

Tricyclic Ethers from Fischer Vinylcarbene Complexes and β -Oxygen-functionalized Organolithium Compounds

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A one-pot synthesis of tricyclic ring systems has been achieved by the Michael addition of β -oxygen-functionalized organolithium compounds to Fischer vinylcarbene complexes followed by an intramolecular alkoxide exchange and intramolecular cyclopropanation reaction.

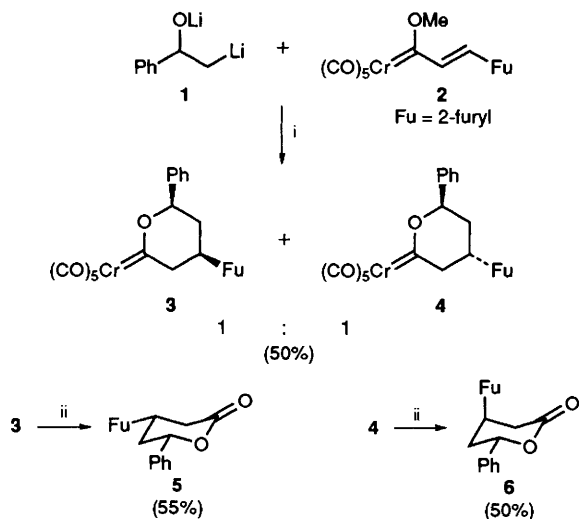
Fischer carbene complexes are receiving increasing interest among synthetic chemists as useful reagents for the synthesis of novel organic compounds.¹ In particular, polycyclic cyclopropane-containing skeletons have been prepared from properly substituted metal carbenes by a tandem sequence of alkyne insertion and cyclopropanation of an alkene by an *in situ* generated non-heteroatom-stabilized vinylcarbene complex.² Herein we report a new, rapid and direct method for the construction of cyclopropane-containing tricyclic frameworks by reaction of Fischer vinylcarbene type complexes with β -oxygen-functionalized organolithium compounds.[†]

Conjugate addition reactions to α,β -unsaturated Fischer carbene complexes is generally best achieved with softer carbon nucleophiles such as enolate anions.⁴ Recently, work has been reported in which the Michael addition is coupled with alkylation of the enolate resulting from the conjugate addition.⁵ Intramolecular alkoxide exchange reaction in Fischer carbene complexes leading to the formation of five- or

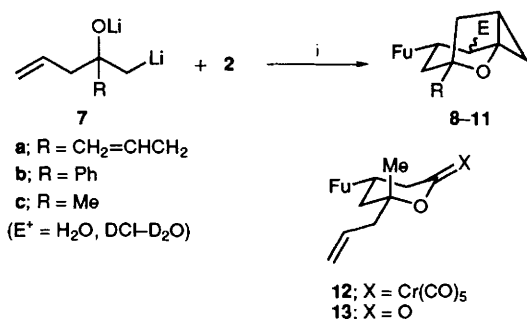
six-membered rings is well-precedented.^{4c,6} On the other hand, intramolecular cyclopropanation reaction of unactivated olefins by heteroatom-stabilized carbene complexes seems to be limited to aryl(alkenyloxy or alkenylamino) metal carbenes.⁷ The cyclopropanated compounds were very minor byproducts when the aryl group on the carbene carbon was changed to an alkyl group.^{7d} One example of this reaction in an alkenyl(alkoxy)metal carbene, induced by light, has been reported.⁸ The work described in this paper involves the Michael addition of very reactive organolithium compounds to a chromium vinylcarbene complex with subsequent intramolecular alkoxide exchange and then intramolecular cyclopropanation reaction of a cyclic aliphatic Fischer carbene with a pendent olefin giving rise to unusual tricyclic structures in a one-pot reaction.

Organolithium compounds **1**, **7** and **14** are very efficiently generated from the corresponding chlorohydrins by successive treatment with butyllithium and lithium naphthalenide at -80°C .^{3,9} As shown in Scheme 1 the reaction of lithium dianion **1** with the α,β -unsaturated Fischer carbene complex **2**¹⁰ led, after addition of water, to an equimolecular mixture of cyclic chromium carbenes **3** and **4** resulting from the conjugate

[†] The preparation of these lithium dianions and their reactivity with different organic electrophiles have been previously described by us.³



Scheme 1 Reagents and conditions: i, (a) tetrahydrofuran (THF), -80°C to room temp., (b) H_2O ; ii, dimethyl sulfoxide (DMSO), Et_2O



Scheme 2 Reagents and conditions: i, (a) THF, -80°C to room temp., (b) E^+

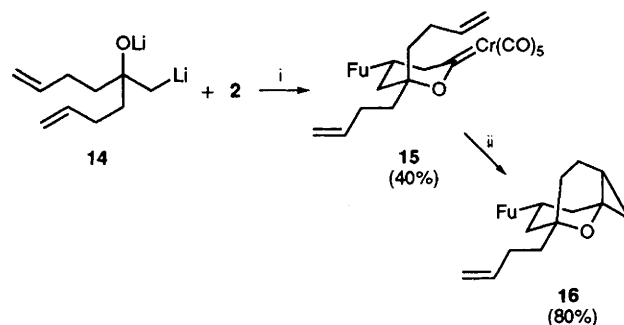
Table 1 Tricyclic ethers **8-11**

Product	R	E	Yield ^a (%)
8	$\text{CH}_2=\text{CHCH}_2$	H	35
9	$\text{CH}_2=\text{CHCH}_2$	D	32
10	Ph	H	28
11	Me	H	14

^a Isolated yield after flash chromatography based on the corresponding precursory chlorohydrin of compounds **7**.

addition reaction followed by spontaneous intramolecular alkoxide exchange. These compounds were separated by flash column chromatography (silica gel; hexane-ethyl acetate, 20:1) and the stereochemistry was established by oxidation of each diastereoisomer **3** and **4** with DMSO¹¹ and analysis of coupling constants of the cyclohexane protons in the lactones **5** and **6** respectively isolated.

The 1,4-addition reaction of allyl substituted organolithium compounds **7** to metal carbene **2**, under the same conditions as above, afforded directly the tricyclic ethers **8-11** as single diastereoisomers [compound **9** ($\text{E} = \text{D}$) was isolated as a mixture of isomers coming from the equatorial or axial position of the deuterium atom]. The suitable position of the double bond made extremely easy the intramolecular formation of the cyclopropane ring. The structures of the tricyclic



Scheme 3 Reagents and conditions: i, (a) THF, -80°C to room temp., (b) H_2O ; ii, THF, 110°C

compounds **8-11** were determined from their ^1H , ^{13}C NMR and LRMS spectra and in the case of compound **8** was confirmed by 1D, 2D NMR experiments. The reaction with the dilithium anion **7c** (R = Me) yielded an equimolar mixture of tricyclic ether **11** and carbene complex **12** having the allyl group in an equatorial position and thus not geometrically disposed to allow the cyclopropanation reaction to occur. These two compounds were more easily separated by flash chromatography (silica gel; hexane-diethyl ether, 5:1) after DMSO oxidation of the reaction mixture, affording product **11** (14% yield) and lactone **13** (14% yield). (Scheme 2 and Table 1).[‡]

The reaction of the bis-homoallyl substituted organolithium compound **14** with Fischer carbene complex **2** (shown in Scheme 3) gave the 2-oxacyclohexylidene carbene complex **15**, which did not undergo the intramolecular cyclopropanation reaction at room temperature. However, the cyclization reaction could be effected easily by heating carbene complex **15** in THF in a sealed flask at 110°C . Under these conditions tricyclic compound **16** was very efficiently formed as a single diastereoisomer.[§]

In conclusion, we have shown the ability of β -oxygen-functionalized organolithium compounds to undergo Michael additions to α,β -unsaturated metal carbene complexes, allowing the synthesis of new functionalized Fischer carbene complexes which can be further functionalized, particularly in the position α to the carbene carbon atom. In addition, the results demonstrate that unactivated alkenes are readily cyclopropanated by aliphatic heteroatom-stabilized chromium carbene complexes through an intramolecular process. We also described an expeditious method for the preparation of strained tricyclic ethers by the direct combination of two acyclic organometallic compounds.

[‡] A typical procedure: to a cooled (-80°C) solution of the corresponding organolithium compound **7**³ (10 mmol) in THF (60 ml) was added carbene complex **2** (10 mmol) under nitrogen and the mixture was stirred overnight allowing the temperature slowly to rise to 20°C . Then H_2O (20 mmol) was added and the reaction was stirred for 0.5 h at room temp. To the reaction mixture was added silica gel (ca. 20 g) at room temp. the solvent was removed and the residue was transferred to the top of a silica gel column and purified by flash chromatography (hexane-ethyl acetate, 10:1). Solvents were evaporated from the fractions containing the corresponding product **8-11**; the residue was dissolved in Et_2O (25 ml) and the solution was saturated with O_2 , irradiated with a 60W light bulb and stirred for 24 h at room temp. to remove the arene-bound chromium tricarbonyl species formed in the evolution of the chromium residue. The resulting mixture was filtered through a Celite pad and the residue, after solvent removal, was chromatographed (hexane-diethyl ether, 5:1) to give the corresponding product **8-11**.

[§] All new compounds have been fully characterized by ^1H and ^{13}C NMR, IR and mass spectra.

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