Synthetic Methods

DOI: 10.1002/ange.201105362

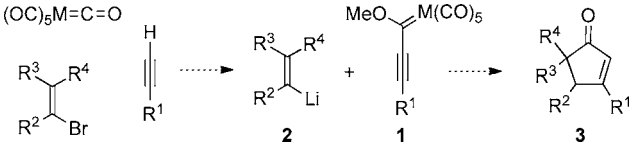
Regio- and Stereoselective Synthesis of Cyclopentenones: Intermolecular Pseudo-Pauson–Khand Cyclization**

José Barluenga, Ana Álvarez-Fernández, Ángel L. Suárez-Sobrino, and Miguel Tomás*

Apart from being a common structural unit in natural products and pharmaceuticals,[1] the cyclopentenone ring does represent a fundamental and versatile building block for the construction of complex molecules.[2] Apart from a number of reports,[3] the Pauson–Khand[4] and, to a lesser extent, the Nazarov cyclization[5] are recognized by far as the most efficient ways to access the cyclopentenone system. However, some drawbacks occasionally limit the generality of these procedures. The Nazarov cyclization suffers from the availability of the divinylketone structures as well as the occurrence of side reactions derived from the oxyallyl cation intermediate. Regarding the popular Pauson–Khand reaction, even though the intramolecular process is recognized as the most efficient access to fused cyclopentenones, there are significant drawbacks in the case of the intermolecular reaction, the major one being the necessity of using highly reactive or strained alkenes.[6,7] In contrast, advances have been made to replace the highly toxic carbon monoxide with more friendly CO sources like aldehydes.[8]

Importantly, the asymmetric version of these processes still requires additional development. The asymmetric Nazarov cyclization of α- and α′-functionalized divinylketones (donor or acceptor groups) has been successfully performed using metal- and organocatalysts.[9] Alternatively, while the intramolecular asymmetric Pauson–Khand reaction has been accomplished with different metal catalysts, the intermolecular version still does represent a challenging goal.[4a] In this context, only Riera, Verdager, and co-workers have reported outstanding achievements using alkyne/$[Co_2(CO)_4L^*]$ complexes and norbornadiene.[10,11]

These facts inspired us to develop a complementary Pauson–Khand cyclopentenone approach (Scheme 1) that is based on 1) simplicity (short experimental protocol and readily available substrates and reagents), and 2) the use of recyclable $[M(CO)_6]$[12] as the source of CO. Overall, the strategy requires a bromoalkene, $[M(CO)_6]$, and an alkyne to generate the cyclopentene ring **3** by cyclization of the corresponding alkenyl lithium **2** and alkynylcarbene complex **1** derivatives.[13]



Scheme 1. New cyclopentenone approach.

A THF solution of the chromium alkynylcarbene **1**, readily made from terminal alkynes and $[Cr(CO)_6]$, was added dropwise at −78 °C to a solution of the alkenyl organollithium **2**, which was generated by metalation of bromoalkenes with *tert*-butyllithium. The reaction was kept at −78 °C for one hour, warmed to room temperature, and then stirred for two hours. The mixture was quenched with aqueous ammonium chloride and demetalated (sunlight). The aqueous layer was extracted (diethyl ether), and the solvents were removed from the collected organic layers. The resulting crude material was treated with concentrated HCl in methylene chloride to hydrolyze the intermediate enol, thus affording exclusively the cyclopentenones **3** in good yields (50–85 %) after chromatographic purification (Scheme 2). The structure of compound **3b** was confirmed by X-ray analysis.[14]

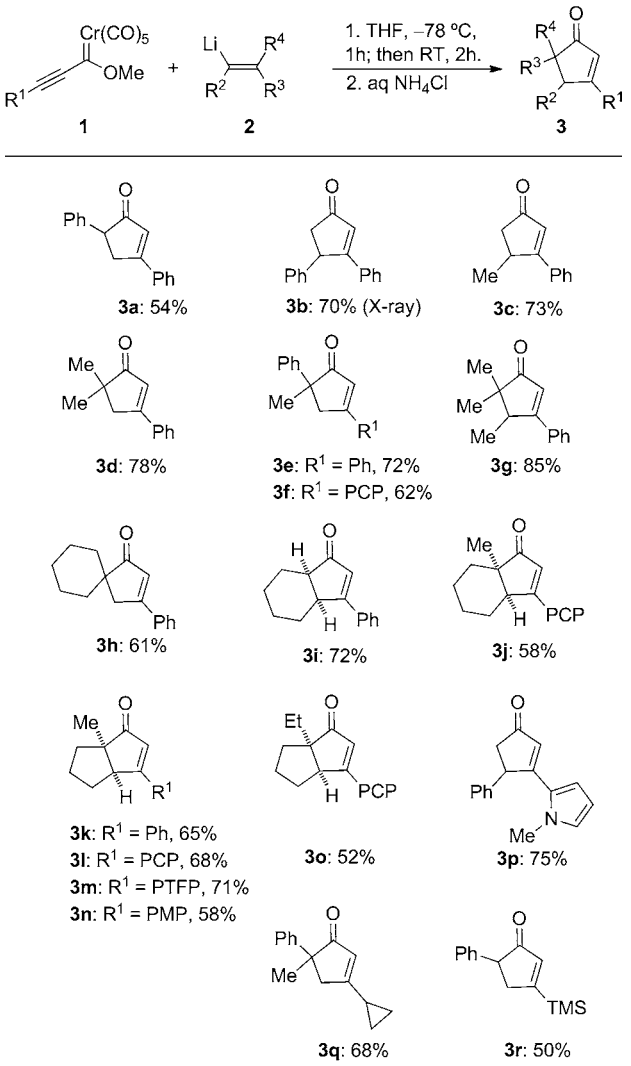
Scheme 2 shows the scope of this [3+2] cyclization. A number of bromoalkenes were first tested with the alkynyl carbenes **1** having aryl substituents with different electronic structures (R^1 = Ar; products **3a–o**). It was found that α- and β-monosubstituted bromoalkenes work satisfactorily (**3a–c**); moreover, both regioisomers are available by simply starting with the appropriate bromoalkene (**3a** versus **3b**). Interestingly, the reaction with β,β-disubstituted and α,β,β-trisubstituted bromoalkenes takes place in higher yields, thus furnishing the cyclopentenones **3d–g** and spirocyclopentenone **3h** having an all-carbon-substituted quaternary center. This protocol also enables access to the cyclopentane- and cyclohexane-fused cyclopentenones **3i–o** in synthetically useful yields. Finally, the reaction works fairly with heteroaryl-, cycloalkyl-, and trimethylsilyl-substituted metal carbenes **1** (**3p**, **3q**, and **3r**, respectively).

A simple approach to understanding this stepwise cyclization is shown in Scheme 3. First, the Michael-type addition of **2** to **1** would form the metallated intermediate **A**. Quenching with aqueous ammonium chloride would provide the *cis*-metallatriene intermediate **B** (best represented as the charged species), which spontaneously undergoes ring closure/metal elimination to the cyclopentadienylether **4**.[15] In

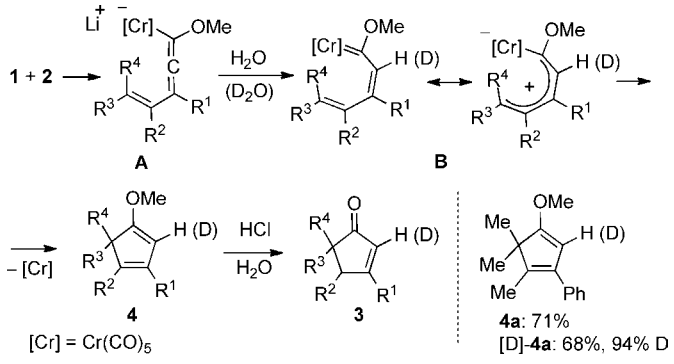
[*] Prof. J. Barluenga, A. Álvarez-Fernández, Dr. Á. L. Suárez-Sobrino, Prof. M. Tomás
Instituto Universitario de Química Organometálica "Enrique Moles", Unidad Asociada al CSIC, Universidad de Oviedo
Julian Clavería 8, Oviedo (Spain)
E-mail: barluenga@uniovi.es

[**] This research was partially supported by the Goverments of Spain (CTQ2010-20517-C02-01) and Principado de Asturias (IB08-088; Severo Ochoa-PCTI predoctoral fellowship to A.A.-F.)

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201105362.



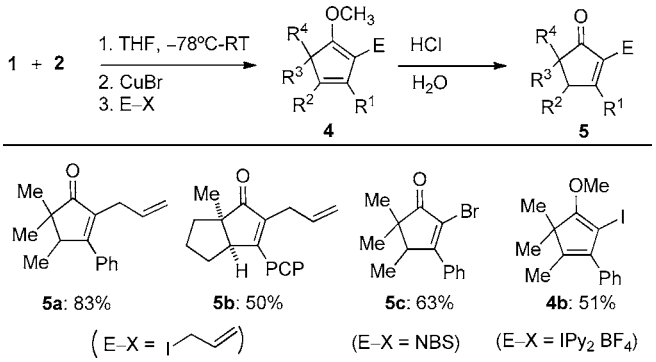
Scheme 2. Cyclopentenones **3** obtained from alkynyl carbenes **1** and vinyllithium compounds **2**. PCP = *p*-chlorophenyl, PMP = *p*-methoxyphenyl, PTFP = *p*-trifluoromethylphenyl, THF = tetrahydrofuran.



Scheme 3. Proposed mechanism for the formation of **3**.

this way, protonated (**4a**) and deuteriated ([D]-**4a**) adducts were isolated with H_2O and D_2O, respectively.[16]

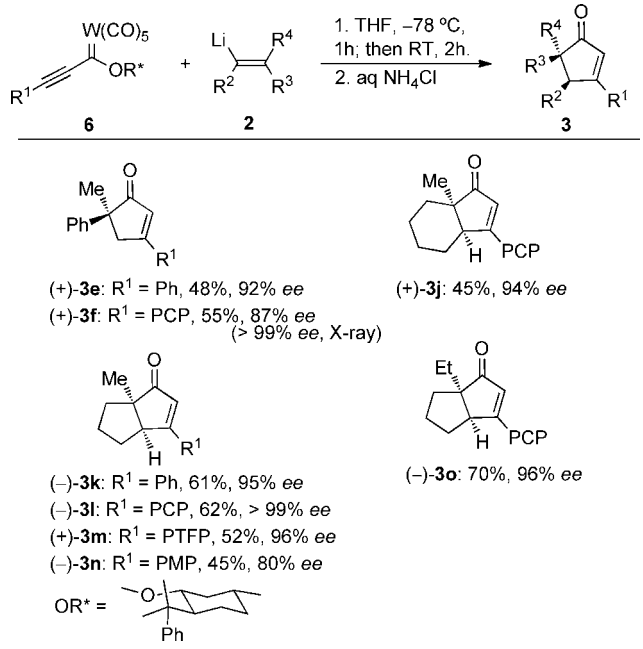
If one assumes the presence of **A**, additional functionalization at C2 might be feasible with other electrophiles (Scheme 4). When a mixture of the carbene **1** and alkenyl lithium **2** was stirred at low temperature, treated with CuBr (1 equiv) at room temperature, and then with reactive



Scheme 4. Functionalization of the cyclopentenones at C2 to give the products **5**. NBS = *N*-bromosuccinimide.

electrophiles (allyl iodide, NBS, bis(pyridine)iodonium tetrafluoroborate), the synthetically valuable cycloadducts **5a–c** and **4b** were isolated in moderate to good yields (51–83%).

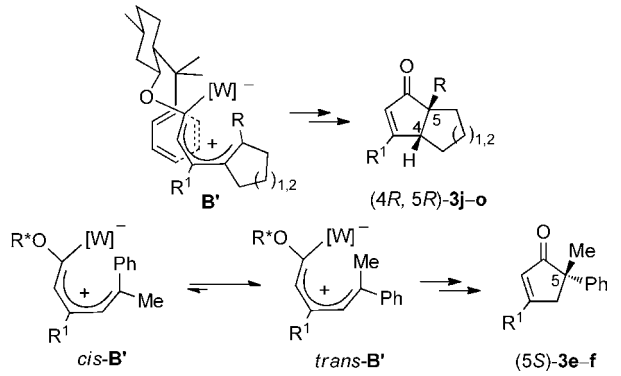
The present methodology seems amenable for the asymmetric cyclization by starting from the chiral nonracemic tungsten carbenes **6** derived from (–)-8-phenylmenthol (Scheme 5).[17] Our goal was to apply this protocol to the enantioselective synthesis of cyclopentenones featuring an all-carbon-substituted quaternary stereogenic center (R^3, $R^4 \neq H$).[18] First, treatment of **6** with methyl- and ethyl-substituted cycloalkenyllithium **2**, under the experimental protocol given for the carbenes **1**, resulted in the formation of cyclohexane- and cyclopentane-fused cyclopentenones (4*R*,5*R*)-**3j–o** in 45–70% yield and greater than 94% *ee* in



Scheme 5. Chiral nonracemic cyclopentenones obtained from a tungsten carbene derived from (–)-8-phenylmenthol **6.**

most cases.[19] When the metal carbene **6** bears an electron-rich aryl substituent (R^1 = PMP) lower selectivity was attained [(−)-**3n**]. In contrast, we found that either (*Z*)- or (*E*)-2-phenylpropenyl lithium (or *Z*/*E* mixtures) underwent cycloaddition with the enantiopure carbenes **6** (R^1 = Ph, PCP), thus leading to cyclopentenones (+)-(*S*)-**3e,f** in moderate yield (48–55%) and high enantioselectivity (87–92%).[19] Crystallization of (+)-**3f** afforded a single crystalline isomer (> 99% *ee*) whose structure was established by X-ray analysis.[14]

Given the mechanistic model in Scheme 3, a possible rational for the stereochemical induction is outlined (Scheme 6). As a result of a π-stacking effect,[20] the 8-



Scheme 6. Induction model proposed for the cyclopentannulation reaction using the (−)-8-phenylmenthol carbene derivatives **6**.

phenylmenthyloxy group would block the bottom face of the C3–C4 bond of the 1-metalla-1,3,5-hexatriene (intermediate **B′**) thus forcing the C6–C2 bond formation to occur through from the top face of the W–C2 carbene moiety. This approach leads to the (4*R*,5*R*)-cycloalkane-fused cyclopentenones **3j–o**. The convergent formation of (+)-(*S*)-**3e,f** could be understood by previous *cis*-**B′**/*trans*-**B′** equilibration with subsequent cyclization of the more stable *trans* species.[21]

In conclusion, a very simple two-step access to polysubstituted cyclopentenones from terminal alkynes, $[M(CO)_6]$, and bromoalkenes is described. Importantly, this protocol enhances to a great extent the challenging intermolecular Pauson–Khand reaction, especially concerning the alkene partner and the asymmetric cyclization. Significant features that reflect the complementarity of the process described herein to the Pauson–Khand reaction are: 1) different types of bromoalkenes are productive and the regiochemistry is completely predetermined, 2) whereas 2-substituted cyclopentenones are obtained from terminal alkynes by the Pauson–Khand reaction, the procedure described herein yields 3-substituted cyclopentenones, 3) a halogen atom can be easily installed at the strategic C2 position, thus allowing additional functionalization, 4) enantiopure cyclopentenones, particularly bicyclic cyclopentenones with an all-carbon-substituted quaternary stereocenter at the bridgehead C5 carbon atom,[22] are readily available with high stereochemical induction (up to 99% *ee*).

Received: July 29, 2011
Published online: November 17, 2011

Keywords: carbenes · chromium · cyclization · enantioselectivity · tungsten

[1] a) S. M. Roberts, M. G. Santoro, E. S. Sickle, *J. Chem. Soc. Perkin Trans. 1* **2002**, 1735–1742; b) A. Rossi, P. Kapahi, G. Natoli, T. Takahashi, Y. Chen, M. Karin, M. G. Santoro, *Nature* **2000**, *403*, 103–108.

[2] F. Rezgui, H. Amri, M. M. El Gaied, *Tetrahedron* **2003**, *59*, 1369–1380.

[3] Selected examples: a) C. P. Davie, R. L. Danheiser, *Angew. Chem.* **2005**, *117*, 6017–6020; *Angew. Chem. Int. Ed.* **2005**, *44*, 5867–5870 (4 + 1 cyclization); b) X. Qi, J. M. Ready, *Angew. Chem.* **2008**, *120*, 7176–7178; *Angew. Chem. Int. Ed.* **2008**, *47*, 7068–7070 (3 + 2 cyclization); c) J. Barluenga, P. Barrio, L. Riesgo, L. A. López, M. Tomás, *J. Am. Chem. Soc.* **2007**, *129*, 14422–14426 (3 + 2 cyclization); d) J. Barluenga, A. Álvarez-Fernández, S. Martínez, A. L. Suárez-Sobrino, M. Tomás, *Tetrahedron Lett.* **2009**, *50*, 3606–3608 (5 + 0 cyclization); e) X. Shi, D. J. Gorin, F. D. Toste, *J. Am. Chem. Soc.* **2005**, *127*, 5802–5803 (gold-catalyzed cycloisomerization of enynyl esters); f) L. Zhang, S. Wang, *J. Am. Chem. Soc.* **2006**, *128*, 1442–1443 (gold-catalyzed cycloisomerization of enynyl esters).

[4] Selected reviews: a) H.-W. Lee, F.-Y. Kwong, *Eur. J. Org. Chem.* **2010**, 789–811; b) J. H. Park, K.-M- Chang, Y. K. Chung, *Coord. Chem. Rev.* **2009**, *253*, 2461–2480; c) S. E. Gibson, N. Mainolfi, *Angew. Chem.* **2005**, *117*, 3082–3097; *Angew. Chem. Int. Ed.* **2005**, *44*, 3022–3037; d) M. Rodríguez-Rivero, J. Adrio, J. C. Carretero, *Synlett* **2005**, 26–41; e) J. Blanco-Urgoiti, L. Añorbe, L. Pérez-Serrano, G. Domínguez, J. Pérez-Castells, *Chem. Soc. Rev.* **2004**, *33*, 32–42; f) L. V. R. Boñaga, M. E. Krafft, *Tetrahedron* **2004**, *60*, 9795–9833; g) N. E. Schore, *Chem. Rev.* **1988**, *88*, 1081–1119.

[5] Selected reviews: a) T. N. Grant, C. J. Rieder, F. G. West, *Chem. Commun.* **2009**, 5676–5688; b) H. Pellissier, *Tetrahedron* **2005**, *61*, 6479–6517; c) A. J. Frontier, C. Collison, *Tetrahedron* **2005**, *61*, 7577–7606; d) M. A. Tius, *Eur. J. Org. Chem.* **2005**, 2193–2206.

[6] For instance, see Refs. [4e] and [4f].

[7] For studies about the factors that influence the reactivity of the alkene/alkyne components, see S. E. Gibson, S. E. Lewis, N. Mainolfi, *J. Organomet. Chem.* **2004**, *689*, 3873–3890.

[8] See ref. [4b] and K. H. Park, I. G. Jung, Y. K. Chung, *Org. Lett.* **2004**, *6*, 1183–1186.

[9] Recent examples: a) P. Cao, C. Deng, Y.-Y. Zhou, X.-L. Sun, J.-C. Zheng, Z. Xie, Y. Tang, *Angew. Chem.* **2010**, *122*, 4565–4568; *Angew. Chem. Int. Ed.* **2010**, *49*, 4463–4466; b) A. K. Basak, N. Shimada, W. F. Bow, D. A. Vidic, M. A. Tius, *J. Am. Chem. Soc.* **2010**, *132*, 8266–8277; c) M. Kawatsura, K. Kajita, S. Hauyase, T. Itoh, *Synlett* **2010**, 1243–1246; d) J. Huang, D. Leboeuf, A. J. Frontier, *J. Am. Chem. Soc.* **2011**, *133*, 6307–6317.

[10] a) Y. Ji, A. Riera, X. Verdaguer, *Org. Lett.* **2009**, *11*, 4346–4346; b) C. Ferrer, A. Riera, X. Verdaguer, *Organometallics* **2009**, *28*, 4571–4576; c) M. Revés, T. Achard, J. Solà, A. Riera, X. Verdaguer, *J. Org. Chem.* **2008**, *73*, 7080–7087; d) J. Solà, M. Revés, A. Riera, X. Verdaguer, *Angew. Chem.* **2007**, *119*, 5108–5111; *Angew. Chem. Int. Ed.* **2007**, *46*, 5020–5023.

[11] For the first intermolecular asymmetric cobalt-catalyzed Pauson–Khand reaction, see: A. Lledó, J. Solà, X. Verdaguer, A. Riera, M. A. Maestro, *Adv. Synth. Catal.* **2007**, *349*, 2121–2128.

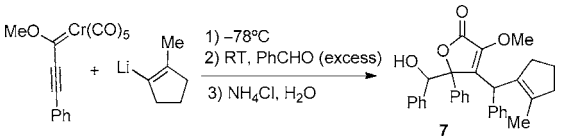
[12] For an appropriate way to recycle $[M(CO)_6]$, see, for instance: R. Aumann, M. Kößmeier, K. Roths, R. Fröhlich, *Synlett* **1994**, 1041–1044.

[13] a) This hypothesis is supported by the fact that indole derivatives actually undergo cyclization with metal carbenes **1** through nucleophilic addition/ring closure. See: J. Barluenga, E. Tudela, A. Ballesteros, M. Tomás, *J. Am. Chem. Soc.* **2009**, *131*, 2096–2097; b) The preparation of **1** is readily performed by addition of the lithium acetylide to $[M(CO)_6]$ and quenching with MeOTf (see the Supporting Information); c) For the reaction of alkynyl carbene complexes with enamines, see: R. Aumann, A. G. Meyer, R. Fröhlich, *Organometallics* **1996**, *15*, 5018–5027, and references therein.

[14] CCDC 835349 (**3b**), 835348 [(+)-**3f**], and 835350 (**7**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[15] This cyclopentannulation of metallahexatrienes is a well-established process in Fischer metal carbene chemistry, though the mechanism remains unclear. See: a) J. Barluenga, F. Aznar, S. Barluenga, *J. Chem. Soc. Chem. Commun.* **1995**, 1973–1974; b) J. Barluenga, M. A. Fernández-Rodriguez, E. Aguilar, *J. Organomet. Chem.* **2005**, *690*, 539–587.

[16] The presumed intermediate **A** could be trapped with benzaldehyde as the electrophile. The reaction does not evolve to the corresponding cyclopentenone, but the lactone **7** was isolated as a mixture of diastereoisomers (52% yield; for the X-ray analysis of the major isomer, see Ref. [14]). The formation of **7** results from a multicomponent cyclization involving intermediate **A**, one CO ligand, and two equivalents of PhCHO.



7

[17] Comparison of Group 6 metal carbenes led us to conclude that chromium carbenes are superior in terms of chemical yield, whereas much higher asymmetric induction was reached with tungsten carbenes. This event has been previously observed. See: J. Barluenga, R. Bernardo de La Rúa, D. de Sáa, A. Ballesteros, M. Tomás, *Angew. Chem.* **2005**, *117*, 5061–5063; *Angew. Chem. Int. Ed.* **2005**, *44*, 4981–4983, and reference [13a].

[18] In the case of $R^3 = Ph$; $R^4 = H$, extensive racemization was observed to occur through a [1,5]-H shift (compound **4**) and/or enolization (compound **3**).

[19] The *ee* values were determined by HPLC analysis using a chiral stationary phase.

[20] G. B. Jones, B. J. Chapman, *Synthesis* **1995**, 475–497.

[21] The *trans* orientation of the Ph would enable a more efficient conjugation of the pentadienyl cation moiety. In fact, replacing Ph with Ph-CH_2-CH_2 (1:1 *E*/*Z* mixture) resulted in less efficient *cis*-**B′**/*trans*-**B′** discrimination and therefore low induction (64% *ee*; see the Supporting Information).

[22] Access to such a relevant structural moiety represents a particular challenge in organic synthesis nowadays. See: B. M. Trost, C. Jiang, *Synthesis* **2006**, 369–396.