimethylsilyloxycyclopropanes **8a–c** (Table 2, entries 6–8) were produced under the experimental conditions summarized in Table 2. Apart from phenylcarbene complex **1a** and lithium enolates **2a–d**, aryl- and heteroarylcarbene complexes **1b–d** reacted successfully with lithium enolates **2f–h**. THF has to be replaced for Et<sub>2</sub>O to avoid polymerization by adding MeOTf; and *i*-Pr<sub>2</sub>NH must be removed to get success in the experiments with Me<sub>3</sub>SiCl. The stereochemical assignment of products **7** and **8** is based on a 2D NMR study<sup>12</sup> effected with compound **7a** and on a single-crystal X-ray diffraction study performed with 1,2-dimethoxycyclopropane **7c**.<sup>13</sup>

This cyclopropanation process involves the diastereoselective formation of intermediates **A**,<sup>2</sup> which subsequently undergo ring closure by intramolecular addition of the alkylchromate moiety to the carbonyl group (Scheme 1).<sup>15</sup> The diastereoselection attained in the cyclization step from either acyclic or cyclic enolates can be rationalized through the reacting conformations **A'** (frontal attack

of the alkylchromate to the ketone carbonyl group) and **A''** (dorsal attack of the alkylchromate to the carbonyl group),<sup>16</sup> respectively. Chelation of the lithium atom to both oxygenated functional groups would be controlling the cyclization process. Intermediates **B**, formed after CO insertion, would account for the formation of compounds **4a,b** by intramolecular addition of an acylchromate species to the ketone carbonyl group as shown in conformation **B'**. While butenolide **5** could be formed through intermediate **C** originated after CO insertion and subsequent  $\beta$ -elimination of the metal fragment and the methoxy group.<sup>8c</sup>

In summary, we have disclosed an efficient and concise synthesis of cyclopropanols<sup>17</sup> by direct combination of methoxycarbene complexes of chromium and  $\beta$ -substituted ketone lithium enolates. This strategy represents a valuable approach to a longstanding elusive reaction in Fischer carbene chemistry.

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**Supporting Information Available:** Experimental procedures, spectral and analytical data for all products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- This heteroannulation reaction is a general process when analogous experiments are conducted with  $\beta$ -unsubstituted ketone lithium enolates.
- <sup>1</sup>H, <sup>13</sup>C, DEPT, HSQC, HMBC, COSY and NOESY NMR spectra were measured and in some cases selective NOE experiments.
- Full details of the X-ray crystal-structure studies of **4a**, **6c,d** and **7c** will be described separately.
- Upon standing (5 °C) they slowly decomposed. In some cases a clean transformation to the corresponding 1,3-diketone has been observed.
- This reactivity has been proposed to explain the reaction of methoxy-(phenyl)carbene complex of Cr with methyl isobutyrate lithium enolate and allylmagnesium bromide; see reference 2b.
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