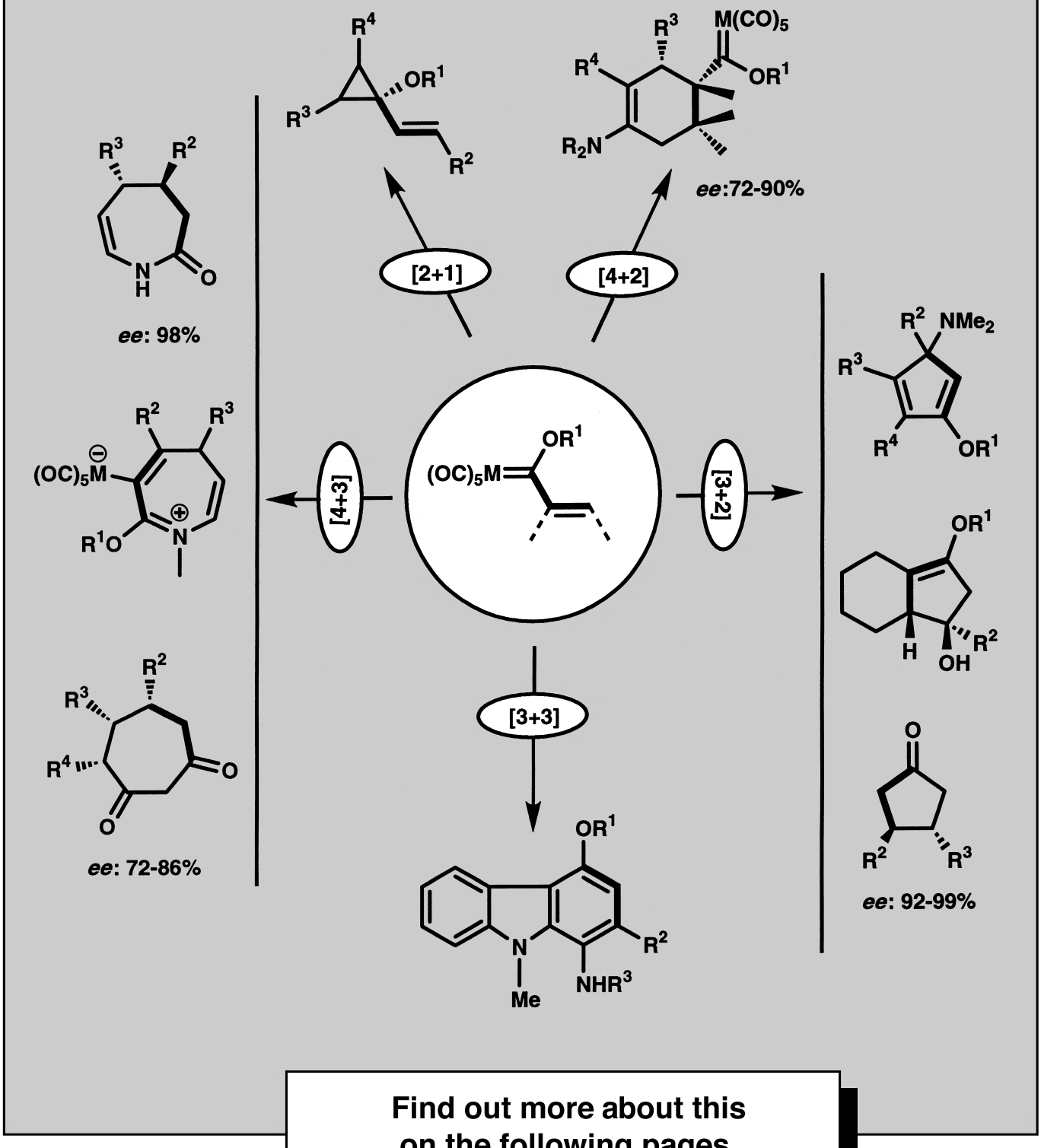
α,β-Unsaturated Fischer Carbene Complexes: A Powerful Tool in Synthesis



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Five- and Seven-Membered Rings from Alkenyl(methoxy)carbene Complexes and Methyl Ketone Enolates**

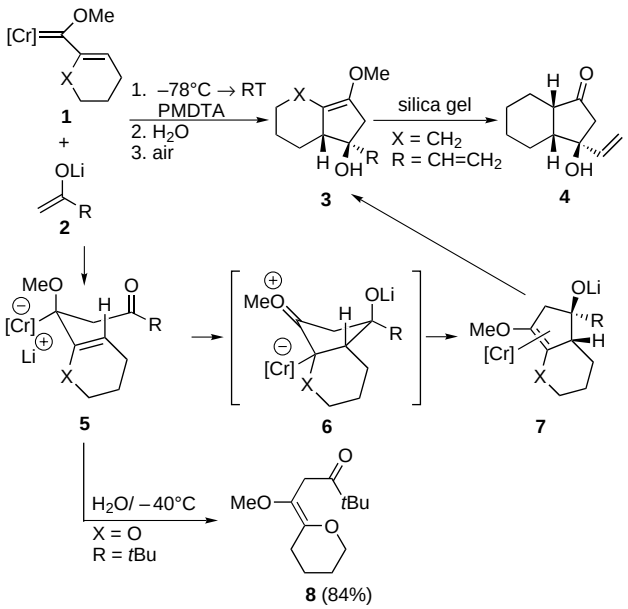
José Barluenga,* Jorge Alonso, Félix Rodríguez, and Francisco J. Fañanás

Dedicated to Professor Heinz Hoberg on the ocassion of his 75th birthday

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] Thus, the formal [3+2] cycloadditions of α,β-unsaturated carbene complexes to siloxy-substituted 1,3-dienes,[3] electron-poor olefins,[4] alkynes,[5] or enamines[6] give rise to functionalized five-membered carbocycles. On the other hand, the formal [4+3] cycloadditions of α,β-unsaturated carbene complexes to 1,3-dienes,[7] 1-azadienes,[8] or 2-azadienes[9] afford functionalized seven-membered rings. Although a domino cyclopropanation–Cope rearrangement[7, 9] was proposed in some cases to explain this latter type of cyclization, we demonstrated that this process involves nucleophilic attack at the carbene carbon atom followed by a cyclization that is promoted by a 1,2-$M(CO)_5$ shift.[8] Moreover, lithium enolates add to α,β-unsaturated carbene complexes in a Michael fashion,[10] and only one example has been reported in which the lithium enolate of acetone reacts with vinylcarbene complexes by 1,2-nucleophilic attack to furnish α,β-unsaturated ketones.[10a] This prompted us to study the reaction of α,β-unsaturated carbene complexes with methyl ketone enolates. Here we report a new diastereoselective route to five- and seven-membered carbocycles under very mild reaction conditions.

The treatment of alkenylcarbene pentacarbonyl complexes **1** with methyl ketone enolates **2** in THF at $-78\,^{\circ}C$ to room temperature led, after hydrolysis and metal decoordination, to the cyclopentenol derivatives **3** in low yields. However, when three equivalents of *N*,*N*,*N*′,*N*′,*N*″-pentamethyldiethylenetriamine (PMDTA) were added to the reaction mixture, compounds **3** were obtained in very good yields and as single diastereomers (Scheme 1 and Table 1). The enol ether group of **3** can be easily hydrolyzed to a carbonyl group. Thus, treatment of **3e** with silica gel quantitatively affords the bicyclic ketone **4** as a single diastereomer (Scheme 1). The relative configurations of **3** and **4** were assigned on the basis of NOESY experiments on **3f** and **4**.

The formation of cyclopentenol derivatives **3** can be explained by assuming a 1,2-addition of the lithium enolates **2** to the carbene complexes **1** to form intermediates **5**. A cyclization induced by an 1,2-migration[6, 8, 11] of the pentacarbonylchromium group leads to **6**. Subsequent elimination of the metal fragment followed by coordination of the metal



Scheme 1. Reaction of α,β-unsaturated methoxycarbene chromium complexes **1** ([Cr] = $(CO)_5Cr$) with methyl ketone enolates **2**. Formation of five-membered rings **3** and proposed mechanism.

Table 1. Formation of cyclopentenol derivatives **3** from alkenylcarbene complexes **1** and methyl ketone enolates **2**.

Entry	Complex	X	Enolate	R	Product	Yield[a]
1	**1a**	CH_2	**2a**	Me	**3a**	86
2	**1b**	O	**2a**	Me	**3b**	91
3	**1b**	O	**2b**	*t*Bu	**3c**	68[b]
4	**1b**	O	**2c**	PhC≡C	**3d**	87 (48)[c]
5	**1a**	CH_2	**2d**	CH_2=CH	**3e**	78 (28)[c]
6	**1b**	O	**2d**	CH_2=CH	**3f**	82 (34)[c]

[a] Based on starting carbene **1**. [b] Product **8** (14%) is also obtained. [c] In parentheses: yield in the absence of PMDTA.

atom to the carbon–carbon double bond furnishes intermediates **7**, which, after hydrolysis and metal decoordination, give rise to bicyclic cyclopentenol derivatives **3**. Support for the above reaction pathways, especially the 1,2-addition, was gained by studying the low-temperature hydrolysis of **5** (X = O, R = *t*Bu), which gave ketone **8**[10a] (Scheme 1). The observed diastereoselectivity in the formation of **3** can be accounted for by invoking a transition state with the same geometric disposition as **5**. Moreover, the higher yields of **3** when PMDTA was used can be rationalized in terms of coordination of the lithium atom to the triamine, which lowers the rigidity of the transition state and thus favors the approach of the allylic carbon atom of the σ-allylchromium moiety to the carbonyl carbon atom.

Encouraged by these good results, we extended the reaction to other alkenylcarbene complexes. Surprisingly, the reaction of complexes **9** with enolates **2a–c** under the above reaction conditions afforded an undetermined complex mixture, in which the major compound corresponds to the hydrolysis of the product of a 1,2-addition similar to that described by Casey et al.,[10a] instead of the expected cyclopentenol derivatives analogous to **3**. However, when the reaction was

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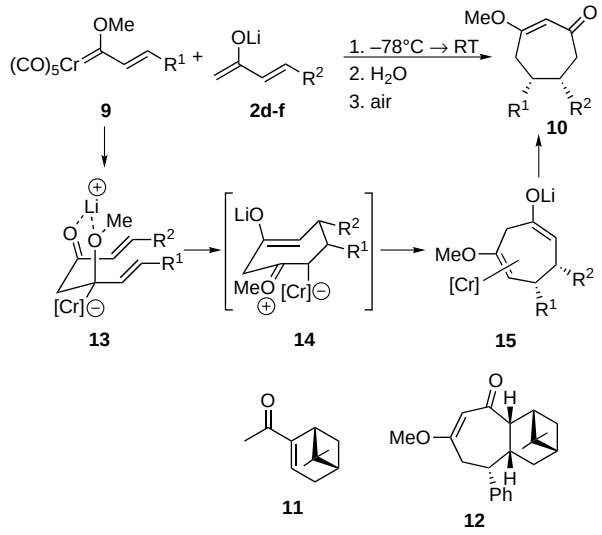
performed with enolates **2d–f**, cycloheptenone derivatives **10** were obtained as single diastereomers (Scheme 2 and Table 2). Here, the best yields were obtained when the reaction was carried out in the absence of PMDTA. The relative *cis* configuration of products **10** was determined on the basis of



Scheme 2. Reaction of α,β-unsaturated methoxycarbene chromium complexes **9** with methyl vinyl ketone enolates **2d–f**. Formation of seven-membered rings **10** and proposed mechanism.

Table 2. Formation of cycloheptenone derivatives **10** from alkenylcarbene complexes **9** and methyl vinyl ketone enolates **2d–f**.

Complex	R^1	Enolate	R^2	Product	Yield[a]
9a	Ph	**2d**	H	**10a**	46
9a	Ph	**2e**	Me	**10b**	44
9a	Ph	**2f**	Ph	**10c**	51
9b	4-$MeOC_6H_4$	**2d**	H	**10d**	52
9b	4-$MeOC_6H_4$	**2f**	Ph	**10e**	43

[a] Based on starting carbene **9**.

the coupling constant ($J_{H5,H6} = 5.5$ Hz)[3b, 12] and NOESY experiments on **10b**. Given the complete *cis* diastereoselectivity for **10** in all cases examined, we carried out a reaction with the homochiral enolate derived from ketone **11** (Scheme 2), which is easily obtained from (−)-myrtenal. The reaction of this enolate with **9a** at −78 °C to room temperature followed by hydrolysis at −78 °C with a solution of ammonium chloride afforded the fused tricyclic compound **12** in 41 % yield with diastereoselectivity greater than 99 %. The structure and absolute configuration of the new stereogenic centers were unequivocally determined by two-dimensional (COSY, HMQC, HMBC, and NOESY) NMR spectroscopic analysis.

A reasonable mechanism that accounts for the formation of cycloheptenone derivatives **10** is outlined in Scheme 2 and involves an initial nucleophilic attack of the enolates **2d–f** at the carbene carbon atom of carbene complexes **9** to give intermediates **13**. Cyclization, induced by a 1,2-migration[6, 8, 11] of the pentacarbonylchromium group leads to **14**. Subsequent elimination of the metal fragment followed by coordination of the metal atom to the carbon–carbon double bond furnishes intermediates **15**, which, after hydrolysis, metal decoordination, and double-bond isomerization, give rise to cycloheptenone derivatives **10**. The generation of the *cis* diastereomers can be explained by invoking a chairlike transition state, derived from **13**, presumably favored by the internal coordination of the oxygen atoms to the lithium atom. The different reaction courses starting from complexes **1** and **9** can be attributed to the substitution pattern in the vinyl moiety of the carbene complex (see Table 1, entries 5 and 6 and Table 2). α-Substitution seems to disfavor the chairlike approach to the seven-membered rings, presumably due to steric hindrance.

In conclusion, we have developed an interesting generalization of the sole example of 1,2-addition of enolates to alkenylcarbene complexes described by Casey et al. almost twenty-five years ago, which represents a new strategy for the diastereoselective synthesis of five- and seven-membered carbocycles. The starting materials are simple methyl ketones and vinylcarbene complexes. These cyclization processes once again demonstrate the ability of the recently described 1,2-$M(CO)_5$ migration to promote unusual umpolung annulations. Investigations to clarify the mechanism and to expand the scope of the [3+2] and [3+4] annulation methodologies to the modification of natural products such as terpenes, sugars, and α-amino acids are underway.

Experimental Section

General procedure for **3** and **10**: To a solution of lithium diisopropylamide (LDA), prepared by adding BuLi (1.1 mmol) to a solution of diisopropylamine (1.1 mmol) in THF (5 mL) at −30 °C, was added at −78 °C the appropriate methyl ketone (1.1 mmol); when PMDTA was used, it was added, freshly distilled (3 mmol), after the methyl ketone. The resulting yellow–orange solution of **2** was stirred for 30 min at the same temperature, and then a solution of the alkenylcarbene complex **1** or **9** (1 mmol) in THF (10 mL) was added dropwise at −78 °C, and stirring was continued while the temperature reached room temperature. The mixture was hydrolyzed with brine (30 mL), extracted with diethyl ether (3 × 15 mL), and the organic layer dried over anhydrous sodium sulfate. The solvent was removed at reduced pressure, and the crude product was dissolved in hexane/ethyl acetate (5/1) and subjected to air oxidation in direct sunlight. After 2–3 h the resulting brown suspension was filtered through Celite. Solvent removal on a rotary evaporator gave the crude products, which were purified by column chromatography (deactivated silica gel, hexane/ethyl acetate 20/1). All compounds gave satisfactory analytical data, including elemental analyses and mass and NMR spectra.

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Spectroscopic Evidence for a 4-Methylidene Imidazol-5-one in Histidine and Phenylalanine Ammonia-Lyases**

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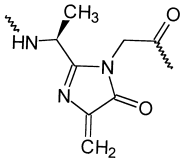
Histidine ammonia-lyase (HAL, histidase, EC 4.3.1.3) and phenylalanine ammonia-lyase (PAL, EC 4.3.1.5) catalyse the nonoxidative deamination of their amino acid substrates to form *trans*-urocanate and *trans*-cinnamate, respectively.[1] HAL initiates histidine degradation both in bacteria and in animals.[2, 3] Its deficiency in humans causes the disease histidinemia.[4] PAL is an important plant enzyme at the crossroads of primary and secondary metabolism. Its product, cinnamate, is the precursor of lignins, flavonoids, and coumarins.

The two enzymes are highly homologous in their amino acid sequence and a prosthetic dehydroalanine was postulated at their active sites.[5–7] Overexpression in *E. coli* combined with mutagenesis experiments showed that the prosthetic group is formed autocatalytically from serines 143 and 202 of HAL and PAL, respectively.[8–10] Recently Schwede et al. solved the 3D structure of HAL by X-ray crystallography.[11] The structure revealed that the prosthetic group is not dehydroalanine but 4-methylidene imidazol-5-one (MIO, **1**). This novel electrophilic group is formed by autocatalytic cyclisation of an Ala–Ser–Gly tripeptide portion of the protein precursor, a process which is concomitant with the elimination of two molecules of water.



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We investigated the UV spectra of wild-type HAL and of the mutant S143A which lacks the MIO group to provide spectroscopic evidence for such a chromophore. Figure 1a shows the UV difference spectra of HAL mutant S143A and wild-type HAL from 240 to 360 nm, measured at enzyme concentrations of 0.2, 0.4, 0.8, and 1.6 mg mL^{-1}. The UV spectrum of wild-type HAL exhibits a discrete maximum between 305 and 310 nm whose intensity grows with increasing enzyme concentration. We propose that this maximum originates from the MIO group, which contains a cross-conjugated double bond system. The mutant lacks this conjugated system and, therefore, it shows no absorption maximum around 308 nm.

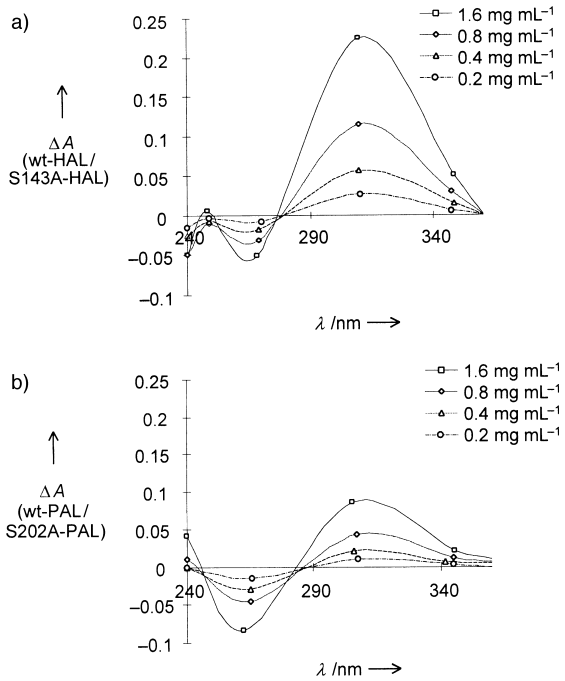

Figure 1. a) UV difference spectra of HAL mutant S143A and wild-type HAL; b) UV difference spectra of PAL mutant S202A and wild-type PAL. wt = wild-type.

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