Communications to the Editor

[3 + 2] Cycloaddition of Fischer Alkenyl Carbene Complexes to Enamines: An Efficient Asymmetric Approach to Cyclopentanoids

José Barluenga,*,† Miguel Tomás,† Alfredo Ballesteros,† Javier Santamaría,† Cecile Brillet,† Santiago García-Granda,‡ Alejandro Piñera-Nicolás,‡ and Jesús T. Vázquez§

Instituto Universitario de Química Organometálica "E. Moles"
Departamento de Química Física y Analítica
Universidad de Oviedo, 33071-Oviedo, Spain
Instituto Universitario de Bio-Orgánica "A. González"
Universidad de La Laguna, 38206-La Laguna, Tenerife, Spain

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Designing new strategies for the selective synthesis of five-membered carbocycles continues to attract the interest of organic chemists.[1] The Pauson−Khand reaction constitutes a powerful tool for the rapid construction of substituted cyclopentenones.[2] Probably, the most efficient access to the cyclopentane ring is based on the [3 + 2] cycloaddition which requires devising appropriate C−C−C synthons of type *I* (C2−C1−C5 + C3−C4 coupling) (Figure 1). Thus, various synthons for dimethylenemethane *IA*[3] and trimethylenemethane *IB*[4] have been elaborated and successfully reacted with electron-deficient alkenes.[1,5] Direct entry into the cyclopentanone ring is not so straightforward and has been accomplished either by ozonolysis of the cycloadducts from *IB* or by cycloaddition of the oxyallyl species *IC* with electron-rich alkenes.[5,6] Studies on the asymmetric version have centered mainly in species *IB* and high selectivity has been reached in some occasions.[4a] Although Fischer carbene complexes

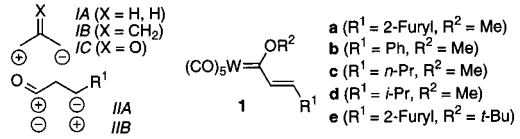
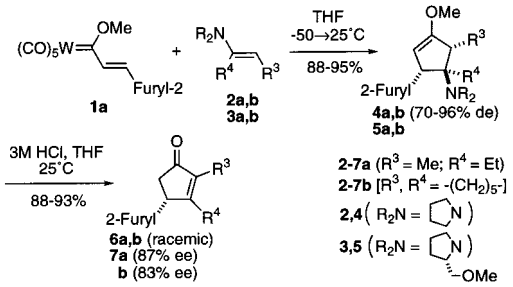


Figure 1.

Scheme 1



have been reported to form cyclopentadiene derivatives,[7] the [3 + 2] cycloaddition of complexes of type **1** toward alkenes leading to cyclopentene derivatives has remained unknown until recently.[8]

Herein we report that tertiary achiral and homochiral enamines smoothly undergo [3 + 2] carbocyclization to pentacarbonyl(alkoxyalkenylcarbene)tungsten(0) complexes **1**[9] and that the cycloaddition formally involves the carbene synthons *IIA* or *IIB* (Figure 1) depending primarily on the nature of the enamine.[10] Therefore the present cyclopentaannulation involves the coupling of C1−C2−C3 and C4−C5 fragments.

The reaction of pyrrolidine enamines **2a**,**b**, derived from 3-pentanone and cycloheptanone, with the tungsten alkenylcarbene complex **1a** in THF, went to completion after 6 h at 25 °C affording cleanly the [3 + 2] cycloadducts **4a**,**b** (Scheme 1). Column chromatography of the crude reaction product furnished pure methoxycyclopentenes **4a** (95%; one diastereoisomer) and **4b** (92%; C-3 epimers, 70% de). Interestingly, the formation of two carbon−carbon single bonds and three stereogenic centers occurred with regio- and stereochemical control. Hydrolysis of **4** with diluted acid provided cyclopentenones **6** (90% for **6a**; 92% for **6b**). To test the facial selectivity of the process the corresponding optically active enamines **3a**,**b**, derived from (*S*)-2-methoxymethylpyrrolidine,[9] were reacted with carbene complex **1a** in THF at 25 °C, affording **5a** (88%) and **5b** (90%) with more than 80% de. Hydrolysis of the resulting diastereomeric mixtures

* Corresponding author. Telephone and Fax: (34) 98 510 34 50. E-mail: barluenga@sauron.quimica.uniovi.es.

† Instituto Universitario de Química Organometálica "E. Moles".

‡ Departamento de Química Física y Analítica (X-ray analysis).

§ Instituto Universitario de Bio-Orgánica "A. González" (CD studies).

(1) (a) Little, R. D. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: New York, 1991; Vol. 5, Chapter 3.1, pp 239−270. (b) Chan, D. M. T. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: New York, 1991; Vol. 5, Chapter 3.2, pp 271−314. (c) Hudlicky, T.; Price, J. D. *Chem. Rev.* **1989**, *89*, 1467. (d) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49.

(2) (a) The Pauson−Khand reaction has been highlighted, see: Geis, O.; Schmalz, H.-G. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2801

(3) For recent examples of dimethylene synthons, see: (a) Zhu, G.; Chen, Z.; Jiang, Q.; Xiao, D.; Cao, P.; Zhang, X. *J. Am. Chem. Soc.* **1997**, *119*, 3836. (b) Knölker, H.-J.; Foitzik, N.; Goesmann, H.; Graf, R.; Jones, P. G.; Wanzl, G. *Chem.—Eur. J.* **1997**, *3*, 538. (c) Choi, G. M.; Yeon, S. H.; Jin, J.; Yoo, B. R.; Jung, I. N. *Organometallics* **1997**, *16*, 5158.

(4) (a) Binger, P.; Fox, D. In *Houben-Weyl: Stereoselective Synthesis*; Helmchen, G., Hoffmann, R., Mulzer, J., Schaumann, E., Eds.; Georg Thieme Verlag: Stuttgart, 1996; Vol. E 21−5, pp 2997−3059. (b) Harrington, P. J. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon: New York, 1995; Vol. 12, Chapter 8.4, pp 923−958. (c) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 1. For recent examples of trimethylene synthons, see: (d) Rosenstock, B.; Gais, H.-J.; Herrmann, E.; Raabe, G.; Binger, P.; Freund, A.; Wedemann, P.; Krüger, C.; Lindner, H. J. *Eur. J. Org. Chem.* **1998**, *257*, 7. (e) Trost, B. M.; Higuchi, R. I. *J. Am. Chem. Soc.* **1996**, *118*, 10094. (f) Lautens, M.; Ren, Y. *J. Am. Chem. Soc.* **1996**, *118*, 9597, 10668. (g) Ghera, E.; Yechezkel, T.; Hassner, A. *J. Org. Chem.* **1996**, *61*, 4959. (h) Yamago, S.; Ejiri, S.; Nakamura, E. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2154. (i) Takahashi, Y.; Tanino, K.; Kuwajima, I. *Tetrahedron Lett.* **1996**, *37*, 5943.

(5) Frühauf, H.-W. *Chem. Rev.* **1997**, *97*, 523.

(6) For instance, see: Masuya, K.; Domon, K.; Tanino, K.; Kuwajima, I. *J. Am. Chem. Soc.* **1998**, *120*, 1724.

(7) (a) Yamashita, A. *Tetrahedron Lett.* **1986**, *27*, 5915. (b) Wulff, W. D.; Bax, B. M.; Brandvold, T. A.; Chan, K. S.; Gilbert, A. M.; Hsung, R. P.; Mitchell, J.; Clardy, J. *Organometallics* **1994**, *13*, 102. (c) Flynn, B. L.; Funke, F. J.; Silveira, C. C.; de Meijere, A. *Synlett* **1995**, 1007. (d) Aumann, R.; Heinen, H.; Dartmann, M.; Krebs, B. *Chem. Ber.* **1991**, *124*, 2343. (e) Aumann, R.; Meyer, A. G.; Fröhlich, R. *Organometallics* **1996**, *15*, 5018.

(8) (a) Hoffmann, M.; Reissig, H.-U. *Synlett* **1995**, 625. (b) Hoffmann, M.; Buchert, M.; Reissig, H.-U. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 283.

(9) Poorer results were reached for chromium carbene complexes. All attempts with tungsten carbene complexes derived from homochiral alcohols [R^2OH= (+)- and (−)-menthol, (−)-8-phenylmenthol)] failed.

(10) For isolated examples of [3 + 2] cyclopentaannulations based on synthons of type *IIA*, see: (a) Huart, C.; Ghosez, L. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 634. (b) Takeda, K.; Fujisawa, M.; Makino, T.; Yoshii, E.; Yamaguchi, K. *J. Am. Chem. Soc.* **1993**, *115*, 9451.

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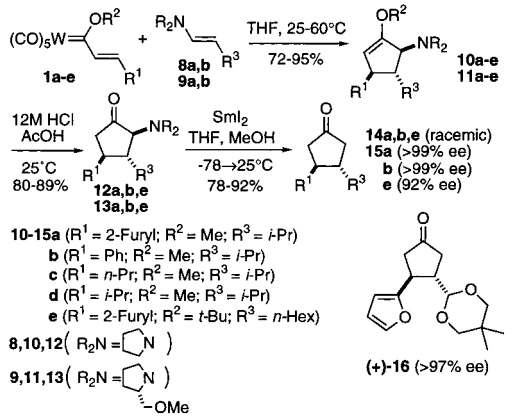
Scheme 2



permitted the isolation of enantiomerically enriched cyclopentenones **7a** (88%, 87% ee) and **7b** (93%, 83% ee).[11]

The reaction of complexes **1** with enamines derived from aldehydes took place in THF at 25 °C (for **1c**,**d**) or 60 °C (for **1a**,**b**,**e**) (Scheme 2). Although a 2:1 regioisomeric mixture of cycloadducts (not shown) formed from enamine **8b** (R^3 = *n*-Hex), the reaction of carbene complexes **1a**−**d** and enamine **8a** (R^3 = *i*-Pr) gave rise to cycloadducts **10a**−**d** (72−95%) with excellent regiocontrol (12:1 for **10a**; >20:1 for **10b**−**d**). Fortunately, we found that the bulkiness of the ultimately removable alkoxy group OR^2 of **1** does play a definitive role in the cyclization and dictates the sense of the regiochemistry. Thus, the carbene complex **1e** (R^2 = *t*-Bu) and the enamine **8b** yielded exclusively **10e** (94%). Remarkably, the cycloadducts **10** were produced as diastereochemically pure materials.[11] Compounds **10a**,**b**,**e** were elaborated into 3,4-disubstituted cyclopentanones **14a**,**b**,**e** by sequential enolether hydrolysis (concentrated HCl, AcOH; 82−89%) to give **12a**,**b**,**e** followed by reductive carbon−nitrogen bond cleavage (SmI_2, THF, MeOH; 78−90%).[11,12] This protocol was applied successfully to the asymmetric synthesis of cyclopentanones using enantiopure enamines **9** (Scheme 2).[9] Thus, the expected substituted cyclopentenes **11a**−**e** were obtained as single regioisomers with excellent chemical yield (74−91%) and complete relative and absolute stereocontrol. Hydrolysis of **11a**,**b**,**e** furnished cyclopentanones **13a**,**b**,**e** (80−84%) which gave rise to enantiomerically enriched *trans*-3,4-disubstituted cylopentanones **15a**,**b**,**e** (90−92%; 92−99% ee) upon reductive cleavage.[11,12] Finally, compound **(+)-16** was efficiently synthesized (30% overall yield, >97% ee) from carbene complex **1a** and malonaldehyde monoacetal enamine.[11,13]

The absolute configuration of compound **7a** was determined by circular dichroism (CD) analysis of the *p*-bromobenzoyl derivative of its reduced alcohol **17** (λ_{max} = 243 nm) (Figure 2). On the basis of the CD allylic benzoate method,[14] the observed negative exciton Cotton effect at 242 nm ($\Delta\epsilon$ = −10.7) established the absolute configuration shown for these compounds. On the other hand, the absolute configuration of **11b** was established by an X-ray analysis performed on its methylammonium iodide **18** (Figure 2).

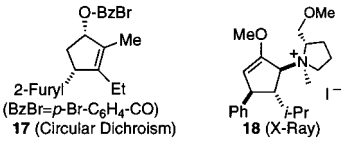


Figure 2.

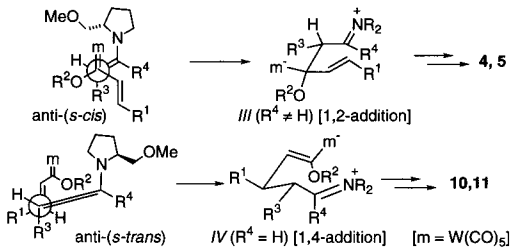


Figure 3.

A possible reaction course is outlined in Figure 3. The formation of cycloadducts **4**,**5** and **10**,**11** implies 1,2-addition (via *III*) and 1,4-addition (via *IV*), respectively, followed by cyclization and $(CO)_5W$ elimination.[15] The structure of **5** is in agreement with a carbene complex-to-enamine *anti-(s-cis)* approach according to the Seebach model for the addition of ketone enamines to nitroalkenes.[16] The absolute stereochemistry of **11** would result from an *anti-(s-trans)* approach, a finding that might provide further insight when applying the Seebach model to aldehyde enamines.

In conclusion, a new protocol for the selective synthesis of cyclopentane derivatives is reported which is based on the rich reactivity and flexibility of group 6 alkenyl carbene complexes. The chemical yields (e.g., the cyclopentanones **15** are formed in >55% unoptimized overall yield from carbenes **1**), the regioselectivity and the relative and absolute stereocontrol are intriguing. In our opinion, these annulation reactions are complementary to previous methodologies for cyclopentenone and cyclopentanone synthesis.

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Supporting Information Available: Characterization data for **4**−**22**, including HPLC assays, X-ray figure and crystallographic data for compound **18** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) The relative stereochemistry of **4** and **10** was determined by 2D-NOESY spectra. The diastereomeric excesses were analyzed by ^{1}H NMR (**4**,**5**: >80%; **10**−**13**: >90%**)** and GC−MS (**11c**: 98.6%; **11d**: 97%). The enantiomeric excess of **7** and **15** was determined by HPLC (Chiracel columns). The enantiomeric excess of **16** was established by ^{13}C NMR (100 MHz) of the acetal derived from (2*S*,3*S*)-2,3-butanediol.

(12) Molander, G. A.; Hahn, G. *J. Org. Chem.* **1986**, *51*, 1135.

(13) Cyclopentanones with two orthogonally masked carbonyl functionalities are highly useful synthons in natural products (ref 1b, pp 308−312). See also: Trost, B. M.; Lynch, J.; Renaut, P.; Steinman, D. H. *J. Am. Chem. Soc.* **1986**, *108*, 284.

(14) Harada, N.; Iwabuchi, J.; Yokota, Y.; Uda, H.; Nakanishi, K. *J. Am. Chem. Soc.* **1981**, *103*, 5590.

(15) For the cyclization model of *III* to **4**,**5**, see: Barluenga, J.; Tomás, M.; Ballesteros, A.; Santamaría, J.; Carbajo, R. J.; López-Ortiz, F.; García-Granda, S.; Pertierra, P. *Chem.—Eur. J.* **1996**, *2*, 88.

(16) (a) Seebach, D.; Missbach, M.; Calderari, G.; Eberle, M. *J. Am. Chem. Soc.* **1990**, *112*, 7625. (b) Seebach, D.; Imwinkelried, R.; Weber, T. In *Modern Synthetic Methods*; Scheffold, R., Ed.; Springer-Verlag: Berlin 1986; Vol. 4, pp 125−259.