*Cyclization Reactions*

# Diastereoselective Synthesis of Cycloheptadienol Derivatives by a Formal [5+2] Carbocyclization Reaction of α,β,γ,δ-Diunsaturated (Methoxy)carbene Complexes with Methyl Ketone Lithium Enolates**

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Fischer-carbene complexes have become valuable building blocks in organic synthesis.[1] In particular, they are very useful for the generation of ring systems.[2] The design of new strategies for the selective synthesis of seven-membered carbocycles continues to be of great interest for organic chemists[3] due to the importance of this skeleton as a part of biologically relevant compounds.[4] The formal [4+3] cyclo-

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addition of α,β-unsaturated carbene complexes to 1,3-dienes,[5] 1-azadienes,[6] or 2-azadienes[7] affords functionalized seven-membered carbo- and heterocycles. The formal [5+2] carbocyclization reactions catalyzed by transition metals are a relatively new set of reactions,[3a,8] and only one example of a [5+2] heterocyclization reaction, in which a Fischer-type carbene complex is involved, has been reported.[1c]

Moreover, lithium enolates add to α,β-unsaturated carbene complexes in a Michael fashion,[9] except in the case of (methoxy)-carbene complexes and methyl ketone lithium enolates, for which a 1,2-addition is observed.[9a,10] In this context, we have recently developed the diastereoselective synthesis of five-membered rings by novel [3+2] and [4+1] carbocyclization reactions,[10] as well as the diastereoselective synthesis of seven-membered rings by a novel [4+3] carbocyclization reaction.[10a]

These results prompted us to study the reaction of α,β,γ,δ-diunsaturated (methoxy)carbene complexes[11] with methyl ketone lithium enolates. Here we report a new diastereoselective route to seven-membered carbocycles under very mild conditions.

The treatment of dienylcarbene pentacarbonyl complexes **1** with methyl ketone lithium enolates **2**, generated by the reaction of silyl enol ethers **3** with butyllithium at temperatures from 0 to 20 °C, in diethyl ether at temperatures from 0 °C to room temperature led, after hydrolysis and purification by column chromatography on deactivated silica gel, to cycloheptadienol derivatives **4** in good yields and as a single diastereoisomer (Scheme 1 and Table 1). The structure and relative configuration of the stereogenic centers were unequivocally determined by X-ray diffraction carried out on compound **4a** (Figure 1).[12,13]

***Table 1:*** Formation of cycloheptadienol derivatives **4** from dienylmethoxycarbene complexes **1** and methyl ketone lithium enolates **2**.

| Entry | Carbene | M Complex | $R^1$ | $R^2$ | Enolate[a] | R | Product [%][b] | Yield |
|---|---|---|---|---|---|---|---|---|
| 1 | **1**[a] | Cr | H | Ph | **2a** | Ph | **4a** | 58 |
| 2 | **1b** | W | H | Ph | **2a** | Ph | **4a** | 86 |
| 3 | **1b** | W | H | Ph | **2b** | 4-$MeOC_6H_4$ | **4b** | 77 |
| 4 | **1b** | W | H | Ph | **2c** | 2-Fu | **4c**[c] | 82 |
| 5 | **1b** | W | H | Ph | **2e** | BuC≡C | **4d** | 76 |
| 6 | **1c** | W | H | 2-Fu | **2d** | $PhCH_2CH_2$ | **4e**[d] | 34 |
| 7 | **1c** | W | H | 2-Fu | **2a** | Ph | **4f**[e] | 84 |
| 8 | **1c** | W | H | 2-Fu | **2f** | TMSC≡C | **4g** | 72 |
| 9 | **1d** | W | Me | Ph | **2a** | Ph | **4h** | 79 |
| 10 | **1c** | W | H | 2-Fu | **2g** | (*E*)-PhCH=CH | **4i**[f] | 48 |
| 11 | **1e** | W | Cl | Ph | **2g** | (*E*)-PhCH=CH | **5b** | 49 |
| 12 | **1f** | W | $(CH_2)_4$ | | **2g** | (*E*)-PhCH=CH | **5c** | 51 |
| 13 | **1f** | W | $(CH_2)_4$ | | **2a** | Ph | **6** | 78 |

[a] Enolates generated by treatment of silyl enol ethers **4** with butyllithium. [b] Yield of isolated product based on starting carbene complexes **1**. [c] A 80:20 mixture of diastereoisomers **4c** and *diast*-**4c**, separable by column chromatography, was obtained. [d] An 88:12 mixture of diastereoisomers **4d** and *diast*-**4d** was obtained. [e] An 94:6 mixture of diastereoisomers **4f** and *diast*-**4f** was obtained. [f] Compound **5a** ($R^1$ = H, $R^2$ = 2-Fu, R = (*E*)-PhCH=CH) (44%) was also obtained.

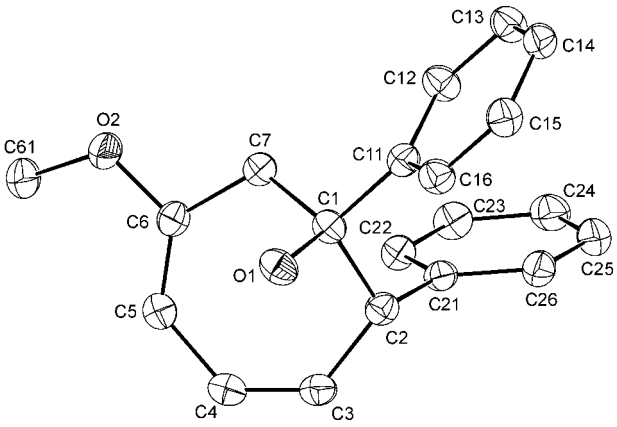
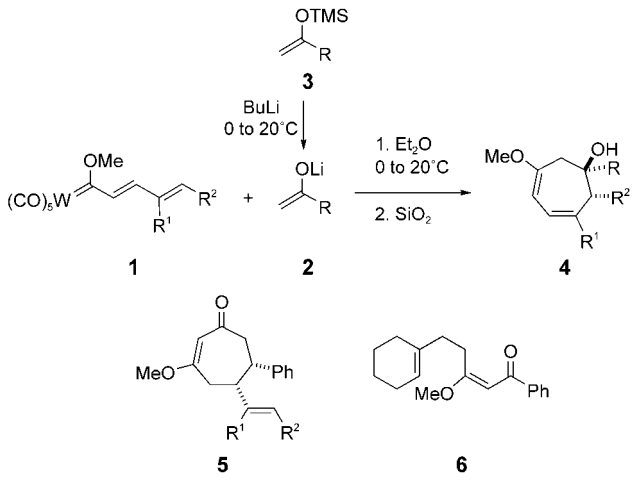



***Figure 1.*** Structure of **4a** (ORTEP plots, 30% probability).



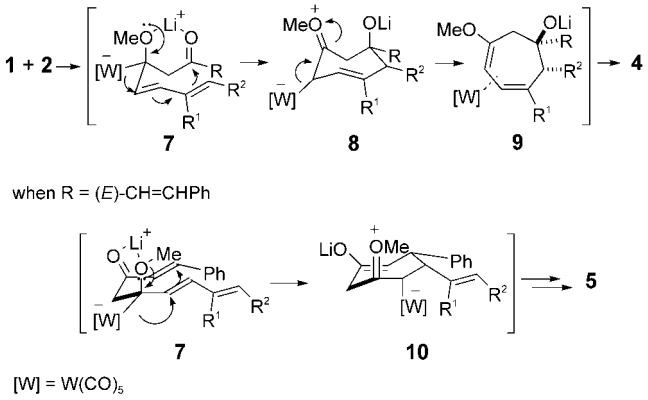

***Scheme 1.*** Synthesis of cycloheptadienol derivatives **4** from dienylcarbene complexes **1** and methyl ketone lithium enolates **2**.

Interestingly, both chromium and tungsten complexes can be used in this reaction, although better yields are obtained for tungsten (Table 1, entries 1, 2), and thus tungsten complexes were exclusively used in further experiments. We have also observed that the presence of an oxygen atom adequately placed in the lithium enolate or in the carbene complex can produce a decrease of the diastereoselectivity of the reaction, being more important in the former case (Table 1, entries 4, 6, and 7). On the other hand, the reaction of γ,δ-substituted carbene complexes with lithium enolates is very dependent on the nature of the substituents. Thus, whereas the reaction of carbene complex **1d** with lithium enolate **2a** led to cycloheptadienol **4h** in good yield (Table 1, entry 9), the reaction of the corresponding γ-chlorocarbene complex **1e** led to an undetermined complex mixture, and the analogous reaction of a γ,δ-cyclic carbene complex **1f** afforded the ketone **6** (Scheme 1 and Table 1, entry 13). Furthermore, in the reaction of alkenyl ketone lithium enolate **2g** with carbene complexes **1** we observed two competitive reaction patterns. The reaction with carbene complex **1c** afforded a mixture of

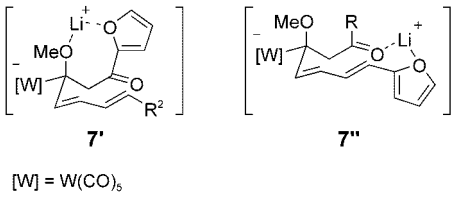
products **4i** and **5a**, which were separable by flash column chromatography, and were derived from a formal [5+2] and [4+3][10a] carbocyclization process, in which the carbene complex acted as a C5 and C3 building block, respectively (Table 1, entry 10). However, the analogous reaction of γ,δ-substituted carbene complexes **1e** and **1f** afforded exclusively and diastereoselectively the [4+3] carbocyclization products **5b** and **5c**, respectively, in moderate yields (Table 1, entries 11 and 12). Finally, the solvent also plays an important role. In fact, the reaction, which works well in diethyl ether, gave rise to an undetermined complex mixture in a more coordinating solvent such as tetrahydrofuran.

In Scheme 2, a tentative mechanism to account for the formation of cycloheptadienol derivatives **4**, cycloheptenone derivatives **5**, and ketone **6** is outlined. We assume first that a




***Scheme 2.*** Proposed mechanism for the formation of compounds **4** and **5**.

1,2-addition of the lithium enolates **2** to the carbene complex **1** could occur to form intermediate **7**. An intramolecular addition of the 5-position of the σ-dienyl metal group to the carbonylic carbon atom, induced by a 1,2-migration of the pentacarbonyl metal fragment,[6,14] would lead to the cyclic intermediate **8**. Further elimination of the metal moiety followed by coordination of the metal atom to the C–C double bonds would give intermediates **9**, which after hydrolysis and metal decoordination, would furnish cycloheptadienol derivatives **4**. Accordingly, when the γ,δ positions are substituted, the cyclization is presumably disfavored, and cycloheptadienol derivatives **4** are either formed with difficulty or not at all. Moreover, in the cases of alkenyl methyl ketone lithium enolates, intermediate **7** could also competitively or exclusively evolve by intramolecular Michael addition of the 3-position of the σ-dienyl metal fragment to the ketone, giving intermediate **10**, which after hydrolysis, metal decoordination, and double-bond isomerization, would give rise to cycloheptenone derivatives **5**.[10a] On the other hand, hydrolysis of intermediate **7** would afford ketone **6**. The preferable generation of the depicted diastereoisomer of **4**, with the R and $R^2$ groups in a *cis* disposition, could be explained by invoking a chairlike transition state with the same geometric disposition as **7**, presumably favored by the internal coordination of the oxygen atoms to the lithium atom. The fact that the analogous reaction carried out in THF, a much more coordinating solvent than diethyl ether, did not give the final product **4** at all, provides support to this considered internal coordination of the lithium atom. On the other hand, the lower diastereomeric excess observed in some cases for lithium enolate **2d** and carbene complex **1c**, both bearing a 2-furyl moiety, can also be explained by considering competitive internal coordinations of the oxygen atoms from the furyl and methoxy or carbonyl groups to the lithium atom as indicated in intermediates **7′** and **7″**, respectively, which would lead to the opposite diastereoisomer (Scheme 3).




***Scheme 3.*** Intermediates **7′** and **7″**.

In conclusion, we have described the 1,2-addition reaction of lithium enolates, derived from simple methyl ketones, to dienylmethoxycarbene complexes, which supposes a new strategy for the diastereoselective synthesis of seven-membered carbocyclic rings. As far as we know, this transformation represents the first example of a formal [5+2] carbocyclization reaction applied to Fischer-type carbene complexes, which nicely complements our previously reported formal [4+3] cyclization reaction.[10a] Importantly, the reaction uses simple starting materials, namely methyl ketones and Fischer-type carbene complexes. Moreover, a mechanism consistent with the experimental data is proposed, in which once again the ability of the recently described 1,2-$(CO)_5M$ migration to promote unusual umpolung cyclizations is demonstrated. Investigations to clarify the mechanism of the reaction, explore its applications in organic synthesis, and the search for a chiral version are underway in our laboratories.

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[12] Crystal structure data for **4a**: $C_{20}H_{20}O_2$, $M_r = 292.36$, colorless plates, crystal dimensions $0.12 \times 0.12 \times 0.05$ mm, monoclinic, space group $P2_1/c$ (determined from the systematic absences), $a = 5.9290(2)$, $b = 17.0610(7)$, $c = 15.0080(5)$ Å, $V = 1492.02(9)$ Å$^3$, $\lambda = 1.5418$ Å, $Z = 4$, $\rho_{calcd} = 1.302$ Mg m$^{-3}$, $F(000) = 624$, $\mu(Cu_{K\alpha}) = 0.649$ mm$^{-1}$. The crystal was held at 200(2) K with an Oxford Cryosystems Cryostream Cooler. Data collection was performed on a Nonius KappaCCD single-crystal diffractometer. A total of 44351 reflections were measured ($\theta_{min} = 3.96°$, $\theta_{max} = 68.29°$; $-7 \le h \le 7$, $0 \le k \le 20$, $0 \le l \le 18$). Multiple observations were averaged ($R_{int} = 0.078$) resulting in 2717 unique reflections, of which 1938 were observed with $I > 2\sigma(I)$. The final cycle of full-matrix least-squares refinement based on 2717 reflections and 279 parameters converged to a final value of $R1$(observed) = 0.0493, $R1$(all data) = 0.0716, $\omega R2$(all data) = 0.1572, $S = 1.092$. Final difference Fourier maps showed no peaks higher than 0.204 e Å$^{-3}$ nor deeper than −0.262 e Å$^{-3}$.

[13] CCDC-236823 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

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