β,β′- and α,*β,β′*-Annulation Reactions of Cyclic Enamines: Enantioselective Synthesis of Bicyclo[3.*n*.1]alkenones (*n* = 2, 3) and Tricyclo[3.3.0.0^{2,8}]octanes from Fischer Alkenyl Carbene Complexes

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Designing efficient, short routes for the stereoselective construction of polycyclic molecules is currently one of the main challenges in synthetic organic chemistry. Among polycyclic targets, much work has been devoted to outline efficient entries into the [3.2.1] and [3.3.1] bicyclic frameworks.[1] In general, this task has been accomplished by reaction of appropriate C3-synthons with cyclic ketones (α,α′-annulation)[2] or, to a lesser extent, with their enamine derivatives (*β,β′*-annulation).[3] In the former case, a number of two-step processes based on α-alkenylation or α-alkynylation followed by induced ring closure have been disclosed.[2] On the other hand, apart from the elegant [3+3]-cyclization of nitroallylic esters and enamines discovered by Seebach,[3a] no highly enantioselective approaches have been reported.[2f,3b] Despite that transition metal complexes have played a paramount role in the area of carbocyclization reactions,[4] there is still an important gap for the [3+3]-carbocyclization reaction mediated or assisted by transition metals.[5]

While studying the potential of group 6 Fischer carbene complexes we have discovered not only a new *β,β′*-annulation ([3+3] cyclization) but also a novel α,*β,β′*-annulation reaction of cyclopentanone and cyclohexanone enamines (Figure 1).[6] The preliminary results of this study are reported now.

First 1-pyrrolidinylcyclopentene **2** was reacted with chromium or tungsten alkenylcarbene complexes **1** in THF at 60 °C for 1.5 h to furnish substituted semibullvalenes **3a**−**c** in around 90% yield after column chromatography purification (Scheme 1). This astonishing result entails the formation of three carbon−carbon bonds and five stereogenic centers with total selectivity in a process that has no precedents in the chemistry of metal carbene complexes. A series of NMR experiments clearly confirmed the connectivity and stereochemistry of compounds **3** (HMQC, HMBC, and NOESY experiments). Additionally, when the chiral, nonracemic carbene complexes **1e**−**g**, derived from (−)-menthol, and **2** were heated in THF at 60 °C for 6 h the cycloadducts **3e**−**g** were formed as a sole isomer.[7] Interestingly, conducting the reaction of complexes **1a**−**d** and enamine **2** in hexane at room temperature resulted in quantitative precipitation of the metal complexes **4a**−**d**.[7] In turn, complexes **4a**−**c** led to semibullvalene derivatives **3a**−**c** by heating in THF at 60 °C for 1.5 h. From a synthetic point of view it was important to find that compounds **4** were transformed very efficiently into bicyclo[3.2.1]oct-2-en-8-ones **5** by treatment with TFA/THF at 0 °C followed by warming in the presence of water.[8]

Actually, the formation of **3** from **1** and **2** can be rationalized via 1,4-addition of the C_β-enamine to the electrophilic alkene carbene complex[9] followed by intramolecular cyclopropanation of the $C_\alpha-C_{\beta'}$ double bond of the newly formed enamine. Importantly, the isolation of the zwitterionic species **4** does represent an unprecedented feature for supporting the accepted

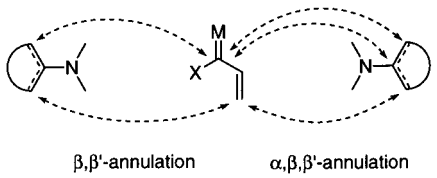
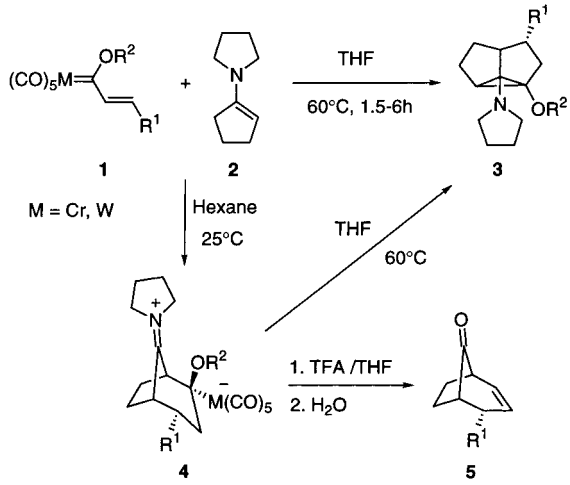


Figure 1.

Scheme 1



Entry	R^1	R^2	Yield (%) 3[a]	4	5[a]
a	2-furyl	Me	85	95	87
b	Ph	Me	88	94	89
c	4-MeO-C_6H_4	Me	[b]	97	91
d	*n*-Pr	Me	–	[c]	60[d]
e	2-furyl	(1*R*,2*S*,5*R*)-menthyl	70		
f	Ph	(1*R*,2*S*,5*R*)-menthyl	73		
g	4-MeO-C_6H_4	(1*R*,2*S*,5*R*)-menthyl	[b]		

[a] Yields from carbene complexes **1**

[b] Attempted purification led to decomposition. Crude **3g** was transformed into compound **9** (70% yield from **1g**) (Reference 7)

[c] Not determined, but **4d** was characterized and transformed into **5d**

[d] A 4:1 *endo*/*exo* mixture was obtained

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(1) For reviews on bicyclo[3.2.1]- and [3.3.1]alkanes, see, respectively: (a) Filippini, M.-H.; Rodriguez, J. *Chem. Rev.* **1999**, *99*, 27. (b) Peters, J. A. *Synthesis* **1979**, 321.

(2) For selenium-induced ring closure, see: (a) Nicolaou, K. C.; Pfefferkorn, J. A.; Cao, G.-Q.; Kim, S.; Kessabi, J. *Org. Lett.* **1999**, *1*, 807. For Hg^{2+}-mediated ring closure, see: (b) Frontier, A. L.; Raghavan, S.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1997**, *119*, 6686. (c) Huang, H.; Forsyth, C. J. *J. Org. Chem.* **1995**, *60*, 5746. For Pd(II)-mediated ring closure, see: (d) Kende, A. S.; Roth, B.; Sanfilippo, P. J.; Blacklock, T. J. *J. Am. Chem. Soc.* **1982**, *104*, 1784 and 5808. For free-radical ring closure, see: (e) Cole, B. M.; Han, L.; Snider, B. B. *J. Org. Chem.* **1996**, *61*, 7832. (f) For enantioselective free-radical ring closure, see: García-Ruano, J. L.; Rumbero, A. *Tetrahedron: Asymmetry* **1999**, *10*, 4427.

(3) (a) Seebach, D.; Missbach, M.; Calderari, G.; Eberle, M. *J. Am. Chem. Soc.* **1990**, *112*, 7625. (b) Butkus, E.; Stoncius, A. *Synlett* **1999**, 234. (c) Byeon, C.-H.; Hart, D. J.; Lai, C.-S.; Unch, J. *Synlett* **2000**, 119.

(4) (a) Frühauf, H.-W. *Chem. Rev.* **1997**, *97*, 523. (b) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49.

(5) (a) While writing this manuscript the [3+3]-carbocyclization of TMM and enamines has appeared, see: Buono, F.; Tenaglia, A. *J. Org. Chem.* **2000**, *65*, 3869. (b) For an isolated example involving Fischer alkenyl carbene complexes, see: Barluenga, J.; Tomás, M.; Rubio, E.; López-Pelegrín, J. A.; García-Granda, S.; Pérez-Priede, M. *J. Am. Chem. Soc.* **1999**, *121*, 3065.

(6) We have previously reported the α,*β*-annulation ([3+2] cyclization) of carbene complexes with enamines of aldehydes as well as of 3-pentanone and cycloheptanone. See: Barluenga, J.; Tomás, M.; Ballesteros, A.; Santamaría, J.; Brillet, C.; García-Granda, S.; Piñera-Nicolás, A.; Vázquez, J. T. *J. Am. Chem. Soc.* **1999**, *121*, 4516.

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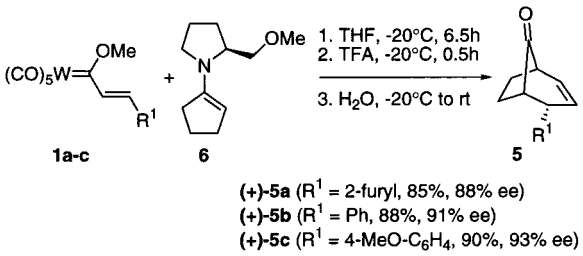
Scheme 2

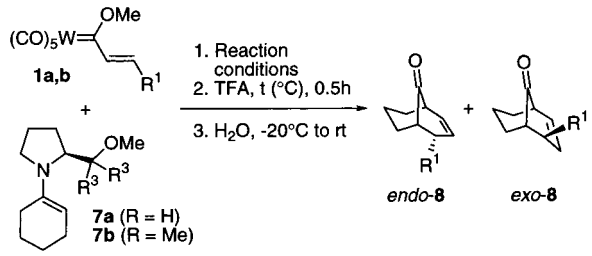


polar pathway for the cyclopropanation reaction of electron-rich alkenes, like enamines, by Fischer carbene complexes.[10] Moreover, the endo orientation of the $M(CO)_5$ fragment precludes the cyclopropanation reaction to involve the participation of a metallacyclobutane species, but rather backside attack of the carbanion-type metal-bonded carbon to the iminium function is thought to occur.[11]

The asymmetric synthesis of bicyclo[3.2.1]oct-2-en-8-ones was best accomplished by using cyclopentanone enamines derived from readily available (*S*)-2-methoxymethylpyrrolidine (Scheme 2). Thus, stirring a solution of tungsten carbene complexes **1a**−**c** and enamine **6** (THF, −20 °C, 6.5 h) followed by TFA quenching and warming with water resulted in the diastereoselective formation of the enantiomerically enriched endo-cycloadducts **5**. Column chromatography purification gave pure **5** with 85−90% yield and high enantiomeric excess (88−93% ee).[12]

Cyclohexanone enamines **7a,b** were also tested toward tungsten complexes **1a,b** (Scheme 3).[13] We found that these enamines are fairly less reactive than the former and that the selectivity of the process is dependent on the reaction conditions and even on the substituent R^1 of the carbene complex. Thus, the reaction of **1a** (R^1 = 2-furyl) and **7a** (THF, −20 °C, 72 h) led to the cycloadduct

Scheme 3



Compound	R^1	R^3	Reaction conditions	Yield (%)	*endo* (ee) : *exo* (ee)
(-)-8a	2-furyl	H	THF / 3d (-20°C)	75	1 (73%) : 2 (98%)
(-)-8a	2-furyl	Me	CH_2Cl_2 / 3d (-20°C)	80	15 (95%) : 1 (98%)
(-)-8b	Ph	Me	THF / 7d (-30°C)	50	>50 (94%) : <1 (--)

8a (75% yield) as a 1:2 mixture of endo/exo isomers. Column chromatography separation afforded pure *endo*-**8a** (73% ee) and *exo*-**8a** (98% ee). On the contrary, the corresponding endo isomer was efficiently formed (80%; *endo*-**8a**/*exo*-**8a** = 15:1; 95% ee) by reacting carbene **1a** with enamine **7b** in CH_2Cl_2 at −20 °C.[14] In turn, the reaction of carbene **1b** and enamine **7b** in THF at −30 °C afforded the *endo*-**8b** with moderate chemical yield and excellent stereoselectivity (50%; *endo*-**8b**/*exo*-**8b** >50:1; 94% ee).[12]

In conclusion, we have demonstrated that alkenyl carbene complexes of chromium and tungsten[15] are very useful C3-synthons for the [3+3] cycloaddition reaction toward cyclopentanone and cyclohexanone enamines. This simple, one-step protocol features a highly diastereo- and enantioselective synthesis of functionalized bicyclo[3.2.1]octane and bicyclo[3.3.1]nonane skeletons[16] having three chiral and two prochiral centers. The novel α,β,β'-annulation reaction of cyclopentanone enamines and alkenyl carbene complexes described here represents the shortest thermal access to tricyclo[3.3.0.$0^{2,8}$]octanes (semibullvalene derivatives),[17] systems known to be precursors of molecules of interest, e.g. triquinanes.[18] Moreover, diastereo- and enantiomerically pure semibullvalenes containing five chiral centers are readily available from menthyl derived carbene complexes. The isolation of intermediates supports the polar pathway for the cyclopropanation of enamines by Fischer carbene complexes.[19]

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Supporting Information Available: Characterization data for **3**−**5** and **8**−**12** and HPLC data for racemic **5,8** and enantioenriched **5,8** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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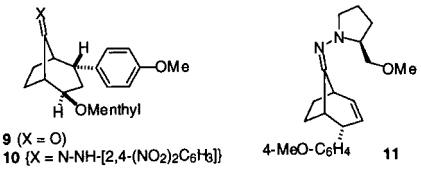
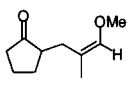
(7) X-ray analyses were performed on compounds **4c**, **10**, and **11** (to be published elsewhere). Compound **10** was obtained from **3g** by thermal ring opening to ketone **9** and derivatization with 2,4-dinitrophenylhydrazine. Compound **11** was obtained by derivatization of ketone **5c** with (*S*)-(−)-1-amino-2-(methoxymethyl)pyrrolidine (SAMP).



The presence of a sole stereoisomer for compounds **3e**−**g** was deduced from the ^1H and ^{13}C NMR of the reaction crude. This was also confirmed from the formation of derivatives **9** and **10** as single isomers.

(8) We agree with a referee who noted that this transformation presumably involves elimination of the alkoxy group to provide a nonstabilized carbene complex which then decomposes via a 1,2 proton shift. See: (a) Casey, C. P.; Brunsvold, W. R. *Inorg. Chem.* **1977**, *16*, 391. (b) Rudler, H.; Audouin, M.; Parlier, A.; Martin-Vaca, B.; Goumont, R.; Durand-Réville, T.; Vaissermann, J. *J. Am. Chem. Soc.* **1996**, *118*, 12045.

(9) The Michael adduct intermediate **12** was obtained (45%) in the reaction of enamine **2** and pentacarbonyl[2-methylpropenylidene(methoxy)]tungsten complex followed by SiO_2 treatment.



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(10) Casey, C. P.; Cesa, M. C. *Organometallics* **1982**, *1*, 87.

(11) This conclusion was previously reached by Brookhart in a sound study on the cyclopropanation reaction by cationic nonstabilized iron carbene complexes. See: Brookhart, M.; Liu, Y.; Goldman, E. W.; Timmers, D. A.; Williams, G. D. *J. Am. Chem. Soc.* **1991**, *113*, 927. (We thank a referee for this observation.) In our case, despite that the endo stereochemical orientation of the anion metal center of **4** is exclusively observed both in the solid state and in THF-d_8 solution, an endo−exo equilibration cannot be definitively ruled out.

(12) The enantiomeric excesses of **5** and **8** were determined by HPLC (Chiracel OB-H and OJ columns).

(13) The reaction of the nonchiral cyclohexanone pyrrolidine enamine and carbene complexes **1a,b** takes place in THF (0 °C, 12 h) to furnish a ca. 5:1 mixture of racemic *endo*-**8**/*exo*-**8** in 80−85% yield.

(14) Running the reaction at −50 °C resulted in increasing the endo/exo ratio to >20:1 and the ee to 98%, though the chemical yield dropped to 52%. The replacement of enamine **7b** with **7a** led to poorer selectivity toward *endo*-**8a** (endo/exo = 5:1; 83% ee).

(15) Either chromium or tungsten complexes **1** were found to work equally well in the formation of racemic **3**−**5**. All the assays leading to **(+)-5** and **(+)-8** were performed with tungsten complexes **1**.

(16) The bicyclo[3.3.1]nonan-2-one skeleton is the central part of a number of terpenes. For instance, see refs 2a−d.

(17) (a) For the arene−alkene photocyclization, see: Wender, P. A.; Siggel, L.; Nuss, J. M. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: New York, 1991; Vol. 5, pp 645−673. (b) For the oxa-di-π-methane rearrangement of bicyclo[2.2.2]octenones to semibullvalenes, see: Lee, T.-H.; Rao, P. D.; Liao, C.-C. *Chem. Commun.* **1999**, 801.

(18) Singh, V. *Acc. Chem. Res.* **1999**, *32*, 324.

(19) Studies aiming to rationalize the different pathways found for cyclic and acyclic enamines toward alkenyl carbenes are being completed. In particular, it can be anticipated that the formation of complexes **4** is a reversible process.