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One-Pot Enantioselective Formation of Eight-Membered Rings from Alkenyl Fischer Carbene Complexes and Ketone Enolates

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Modern organic chemistry demands new strategies and technologies to obtain new compounds in a fast, clean, and efficient way. Among these procedures, sequential reactions (domino or consecutive) offer the opportunity to build up complex molecules, frequently with high stereoselectivity, from simple and easily available substrates.[1] On the other hand, the importance of eight-membered rings in organic chemistry is due to its presence in the structural core of a large number of natural targets with promising biological activities.[2] As a consequence, the search for new strategies for the stereoselective construction of this type of rings is clearly a field of great significance in synthesis.[3] The use of metal-based methods to obtain medium-size rings has seen a considerable increase in the past decade[4] due to the advantage of these metal-promoted inter- and intramolecular cyclizations over other methodologies in the gain of entropy, reactivity, and stereoselectivity.[5] As part of a program concerned with the development of new methods for the synthesis of medium-size rings mediated by Fischer carbene complexes,[6] herein we report an easy and enantioselective "one-pot" synthesis of eight-membered carbocycles from alkenyl Fischer carbene complexes following two different approaches: by the use of chiral boroxycarbene complexes and achiral enolates, and by the use of methoxycarbene complexes and chiral ketone enolates.

We argued that eight-membered rings such as **1** could be obtained from **2** by a selective cyclopropane ring expansion (Figure 1). Due to the ability of Fischer carbene complexes to give cyclopropanation reactions with olefins,[7] we believed that tricyclic compounds **2** could be derived from carbene complex **3**, obtained from alkenyl carbene complexes **4** and enolates derived from ketones **5**. In this context, we have previously reported the racemic synthesis of tricyclic ethers **2**;[8] however, the chiral version of this reaction using alkenylcarbene complexes **4**, where the methoxy group was substituted by a (−)-8-phenylmenthyloxy group, failed, and open-chain products were obtained instead of the corresponding cyclic compounds **2** and/or **3**.[9] These studies indicated that small alkoxy groups in **4** were necessary to obtain cyclic compounds. Taking into account this limitation, two different approaches could be devised in order to obtain the corresponding cyclic compounds in an enantioselective way: (i) by the use of a chiral oxy group, easily transformed into a methoxy group, at the alkenyl Fischer carbene complex **4**, and (ii) by the use of a chiral enolate derived from ketone **5**. Thus, first, we carried out the sequence of reactions shown in Scheme 1. Alkenyl boroxycarbene complex **6**, derived from (−)-chlorodiisopinocampheylborane,[10] was treated with lithium enolate **7**, derived from cyclohexanone, from −100 °C to room temperature. The reaction was followed by IR, indicating total transformation of the starting alkenyl carbene complex **6** into a new acyltungstenate-type complex. This kind of compounds are known to react with alkylating agents to give conventional Fischer carbene complexes. So, treatment of the reaction crude with excess of methyl triflate gave rise to the new carbene complex **8** in 45% yield and 40% ee.[11,12] Some improvements on the yield and enantioselectivity were reached by the use of (−)-sparteine[13] as cosolvent of the reaction. Under these conditions, a match situation between both chiral substrates led to complex **8** in 55% yield and 55% ee.[11,14] Despite the moderate enantioselectivity of the reaction, it is important to remark that this is the first example of an enantioselective reaction using a dialkylborane as the chiral auxiliary on a Fischer carbene complex.

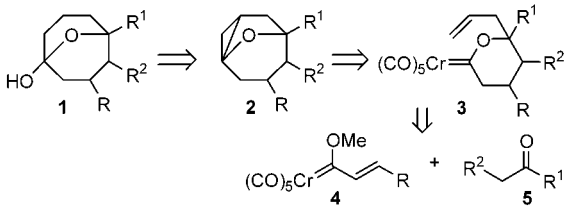
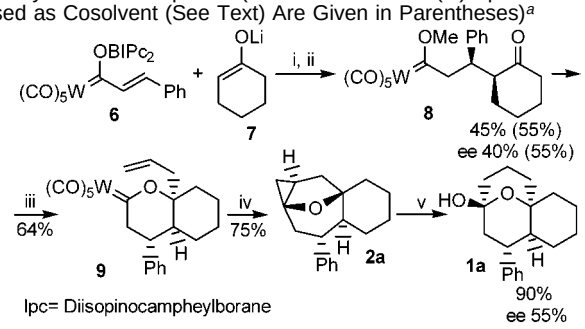


Figure 1. Retrosynthetic analysis.

Scheme 1. Eight-Membered Carbocycles from Alkenyl Boroxycarbene Complexes (Yield and Ee when (−)-Sparteine Is Used as Cosolvent (See Text) Are Given in Parentheses)[a]



[a] Reagents and conditions: (i) cyclohexanone, LDA, Et_2O, −30 °C, 15 min, then **6**, Et_2O, −100 °C; (ii) MeOTf, 0 °C; (iii) 2 equiv of CH_2CHCH_2MgBr, Et_2O, −50 °C; (iv) THF, 90 °C; (v) HCl, acetone, RT.

To investigate the feasibility of our strategy to obtain eight-membered carbocycles, we decided to try the remaining steps of our synthetic plan. Thus, addition of allylmagnesium bromide (2 equiv) to **8** gave the new cyclic carbene complex **9** (tungsten complex analogous to **3**) in 64% yield as a single diastereoisomer. Warming of this complex in THF at 90 °C in a sealed tube led to the tetracyclic compound **2a**, again, as a single diastereoisomer in 75% yield. Further treatment of this compound with hydrochloric acid in acetone resulted in the diastereoselective expansion of the cyclopropane ring to give eight-membered hemiacetal **1a** (90% yield, 55% ee for the product obtained from compound **8** using (−)-sparteine as cosolvent).[11]

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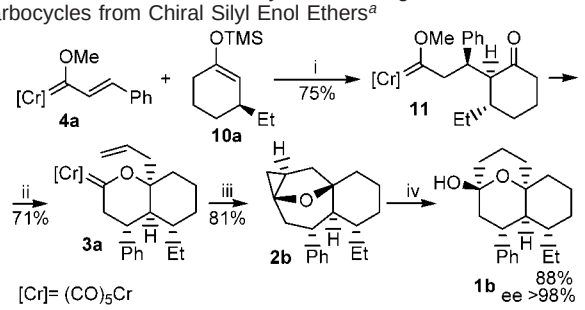
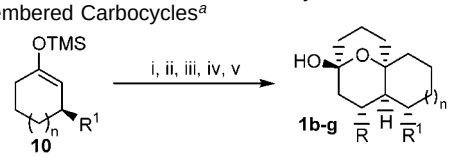
Scheme 2. Enantioselective Synthesis of Eight-Membered Carbocycles from Chiral Silyl Enol Ethers[a]



[a] Reagents and conditions: (i) **10a**, BuLi, THF, 0 °C, 30 min, then **4a**, THF, −78 °C; (ii) 3 equiv of CH_2CHCH_2Li, THF, −78 °C to RT; then SiO_2; (iii) THF, 90 °C; (iv) HCl, acetone, RT.

Scheme 3. One-Pot, Enantioselective Synthesis of Eight-Membered Carbocycles[a]



10	R^1	n	4	R	1	yield(%)	ee(%)
10a	Et	1	**4a**	Ph	**1b**	76	>98
10a	Et	1	**4b**	4-$MeOC_6H_4$	**1c**	72	>98
10a	Et	1	**4c**	2-Furyl	**1d**	82	>98
10a	Et	1	**4d**	2-Thienyl	**1e**	80	>98
10b	Me	1	**4c**	2-Furyl	**1f**	78	>98
10c	Et	2	**4c**	2-Furyl	**1g**	69	>98

[a] Reagents and conditions: (i) **10**, BuLi, THF, 0 °C, 30 min, then **4**, THF, −78 °C; (ii) CH_2CHCH_2Li, THF, −78 °C to RT; (iii) H_3PO_4; (iv) THF, 90 °C; (v) HCl, acetone, RT.

At this point, the viability of the method to obtain eight-membered rings had clearly been demonstrated; however, some improvements on the enantioselectivity of the process were desirable. For this reason, we decided to investigate the reaction between chiral enolates and alkenyl methoxycarbene complexes. Taking advantage of some recent and excellent works about the catalytic enantioselective synthesis of ketones from enones,[15] we carried out the enantioselective synthesis of silyl enol ether **10a**.[16]

Thus, reaction of **10a** (98% ee), easily obtained from 2-cyclohexenone, with butyllithium in THF generated the corresponding lithium enolate, which reacted with chromium alkenyl carbene complex **4a** to give product **11** as a single diastereoisomer (Scheme 2). Further reaction with allyllithium (3 equiv) diastereoselectively led to the new cyclic carbene complex **3a** (>98% ee).[11] Warming a solution of this complex in THF at 90 °C in a sealed tube gave tetracyclic compound **2b** as a single diastereoisomer (>98% ee).[11] Finally, treatment of cyclopropyl derivative **2b** with hydrochloric acid in acetone afforded eight-membered hemiketal **1b** as a single diastereoisomer (>98% ee).[11] The structure of compound **1b** was unequivocally determined by X-ray structure analysis.[17]

Attracted by the possibility of performing the sequence of reactions described in Scheme 2 following a "one pot" procedure, we decided to carry out the sequential transformation of silyl enol ethers **10a**−**c**[15] into eight-membered hemiacetals **1b**−**g** without the isolation of any intermediate, as depicted in Scheme 3. Following this strategy, compounds **1b**−**g** were obtained, each as a single diastereoisomer in high yield and as an enantiomerically pure compound. It is important to note that the "one-pot" procedure was much more efficient (76% yield for **1b**) than the multistep process (37% global yield for **1b**).

In summary, we have developed a new route to the enantioselective synthesis of eight-membered carbocycles from alkenylcarbene complexes. For the first time, chiral auxiliaries derived from dialkylboranes and attached to the carbene complex were used in an enantioselective reaction. Moreover, the use of chiral ketone enolates allowed the efficient one-pot synthesis of eight-membered rings with up to five stereogenic centers in a sequence involving the coupling of three components in very high ee. Further studies on this subject are underway in our laboratories and will be published shortly.[14,17]

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Supporting Information Available: Experimental procedures and characterization data for all new compounds (PDF). This material is available free of charge via the Internet at htpp://pubs.acs.org.

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