

Specific Synthesis of 1,2- and 1,3-Dialkylidenecycloheptanes by [3+2+2] Cyclization of Alkenyl Fischer Carbene Complexes and Allenes

José Barluenga,^{*,†} Rubén Vicente,[†] Pablo Barrio,[†] Luis A. López,[†] Miguel Tomás,[†] and Javier Borge[‡]

Instituto Universitario de Química Organometálica "Enrique Moles", Unidad Asociada al CSIC, and Departamento de Química Física y Analítica, Universidad de Oviedo, Julián Clavería 8, 33071 Oviedo, Spain

Received July 28, 2004; E-mail: barluenga@uniovi.es

The development of new, efficient methods for the construction of carbocycles from single acyclic blocks represents an important ongoing challenge for synthetic organic chemists. In particular, dialkylidenecycloalkanes are valuable building blocks for further structural elaboration. Among these compounds, the 1,2-dialkylidenecycloalkanes are relatively accessible from 1,*n*-enynes via transition-metal-catalyzed cycloisomerization reactions.¹ In this regard, while the cycloisomerization of 1,6-enynes to cyclopentane derivatives has been very efficiently performed and that of 1,7-enynes to the cyclohexane ring works fairly well, the cyclization of 1,8-enynes to the 1,2-dialkylidenecycloheptane derivatives has been reported to fail.^{2,3} Taking advantage of the chance of success that allenes⁴ offer to accomplish this task, and based on our own experience on Fischer carbene complexes,^{5,6} we present a new access to 3,4- and 2,4-dialkylidenecycloheptanones by nickel(0)-mediated and rhodium(I)-catalyzed [3+2+2] cyclization of alkenyl carbene complexes and allenes.⁷

First, we found that the treatment of chromium alkenyl carbene complexes **1a–d** with 1,1-dimethylallene **2a** (3 equiv) at $-10\text{ }^{\circ}\text{C}$ in acetonitrile in the presence of $[\text{Ni}(\text{cod})_2]$ (1 equiv), followed by warming to room temperature over 2 h, resulted in the formation of the [3+2+2] cycloadducts **3**. Chromatographic purification of **3** led to the 3,4-diisopropylidenecycloheptanone derivatives **4** in moderate yields (40–56% overall yield) (Scheme 1; Table 1, entries 1–4).⁸ It is interesting to note that not only a stereogenic center (C_6) is created along the reaction course, but axial chirality arises from the atropisomerism about the $\text{sp}^2\text{--}\text{sp}^2$ single bond of the butadiene unit ($\text{C}_3\text{--}\text{C}_4$) (see Figure 1 for the X-ray structure of compound **4a**; $\text{C}_8\text{--}\text{C}_3\text{--}\text{C}_4\text{--}\text{C}_{11}$ dihedral angle = 89.5°).^{9,10} Also noteworthy is the selectivity of the process: (i) three C–C bonds are regioselectively formed; (ii) the less substituted C=C of the allene is solely involved (head-to-head allene–allene coupling); and (iii) only one diastereoisomer is detected.

In accordance with a previous report,^{6d} we propose that the nickel carbene **I**, formed by chromium–nickel exchange, inserts a single allene unit through the less substituted C=C bond to generate metallacycle species **II**. In the present case, this intermediate does not undergo reductive metal elimination, but the insertion of a second allene into the more reactive C(allyl)–Ni bond takes place to afford the species **III**, which in turn evolves to the observed [3+2+2] cycloadduct by reductive metal elimination. At this point, the crucial role of the solvent arises, as we previously found that the [3+2] cyclization resulting from a single allene insertion occurs exclusively if the reaction is performed in toluene.^{6d} We argue that, in the present case, the half-life of the species **II** is enhanced by Ni–acetonitrile coordination,¹¹ thus allowing species **II** to suffer another allene insertion.

Scheme 1. Ni(0)-Mediated [3+2+2] Cyclization of Chromium Alkenyl Carbene Complexes **1a–d** with Allene **2a**

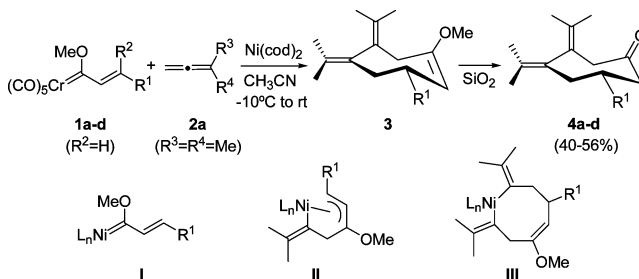


Table 1. Cyclization of Carbene Complexes **1** and Allenes **2** to Cycloheptane Derivatives **4** (Scheme 1) and **5** (Scheme 2) in the Presence of Ni(0) and Rh(I)

entry	R ¹	R ²	R ³	R ⁴	4 (%) ^{a,b}	5 (%) ^a
1	<i>p</i> -MeOC ₆ H ₄	H	Me	Me	4a (53)	5a (55)
2	^t Bu	H	Me	Me	4b (40)	5b (61)
3	Ph	H	Me	Me	4c (52)	
4	2-furyl	H	Me	Me	4d (56)	
5	^t Bu	H	Me	Me		5c (70)
6	^t Bu	H	Me	Me		5d (58)
7	Me	H	Me	Me		5e (60)
8	ferrocenyl	H	Me	Me		5f (63)
9	Me	Me	Me	Me		5g (71)
10	Me	H	–(CH ₂) ₅ –			5h (64)
11	Me	Me	Ph	Ph		5i (55)
12	Me	H	Ph	H		5j (50)

^a Yields of isolated products. ^b Overall yield from carbene complex **1**.

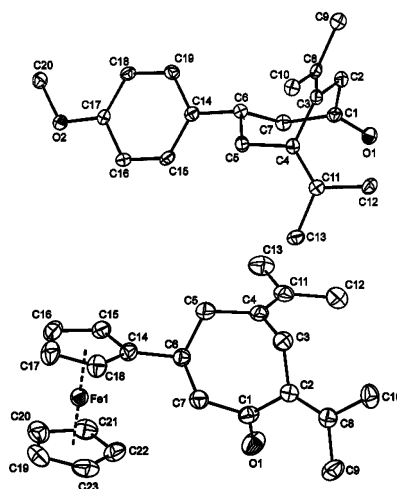


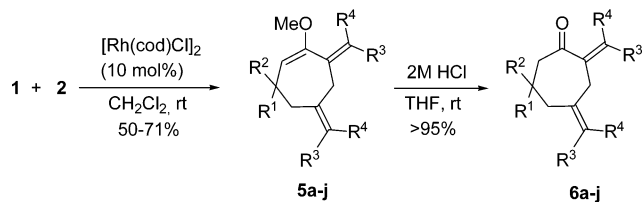
Figure 1. X-ray structures of **4a** (top) and **6f** (bottom) (ellipsoids at 30% probability level).

Next, we questioned whether the $[\text{Rh}(\text{naphthalene})(\text{cod})]^+$ -catalyzed [3+2] cyclization of carbenes **1** and allenes, recently reported by us,^{6d} could also be switched to the [3+2+2] cyclization

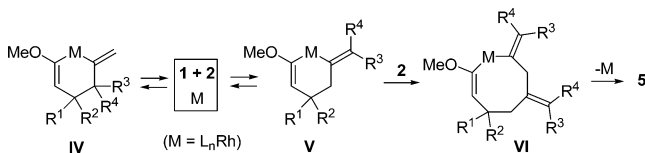
[†] Instituto Universitario de Química Organometálica "Enrique Moles".

[‡] Departamento de Química Física y Analítica.

Scheme 2. Rh(I)-Catalyzed [3+2+2] Cyclization of Chromium Alkenyl Carbene Complexes **1** with Allenes **2**



Scheme 3. Proposed Mechanism for the Rh(I)-Catalyzed [3+2+2] Cyclization of Chromium Alkenyl Carbene Complexes **1** with Allenes **2**



by modifying the catalyst. This was brought about by using $[Rh(cod)Cl]_2$, instead of the cationic catalyst $[Rh(naphthalene)(cod)]^+$.¹¹ When carbene complexes **1** were mixed with 1,1-disubstituted allenes **2** (3 equiv) (CH_2Cl_2 , 25 °C, 18–36 h) in the presence of 10 mol % of $[Rh(cod)Cl]_2$, 1,3-dialkylidenecycloheptene derivatives **5a–i** were obtained with total regioselectivity and in moderate yields (55–71% after column chromatography) (Scheme 2; Table 1, entries 1, 2, 5–11). In turn, acid hydrolysis of **5a–i** produces quantitatively 2,4-dialkylidenecycloheptanones **6a–i**.⁸ The X-ray structure of **6f** is displayed in Figure 1. The cyclization involves regioselective formation of three C–C bonds through the less substituted allene C=C bond (head-to-tail allene–allene coupling). Moreover, the cycloadduct **5j** ($R^3 = Ph$, $R^4 = H$; entry 12) is formed from phenylpropadiene as a sole *E,E* diastereoisomer (NOESY 1H NMR experiments performed on **6j**).

At this early stage, a mechanistic proposal to cycloadducts **5** is tentatively suggested in Scheme 3. Chromium–rhodium exchange followed by reversible metalla-[4+2] cycloaddition would produce intermediate **IV**, which would evolve to the thermodynamically more stable metallacycle **V**. Insertion of a second molecule of allene would give rise to the metallacyclooctene species **VI**, which would yield compounds **5** upon reductive elimination.¹²

In conclusion, we have found that 1,2- and 1,3-dialkylidenecycloheptane¹³ derivatives are chemo-, regio-, and diastereoselectively synthesized by the [3+2+2] cyclization of chromium alkenyl-(methoxy)carbene complexes and allenes in the presence of Ni(0) and Rh(I), respectively. The carbene nature of the nickel carbene complexes^{6a} accounts for the formation of metallacycle **II** via [2+2] cycloaddition to allene, while the low carbene character of Fischer rhodium carbene complexes^{6b} must be responsible for the different insertion mode to form the regioisomeric metallacycle **IV**.¹⁴ In both cases, the stabilization of the metallacyclohexene species **II**, **IV** seems crucial to retard the metal elimination and thus allow the second allene insertion to occur. In terms of scope, 1-substituted and 1,1-disubstituted allenes do work well, and a wide array of carbene complexes **1** can be employed. This study brings to us the belief that new ways to expand the usefulness of α,β -unsaturated alkoxy carbene complexes can still be devised by combining them with a diversity of transition metals and unsaturated substrates.

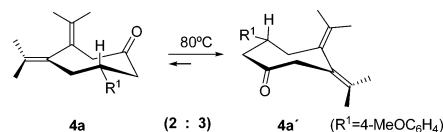
Acknowledgment. This paper is dedicated to Professor Pedro Molina on the occasion of his 60th birthday. Financial support for this work is acknowledged (BQU2001-3853 and PR-01-GE-9). R. V.

and P.B. thank the Ministerio de Ciencia y Tecnología and the Principado de Asturias for predoctoral fellowships. We are also grateful to Dr. César J. Pastor (Universidad Autónoma, Madrid) and Dr. Alberto Soldevilla (Universidad de la Rioja) for their assistance in the collection of the X-ray data.

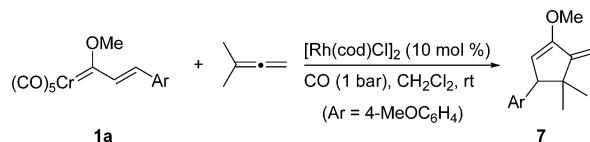
Supporting Information Available: Experimental procedures and spectral and analytical data for **4–6** (PDF); X-ray crystallographic data for **4a** and **6f** (CIF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

References

- (1) (a) Trost, B. M.; Lautens, M. *J. Am. Chem. Soc.* **1985**, *107*, 1781. For a review, see: (b) Trost, B. M.; Krische, M. J. *Synlett* **1998**, 1.
- (2) Trost, B. M. *Acc. Chem. Res.* **1990**, *23*, 34.
- (3) The synthesis of dialkylidenecycloheptane derivatives in low yields (<20%) via palladium-catalyzed cyclization–hydroxylation of 1,8-nonadiyne has been recently reported: Uno, T.; Wakayanagi, S.; Sonoda, Y.; Yamamoto, K. *Synlett* **2003**, 1997.
- (4) (a) Pasto, D. J.; Huang, N.-Z. *Organometallics* **1985**, *4*, 1386. (b) Pasto, D. J.; Huang, N.-Z.; Eigenbrot, C. W. *J. Am. Chem. Soc.* **1985**, *107*, 3160. (c) Saito, S.; Hirayama, K.; Kabuto, C.; Yamamoto, Y. *J. Am. Chem. Soc.* **2000**, *122*, 1076.
- (5) Representative review on Fischer carbene complexes: Wulff, W. D. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon: New York, 1995; Vol. 12, p 469.
- (6) (a) Ni-mediated [3+2+2] cyclization with alkynes: Barluenga, J.; Barrio, P.; López, L. A.; Tomás, M.; García-Granda, S.; Alvarez-Rúa, C. *Angew. Chem., Int. Ed.* **2003**, *42*, 3008. (b) Rh-catalyzed [3+2] cyclization with alkynes: Barluenga, J.; Vicente, R.; López, L. A.; Rubio, E.; Tomás, M.; Alvarez-Rúa, C. *J. Am. Chem. Soc.* **2004**, *126*, 470. (c) Götter-Schnetmann, I.; Aumann, R. *Organometallics* **2001**, *20*, 346. (d) Ni-mediated and Rh-catalyzed [3+2] cyclization with allenes: Barluenga, J.; Vicente, R.; Barrio, P.; López, L. A.; Tomás, M. *J. Am. Chem. Soc.* **2004**, *126*, 5974.
- (7) Thermal reactions of Fischer carbene complexes with allenes: (a) Aumann, R.; Uphoff, J. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 357. (b) Aumann, R.; Melchers, H.-D. *J. Organomet. Chem.* **1988**, *355*, 351. (c) Aumann, R.; Trentmann, B. *Chem. Ber.* **1989**, *122*, 1977. (d) Hwu, C.-C.; Wang, F. C.; Yeh, M.-C. P.; Sheu, J.-H. *J. Organomet. Chem.* **1994**, *474*, 123.
- (8) Compounds **4–6** were characterized by NMR techniques (including HMQC, HMBC, COSY, and NOESY).
- (9) Heating **4a** in toluene-*d*₈ above 80 °C in the NMR tube affords a ca. 2:3 mixture of diastereoisomers **4a/4a'**.



- (10) For some examples of nonplanar conformations for 1,3-butadienes, see: (a) Kiefer, E. F.; Levek, T. J.; Bopp, T. T. *J. Am. Chem. Soc.* **1972**, *94*, 4751. (b) Bechert, G.; Mannschreck, A. *Chem. Ber.* **1981**, *114*, 2365. (c) Bechert, G.; Mannschreck, A. *Chem. Ber.* **1983**, *116*, 264.
- (11) It is well established that the metal reductive elimination is retarded by σ -donor ligands and facilitated by cationic metal complexes: Collman, J. P.; Hegedus, L. S.; Norton, J. R.; Finke, R. G. *Principles and Applications of Organotransition Metal Chemistry*; University Science Books: Mill Valley, CA, 1987.
- (12) In the case of cationic rhodium(I) catalyst, the intermediate of type **IV** undergoes metal elimination faster than equilibration to intermediate of type **V** (ref 6d). Conversely, when the reaction with neutral Rh(I) catalyst is effected in the presence of a good π -acceptor ligand which favors the metal elimination (ref 11), e.g. CO, the process actually results in the clean formation of cyclopentene **7** (88% yield).



- (13) Regarding the 1,3-dialkylidenecycloheptane ring, a SciFinder search reveals that only the 2,7-dialkylidenecycloheptanone skeleton is known.
- (14) One reviewer has pointed that a product-driven argument (Ni π -allyl species **II** vs Rh vinyl species **IV/V**) can be taken into consideration.

JA045459Y