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J. Am. Chem. Soc., **2007**, 129 (46), 14422-14426• DOI: 10.1021/ja075106+ • Publication Date (Web): 30 October 2007

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Published on Web 10/30/2007

A General and Regioselective Synthesis of Cyclopentenone Derivatives through Nickel(0)-Mediated [3 + 2] Cyclization of Alkenyl Fischer Carbene Complexes and Internal Alkynes

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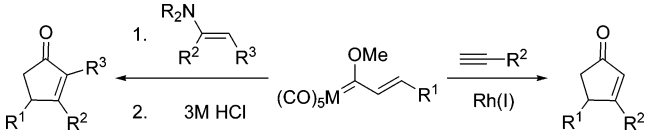
Abstract: A broad range of substituted 2-cyclopentenone derivatives **3**−**6** are synthesized by the nickel-(0)-mediated [3 + 2] cyclization reaction of chromium alkenyl(methoxy)carbene complexes **1** and internal alkynes **2**. The reaction takes place with complete regioselectivity with both unactivated alkynes and activated alkynes (electron-withdrawing and electron−donating substituted alkynes). Representative cycloadducts containing boron and tin substituents are further demonstrated to be active partners in classical Pd-catalyzed C−C coupling processes to allow the production of 2-aryl- and 2-alkynyl-substituted cyclopentenones **9**−**13**.

Introduction

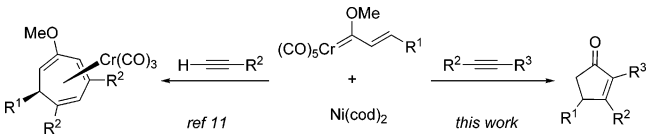
Cyclopentenones are important structural motifs of natural products and pharmaceuticals.[1] They are also of interest as useful synthons for the construction of more complex molecules.[2] Although a number of powerful methodologies for the synthesis of the 2-cyclopentenone skeleton, including the Nazarov cyclization[3] and the Pauson−Khand reaction,[4] are currently available, the scope of these processes has been limited due to the poor reactivity and selectivity of simple reactive counterparts or to functional group compability. As a result, the development of new methodologies for the synthesis of cyclopentenones from readily available substrates continues to be an important pursuit in synthetic organic chemistry.[5]

On the other hand, the cyclization between appropriate C3 and C2 units are rather uncommon due to the difficulty of accessing three-carbon dipolar species. In this respect, symmetrical oxyallyl cation species (2-oxa-1,3-dipoles) have become somewhat useful toward activated alkenes.[6] In recent years, we and others have discovered that group 6 Fischer alkenyl carbene complexes behave as efficient 1-oxa-1,3-dipole equivalents.[7] For instance (Scheme 1), their reaction with enamines provides cyclopentenones via the [3 + 2] cyclization and amine elimination sequence,[8] whereas the direct entry into 3,4-disubstituted 2-cyclopentenones has been brought about only in the case of terminal or electron-poor alkynes by running the cyclization reaction in the presence of catalytic amounts of Rh(I).[9,10]

Scheme 1. Synthesis of Cyclopentenones from Fischer Alkenylcarbene Complexes



Scheme 2. Ni(0)-Mediated Reactions of Fischer Alkenylcarbene Complexes and Alkynes



Interestingly, a different type of reactivity was found for chromium(0) carbene complexes in the presence of nickel(0).

(1) Review: Roberts, S. M.; Santoro, M. G.; Sickle, E. S. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1735.
(2) For a review, see: Rezgui, F.; Amri, H.; Gaied, M. M. E. *Tetrahedron* **2003**, *59*, 1369.
(3) For selected reviews, see: (a) Habermas, K. L.; Denmark, S. E.; Jones, T. K. *Org. React.* **1994**, *45*, 1. (b) Frontier, A. J.; Collison, C. *Tetrahedron* **2005**, *61*, 7577. (c) Pellissier, H. *Tetrahedron* **2005**, *61*, 6479.
(4) For selected reviews, see: (a) Laschat, S.; Becheanu, A.; Bell, T.; Baro, A. *Synlett*, **2005**, 2547. (b) Gibson, S. E.; Stevenazzi, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 1800. (c) Sugihara, T.; Yamaguchi, M.; Nishizawa, M. *Chem.-Eur. J.* **2001**, *7*, 1589. (d) Brummond, K. M.; Kent, J. L. *Tetrahedron* **2000**, *56*, 3263. (e) Chung, Y. K. *Coord. Chem. Rev.* **1999**, *188*, 297. (f) Oliver, G.; Schmalz, H. *Angew. Chem., Int. Ed.* **1998**, *37*, 911. (g) Schore, N. E. *Org. React.* **1991**, *40*, 1.
(5) For a review on transition metal-mediated routes to cyclopentenones, see: (a) Gibson, S. E.; Lewis, S. E.; Mainolfi, M. *J. Organomet. Chem.* **2004**, *689*, 3873. For recent approaches to the cyclopentenone skeleton, see: (b) Davie, C. P.; Danheiser, R. L. *Angew. Chem., Int. Ed.* **2005**, *44*, 5867. (c) Shi, X.; Gorin, D. J.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 5802. (d) Herndon, J. W.; Zu, J. *Org. Lett.* **1999**, *1*, 15. (e) Zhang, L.; Wang, S. *J. Am. Chem. Soc.* **2006**, *128*, 1442. (f) Moser, W. H.; Feltes, L. A.; Sun, L.; Giese, M. W.; Farrell, R. W. *J. Org. Chem.* **2006**, *71*, 6542. (g) Kurahashi, T.; Wu, Y.-T.; Meindl, K.; Rühl, S.; de Meijere, A. *Synlett* **2005**, 805.
(6) For instance, see: Masuya, K.; Domon, K.; Tanino, K.; Kuwajima, I. *J. Am. Chem. Soc.* **1998**, *120*, 1724.
(7) For isolated examples of [3 + 2] cyclopentannulations based on 1-oxa-1,3-dipole equivalents, 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*, 9351.
(8) (a) 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. For other [3 + 2] cycloadditions involving a three-carbon−atom synthon alkenylcarbene ligand, see, for example: (b) Hoffmann, M.; Buchert, M.; Reissig, H.-U. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 283. (c) Flyn, B. L.; Funke, F. J.; Silveira, C. C.; de Meijere, A. *Synlett* **1995**, 1007. (d) 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.
(9) Barluenga, J.; Vicente, R.; López, L. A.; Rubio, E.; Tomás, M.; Álvarez-Rúa, C. *J. Am. Chem. Soc.* **2004**, *126*, 470.
(10) The reaction of group 6 alkenyl Fischer carbene complexes with alkynes leads to substituted phenols (benzannulation or Dötz reaction): Dötz, K. H. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 587.

10.1021/ja075106+ CCC: $37.00

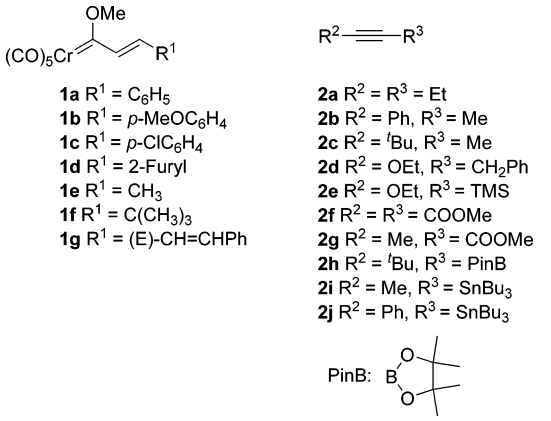


Figure 1. Fischer carbene complexes **1** and alkynes **2** used in this work.

In particular, the reaction of alkenylcarbene complexes of Cr(0) with *terminal alkynes* gave neither benzannulation nor [3 + 2] cyclization products, but a novel [3 + 2 + 2] carbocyclization was accomplished (Scheme 2).[11] In this article, we report on the $Ni(cod)_2$-mediated reaction of chromium alkenylcarbene complexes with a variety of internal alkynes that allowed establishing a general and selective access to an array of substituted cyclopentenones which complements existing methodologies.

The carbene complexes **1a**−**g** and internal alkynes **2a**−**j** outlined in Figure 1 were employed to undertake the present study.

Results and Discussion

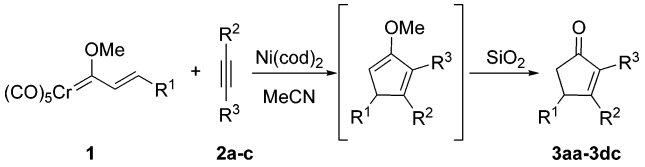
Nickel(0)-Mediated Reactions of Chromium Alkenylcarbene Complexes 1 and Unactivated Alkynes 2a−**c.** On the outset, we treated alkenylcarbene complex **1a** (R^1 = Ph) with 3-hexyne **2a** (3 equiv) at −10 °C in acetonitrile in the presence of a stoichiometric amount of $Ni(cod)_2$, and the reaction mixture was allowed to warm to 20 °C over 2 h. The solvent and excess of alkyne were removed in vacuo, and the resulting residue was subjected to column chromatography. Thus, the initially formed enolether underwent hydrolysis to furnish pure cyclopentenone **3aa** in 56% overall yield (Table 1, entry 1). Neither the [3 + 2 + 2] cyclization product[11] nor the phenol derivative resulting from the Dötz reaction[10] were observed in the crude reaction mixture.

Next, the issue of the regiochemistry of this new [3 + 2] cyclization reaction was addressed by reacting 1-phenylpropyne **2b** with a series of alkyl-, aryl-, and heteroaryl-substituted carbene complexes **1**. In all the cases examined, the reaction exhibited complete regioselectivity yielding the 3-phenylsubstituted cyclopentenones **3ab**−**fb** (R^2 = Ph) in 52−71% yield (Table 1, entries 2−7). The reaction takes place also with total regioselectivity in the case of the *tert*-butylmethylacetylene **2c** yielding the cyclopentenones **3bc** and **3dc** in acceptable yield (Table 1, entries 8 and 9).

The regiochemistry of compounds **3ab**−**3dc** was ascertained by NMR experiments (including HSQC, HMBC, COSY, and NOESY). Moreover, an X-ray analysis was performed on compound **3db** (see Supporting Information).

Nickel(0)-Mediated Reactions of Chromium Alkenylcarbene Complexes 1 and Activated Alkynes 2d−**g.** The study about the suitability of alkynes having electron-withdrawing and -donating substituents to undergo this [3 + 2] cyclization was then investigated. In such an event it would allow access to functionalized cyclopentenones and thus would importantly expand the scope of the reaction.

Table 1. [3+2] Cyclization Reaction of Chromium Alkenylcarbene Complexes **1** with Nonactivated Internal Alkynes **2a**−**c**

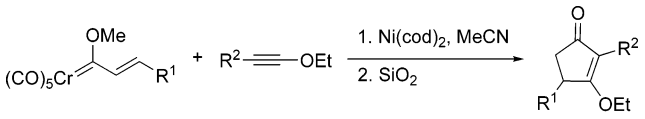


1 **2a-c** **3aa-3dc**

entry	carbene/alkyne	R^1	R^2	R^3	**3** (%)[a]
1	**1a**/**2a**	Ph	Et	Et	**3aa** (56)
2	**1a**/**2b**	Ph	Ph	Me	**3ab** (58)
3	**1b**/**2b**	*p*-$MeOC_6H_4$	Ph	Me	**3bb** (68)
4	**1c**/**2b**	*p*-ClC_6H_4	Ph	Me	**3cb** (71)
5	**1d**/**2b**	2-Furyl	Ph	Me	**3db** (65)
6	**1e**/**2b**	Me	Ph	Me	**3eb** (56)
7	**1f**/**2b**	*t*-Bu	Ph	Me	**3fb** (52)
8	**1b**/**2c**	*p*-$MeOC_6H_4$	*t*-Bu	Me	**3bc** (55)
9	**1d**/**2c**	2-furyl	*t*-Bu	Me	**3dc** (65)

[a] Yields of isolated products after column chromatography.

Table 2. [3 + 2] Cyclization Reaction of Chromium Alkenylcarbene Complexes **1** with Electron-Rich Alkynes **2d**,**e**



1 **2d,e** **3ad-3fe**

entry	carbene/alkyne	R^1	R^2	**3** (%)[a]
1	**1a**/**2d**	Ph	CH_2Ph	**3ad** (48)
2	**1d**/**2d**	2-furyl	CH_2Ph	**3dd** (43)
3	**1f**/**2d**	*t*-Bu	CH_2Ph	**3fd** (41)
4	**1a**/**2e**	Ph	TMS	**3ae** (49)
5	**1b**/**2e**	*p*-$MeOC_6H_4$	TMS	**3be** (47)
6	**1d**/**2e**	2-furyl	TMS	**3de** (45)
7	**1f**/**2e**	*t*-Bu	TMS	**3fe** (40)

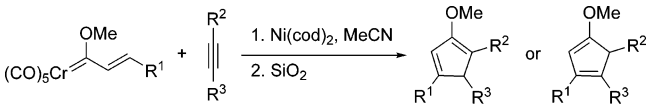
[a] Yields of isolated products after column chromatography.

First, we studied the reaction of representative carbene complexes with electron-rich alkynes, such as benzyl- and trimethylsilyl-substituted ynol ethers **2d**,**e**, under the above reaction conditions. Although the chemical yields of this cyclization reaction were rather moderate (40−49%), the resulting cycloadducts **3ad**−**fe** were formed as a sole regioisomer (Table 2). The regiochemistry of the cycloadducts was readily inferred by 2D NOESY experiments which clearly reveal a vicinal arrangement between the R^1 and OEt appendages. Structurally, the cyclopentenones prepared feature a synthetically useful functionalization since the ethoxy (entries 1−7) and TMS (entries 4−7) substituents are potentially exchangeable with nucleophiles and electrophiles, respectively.

Next, the reaction of chromium alkenylcarbene complexes **1** toward electron-deficient alkynes **2f**,**g** was explored, and the results are collected in Table 3. Thus, stirring a mixture of carbene **1**, the acetylene diester **2f**, and $Ni(cod)_2$ in acetonitrile followed by solvent removal and column chromatography purification resulted in the formation of the cyclopentadiene tautomers **4** (entries 1−2) or **5** (entries 3−4), depending on the

(11) Barluenga, J.; Barrio, P.; López, L. A.; Tomás, M.; García-Granda, S.; Álvarez-Rúa, C. *Angew. Chem., Int. Ed.* **2003**, *42*, 3008.

Table 3. [3 + 2] Cyclization Reaction of Chromium Alkenylcarbene Complexes **1** with Electron-Poor Internal Alkynes **2f**,**g**

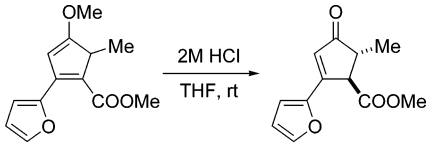


1 **2f-g** **4** **5**

entry	carbene/alkyne	R^1	R^2	R^3	**4/5** (%)[a]
1	**1a**/**2f**	Ph	CO_2Me	CO_2Me	**4af** (53)
2	**1d**/**2f**	2-furyl	CO_2Me	CO_2Me	**4df** (62)
3	**1e**/**2f**	Me	CO_2Me	CO_2Me	**5ef** (51)
4	**1g**/**2f**	*(E)*-CH=CHPh	CO_2Me	CO_2Me	**5gf** (66)
5	**1d**/**2g**	2-furyl	Me	CO_2Me	**5dg** (58)

[a] Yields of isolated products after column chromatography.

Scheme 3. Acid Hydrolysis of Cyclopentadiene Derivative **5dg**



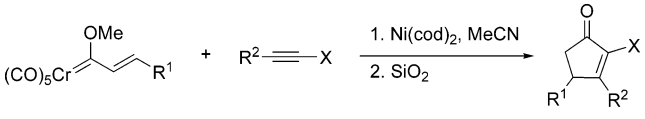
5dg **6**

substitution pattern. In the same way, the cyclization of carbene **1d** with methyl 2-butynoate **2g** provided the cyclopentadiene **5dg** as the sole isomer (entry 5). The regiochemistry of **5dg** was readily inferred by 2D NOESY experiments. A positive NOE interaction between the C_3−H of the furyl substituent (R^1) and the CH_3O of the methoxycarbonyl group (R^3) allowed us to confirm the vicinal arrangement of these groups.

Furthermore, compound **5dg** was quantitatively transformed into the functionalized *trans*-cyclopentenone **6** upon treatment with aqueous hydrochloric acid (Scheme 3). The structure of **6** has been determined by an X-ray crystal analysis after crystallization from CH_2Cl_2/Et_2O (see Supporting Information).

Nickel(0)-Mediated Reactions of Chromium Alkenylcarbene Complexes 1 with Boron- and Tin-Substituted Alkynes 2h−j. Having in mind the potential of the carbon−boron and carbon−tin linkages for carbon−carbon coupling, the preparation of boron- and tin-substituted cyclopentenones was then envisaged by using boron- and tin-substituted alkynes (Table 4).[12,13] Gratifyingly, we found that 2-(3,3-dimethylbutynyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane **2h** (PinB = pinacol boronate) and tributyltin alkynes **2i**,**j** smoothly react with complexes **1** under the above reaction conditions to provide cyclopentenones **3bh**−**dj** in 40−75% yield after column chromatography purification. The cyclization proved to be totally regioselective, affording 2-heteroatom substituted 2-cyclopentenones, except for cycloadducts resulting from methyltributyltinacetylene **2i** wherein a separable 10:1 mixture of 2- and 3-tributyltin-substituted cyclopentenones was obtained (entries 4 and 5). The regiochemistry of the cycloadducts was readily inferred by 2D NOESY experiments which clearly reveal a vicinal arrangement between the R^1 and R^2 groups. This assignment is chemically supported since the tributyltin-phenyl

Table 4. [3 + 2] Cyclization Reaction of Chromium Alkenylcarbene Complexes **1** with Boron- and Tin-Alkynes **2h**−**j**

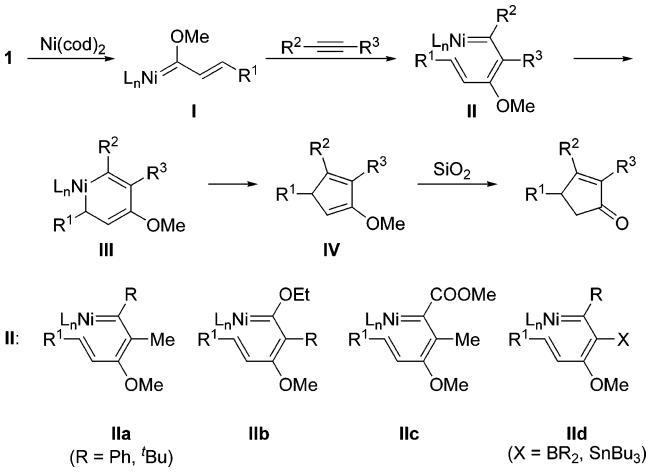


1 **2h-j** **3bh-3dj**

entry	carbene/alkyne	R^1	R^2	X	**3** (%)[a]
1	**1b**/**2h**	*p*-$MeOC_6H_4$	*t*-Bu	PinB	**3bh** (47)
2	**1c**/**2h**	*p*-ClC_6H_4	*t*-Bu	PinB	**3ch** (40)
3	**1d**/**2h**	2-furyl	*t*-Bu	PinB	**3dh** (43)
4	**1b**/**2i**	*p*-$MeOC_6H_4$	Me	Bu_3Sn	**3bi** (44)[b]
5	**1d**/**2i**	2-furyl	Me	Bu_3Sn	**3di** (45)[b]
6	**1a**/**2j**	Ph	Ph	Bu_3Sn	**3aj** (75)
7	**1c**/**2j**	*p*-ClC_6H_4	Ph	Bu_3Sn	**3cj** (51)
8	**1d**/**2j**	2-furyl	Ph	Bu_3Sn	**3dj** (70)

[a] Yields of isolated products after column chromatography. [b] A separable 10:1 mixture of regioisomers was obtained.

Scheme 4. Proposed Mechanism for the Formation of Cyclopentenones **3** and Cyclopentadienes **4** and **5**



exchange in compound **3bi** affords the opposite regioisomer of **3bb** which is reported in Table 1 (vide infra; Scheme 5, compound **10**).

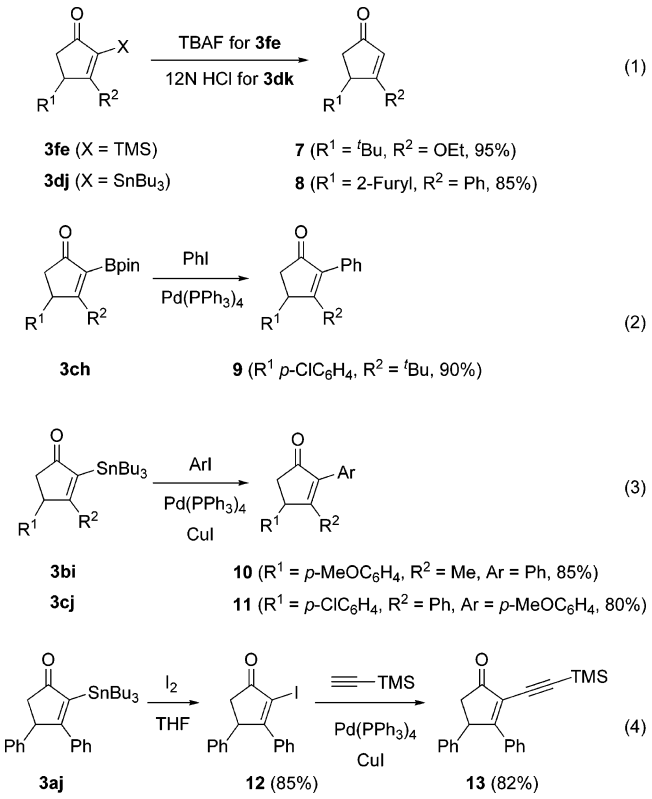
Proposed Mechanism. A possible pathway for the formation of cyclopentenones **3** and cyclopentadienes **4** and **5** is depicted in Scheme 4. This is based on the previously reported Ni(0)-mediated [3 + 2 + 2] cyclization of chromium carbenes **1** with terminal alkynes which was proposed to involve Cr−Ni exchange followed by two consecutive nickel carbene−alkyne insertion reactions and cyclization.[11] Thus, the regioselective insertion of a disubstituted alkyne unit into the nickel carbene complex **I** would generate the new carbene species **II** which do not undergo a second alkyne insertion; however, ring-closing leading to cyclopentadienes **IV**, probably through the nickelacyclohexadiene species **III**, seems to be the preferred pathway.[14,15] Since the origin of the regioselectivity lies on the alkyne insertion step, the corresponding species **IIa**−**d** arising from the different types of alkynes are independently displayed (Scheme 4, bottom). In all cases (**IIa**,[16] **IIb**,[17] **IIc**,[18] **IId**[12,13]), the sense of selectivity follows the trend found in the insertion of these types of alkynes into Fischer carbene complexes of chromium.

(12) For the benzannulation reaction of chromium Fischer carbene complexes with alkynylboronates, see: (a) Davies, M. W.; Johnson, C. N.; Harrity, J. P. *Chem. Commun.* **1999**, 2107. (b) Davies, M. W.; Johnson, C. N.; Harrity, J. P. A. *J. Org. Chem.* **2001**, *66*, 3525.

(13) For the benzannulation reaction of chromium Fischer carbene complexes with stannylacetylenes, see: Chamberlin, S.; Waters, M. L.; Wulff, W. D. *J. Am. Chem. Soc.* **1994**, *116*, 3113.

(14) None of the intermediates **I**−**IV** could be detected under the standard reaction conditions. On the other hand, no reaction was observed under milder conditions.

Scheme 5. Some Useful Synthetic Transformations of Cyclopentenones **3** (see the Text and the Supporting Information for the Reaction Conditions)



Useful Synthetic Transformations of Cyclopentenones 3. Finally, a few transformations of those 2-heteroatom-substituted cyclopentenones (vide supra) are shown which may have application for designing new synthetic routes to cyclopentenone derivatives (Scheme 5, eq 1−4). First, the protonolysis of the C−Si and C−Sn bonds was readily accomplished starting from **3fe** (1.1 equiv of TBAF, THF, rt) and **3dj** (12 N HCl, MeOH, rt), respectively, to provide 3,4-disubstituted cyclopentenones **7**−**8** (85−95% yield) which are not directly accessible from the corresponding alkenylcarbene complexes and terminal alkynes (eq 1). The hindered boron-substituted cyclopentenone **3ch** was selected for the Suzuki coupling reaction. Thus, treatment of **3ch** with iodobenzene under the standard reaction conditions [$Pd(PPh_3)_4$ (10 mol %), Na_2CO_3, DME:H_2O (3:1), 85 °C] produced the 2-phenylcyclopentenone **9** in 90% yield (eq 2). Cyclopentenone stannanes also were found to work well toward iodoarenes (Stille coupling) (eq 3). Thus, unsymmetrically substituted 2,4-diaryl- and 2,3,4-triaryl-2-cyclopentenones **10**−**11** are easily accessible as a single regioisomer by coupling of the [3 + 2] stannane adducts **3bi** and **3cj** with the corresponding iodoarene [80−85% yield; $Pd(PPh_3)_4$ (10 mol %), CuI (1 equiv), DMF, 60 °C]. In addition, the cyclopentenone stannanes are useful precursors of the 2-halo-2-cyclopentenone framework whose importance comes not only from its potential in coupling reactions but also because of the antitumor activity associated with this structural motif.[1] Thus, the tributyltin−iodine exchange was accomplished by treatment of cyclopentenone **3aj** with I_2 in THF affording 2-iodo-2-cyclopentenone **12** in 85% yield (eq 4). Finally, the Sonogashira coupling of **12** toward trimethylsilylacetylene efficiently produced the 2-alkynyl-2-cyclopentenone **13** [82% yield; $Pd(PPh_3)_4$ (10 mol %), CuI (10 mol %) THF/Et_3N (10:1), rt].

The Contribution of the Present Cyclization within the Cyclopentenone Synthesis Area. Last, it may be appropriate to set up the present reaction within the scenario of the cyclopentenone synthesis through carbocyclization reactions. In this respect, there are two particularly useful strategies which are based on [3 + 2] and [2 + 2 + 1] cyclization reactions. While the former has not been developed to a great extent primarily because of the difficulty of accessing all-carbon 1,3-dipoles (for instance, trimethylenemethane species and oxyallyl cations), the Pauson−Khand reaction is recognized as the most powerful access to the 2-cyclopentenone ring, particularly for synthesis of fused cyclopentenones via intramolecular cyclization. We would like to emphasize at this point the synthetic complementarity of the Pauson−Khand reaction and the procedure described in this work for the synthesis of 2-cyclopentenones (Figure 2). The former consists of a multicomponent cyclization (alkene + alkyne + CO) wherein the regiochemical course is well defined, the larger substituents of alkyne and alkene being placed at the C-2 and C-5 positions of the cyclopentenone ring.[4,19] Moreover, using activated alkynes results in the formation of cyclopentenones with the activating group (electron-donating) at C-2. The successful participation of stannylalkynes and alkynylboronic esters in the Pauson−Khand reaction has not been reported.[20] In the present work a completely different approach is established that is based on

(15) In relation to the different ability of terminal versus internal alkynes to participate in a multiple insertion sequence, there is a precedent in the chemistry of simple chromium carbenes. (a) Wulff, W. D.; Kaesler, R. W.; Petersen, G. A.; Tang, P.-C. *J. Am. Chem. Soc.* **1985**, *107*, 1060 (double insertion of terminal alkynes). (b) Challener, C. A.; Wulff, W. D.; Anderson, B. A.; Cheamberlin, S.; Faron, K. L.; Kim, O. K.; Murray, C. K.; Xu, Y.-C.; Yang, D. C.; Darling, S. D. *J. Am. Chem. Soc.* **1993**, *115*, 1359 (single insertion of internal alkynes). We also found a different behavior in the Ni(0)-mediated reactions of simple chromium aryl and alkyl carbene complexes with alkynes: thus, while terminal alkynes afforded cycloheptatriene derivatives resulting from a [2 + 2 + 2 + 1] cyclization (ref 11), internal alkynes yielded cyclopentadienes arising from a [2 + 2 + 1] cyclization (Barluenga, J.; Barrio, P.; Riesgo, L.; López, L. A.; Tomás, M. *Tetrahedron* **2006**, *62*, 7547)

(16) For the regioselectivity of the insertion of 1-phenylpropyne into the Cr═C bond of Fischer carbene complexes, see: (a) Dötz, K. H.; Mühlemeier, J.; Schbert, U.; Orama, O. *J. Organomet. Chem.* **1983**, *247*, 187. See also: (b) Barluenga, J.; López, L. A.; Martínez, S.; Tomás, M. *J. Org. Chem.* **1998**, *63*, 7588.

(17) The reaction of chromium Fischer carbene complexes with alkoxyacetylenes has been much less studied. For an isolated example, see: Yamashita, A.; Toy, A. *Tetrahedron Lett.* **1986**, *27*, 3471.

(18) The regioselectivity of the benzannulation reaction of alkenyl Fischer carbene complexes of chromium with alkynes bearing electron-withdrawing groups has been investigated: Wulff, W. D.; Chang, K.-S.; Tang, P.-C. *J. Org. Chem.* **1984**, *49*, 2293.

(19) For an exception to this general trend, see: Goettmann, F.; Le Floch, P.; Sanchez, C. *Chem. Commun.* **2006**, 180.

(20) For an isolated, low-yield example of an intramolecular Pauson−Khand reaction, see: Mukai, C.; Kozaka, T.; Suzuki, Y.; Kim, I. J. *Tetrahedron* **2004**, *60*, 2497.

(21) See, for example: Kraft, M. E. *Tetrahedron Lett.* **1988**, *29*, 999.

(22) The Pauson−Khand reaction of electron-rich alkynes to yield 2-heterosubstituted cyclopentenones has been reported. For ynamines, see: (a) Balsells, J.; Vázquez, J.; Moyano, A.; Pericàs, M. A.; Riera, A. *J. Org. Chem.* **2000**, *65*, 7291. (b) Shen, L.; Hsung, R. P. *Tetrahedron Lett.* **2003**, *44*, 9353. For alkoxyacetylenes, see: (c). Verdaguer, X.; Vázquez, J.; Fuster, G.; Bernardes-Génisson, V.; Greene, A. E.; Moyano, A.; Pericàs, M. A.; Riera, A. *J. Org. Chem.* **1998**, *63*, 7037. For acetylene thioethers, see: (d) Marchuela, I.; Montenegro, E.; Panov, D.; Poch, M.; Verdaguer, X.; Moyano, A.; Pericàs, M. A.; Riera, A. *J. Org. Chem.* **2001**, *66*, 6400.

(23) For regiochemical studies of intermolecular Pauson−Khand reactions involving internal electron-deficient alkynes, see: (a) Kraft, M. E.; Romero, R. H.; Scott, I. L. *J. Org. Chem.* **1992**, *57*, 5277. (b) Hoye, T. R.; Suriano, J. A. *J. Org. Chem.* **1993**, *58*, 1659.

(24) For the intramolecular Pauson−Khand reaction of enynes with a trimethylgermyl group at the alkyne terminus, see: (a) Mukai, C.; Kozakz, T.; Suzuki, Y.; Kim, I. J. *Tetrahedron Lett.* **2002**, *43*, 8575. (b) See also ref 20.

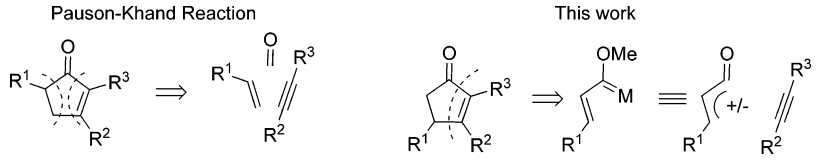


Figure 2. Complementary approaches to the cyclopentenone skeleton synthesis.

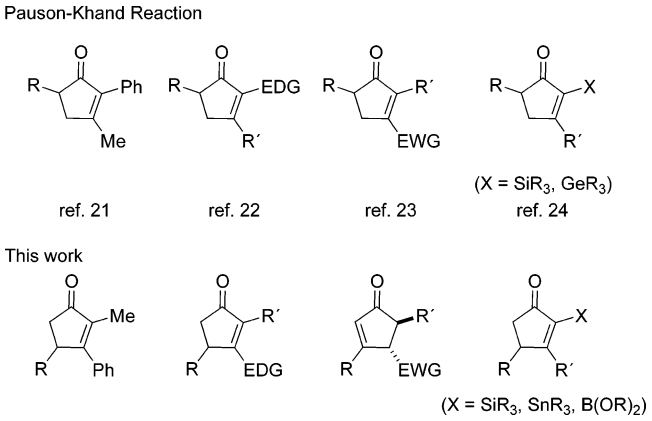


Figure 3. Diverse cyclopentanone structures available by combining the PKR and the [3 + 2] methodology described in this work.

the [3 + 2] cyclization between a very unusual C3 dipole equivalent $[(O{=}C{-}CH{=}CHR]^{\pm}$ and alkynes of a different sort.

According to the above comments, the great synthetic diversity in the area of the cyclopentenone skeleton that can be reached by combining the Pauson−Khand reaction and the cyclization of metal carbene complexes with alkynes is summarized in Figure 3.

In summary, we have described a general and simple experimental procedure for the synthesis of polysubstituted cyclopentenones from readily available starting materials. The reaction takes place with total regiochemistry with a number of nonsymmetrical alkynes. The wide scope of the process is noteworthy as neutral and activated alkynes as well as silicon-, boron-, and tin-substituted alkynes are suitable partners in this cyclopentenone annelation. Since most of these types of cyclopentenones are not accessible by established methodologies, the reported process complements previously reported approaches to the cyclopentenone skeleton. Further studies aimed at the development of catalytic and asymmetric variants of this cyclization are underway.

Acknowledgment. We are grateful to the Ministerio de Educación y Ciencia (MEC, Project CTQ2004-08077), the Principado de Asturias (Project PR-01-GE-9), and the Fundación Ramón Areces for the support of this research. We acknowledge the MEC for a predoctoral fellowship to L.R. We are also grateful to Dr. César J. Pastor (SidI, Universidad Autónoma de Madrid) for his assistance in the collection of the X-ray data.

Supporting Information Available: Full experimental details and spectral and analytical data for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

JA075106+