Stereoselective Synthesis of Pentacarbonyl(3-oxa-2-bicyclo[3.1.0]hexylidene)- and Pentacarbonyl(cyclopropylmethoxymethylene)tungsten Compounds on the Route to Cyclopropane-γ-lactones and -carboxylates

Saverio Florio,*,† Filippo M. Perna,† Renzo Luisi,† José Barluenga,*,‡
Francisco J. Fañanás,‡ and Félix Rodríguez‡

*Dipartimento Farmaco-Chimico, Universitá di Bari, Via E. Orabona 4, I-70126-Bari, Italy,
CNR, Istituto di Chimica dei Composti Organometallici "ICCOM", Sezione di Bari, Italy, and
Instituto Universitario de Química Organometálica "Enrique Moles", Unidad Asociada al
CSIC Julián Clavería, 8, Universidad de Oviedo, 33006 Oviedo, Spain*

florio@farmchim.uniba.it

Received July 23, 2004

The diastereoselective synthesis of pentacarbonyl-3-oxa-2-bicyclo[3.1.0]hexylidene- and pentacarbonyl(cyclopropylmethoxymethylene)tungsten compounds **4** and **9** by the reaction of lithiated oxazolinyloxiranes **2** and **8** and Fischer carbene tungsten complexes **3** is described. A mechanism for the formation of **4** and **9** is reported as well as their oxidation to cyclopropane-γ-lactone **13** and -carboxylate **14**.

Functionalized cyclopropanes including cyclopropane-γ-lactones are extremely useful synthetic intermediates.[1] In particular, fused bicyclic cyclopropane-γ-lactones[2] have been reported as key intermediates for the preparation of target molecules of pharmaceutical interest such as (+)-ambruticine S,[3] furofuran lignans,[4] NMDA receptor antagonists,[5] ligands of histamine H_3 receptors,[6] and Grb_2-SH2 domain.[7]

Fischer-type carbene complexes have become in recent years valuable synthetic tools in organic chemistry.[8] In particular, α,β-unsaturated carbene complexes proved to be very useful reagents.[9] Our previous work, focused on the reaction of halomethyllithiated derivatives and alkenylcarbene complexes to prepare cyclopropanecarboxylates in an enantioselective way[10] jointly with our long-standing experience in the field of lithiated oxiranes,[11] prompted us to evaluate the opportunity of developing a synthetic route to oxazolinyl cyclopropane-γ-lactones based on the reaction between lithiated oxirane derivatives and alkenyl carbene complexes, according to the retrosynthetic approach shown in Figure 1, which envisages a cascade process involving a Michael addition reaction, oxirane ring-opening-promoted cyclopropanation, and lactonization. Interest for this kind of cyclopropane-γ-lactones resides also in the fact that the oxazoline moiety is amenable to synthetic elaborations.[12]

---

† Universitá di Bari and CNR.

‡ Universidad de Oviedo.

[1] (a) von Angerer, S. In *Carbocyclic Three- and Four- Membered Ring Compounds. Methods of Organic Chemistry*; de Meijere, A., Ed.; Houben-Weyl: New York, 1997; Vol. E17c, pp 2121−2153. (b) Wong, H. N. C.; Hon, M. Y.; Tse, C. W.; Yip, Y. C.; Tanko, J.; Hudlicky, T. *Chem. Rev.* **1989**, *89*, 165. (c) Reissig, H. U. *Top. Curr. Chem.* **1988**, *144*, 73. (d) Reissig, H. U.; Zimmer, R. *Chem. Rev.* **2003**, *103*, 1151. (e) Benedetti, F.; Berti, F.; Risaliti, A. *Tetrahedron Lett.* **1993**, *34*, 6443. (f) Takano, S.; Sato, N.; Akijama, M.; Ogasawara, K. *Heterocycles* **1985**, *23*, 2859. (f) Kazuta, Y.; Tsujita, R.; Yamashita, K.; Uchino, S.; Kohsaka, S.; Matsuda, A.; Shuto, S. *Biorg. Med. Chem.* **2002**, *10*, 3829.

[2] For some recent papers on the synthesis of these compounds, see: (a) Fillion, E.; Beingessner, R. L. *J. Org. Chem.* **2003**, *68*, 9485. (b) Saha, B.; Uchida, T.; Katsuki, T. *Tetrahedron: Asymmetry* **2003**, *14*, 823. (c) Reichelt, A.; Gaul, C.; Frey, R. R.; Kennedy, A.; Martin, S. F. *J. Org. Chem.* **2002**, *67*, 4062. (d) Benedetti, F.; Berti, F.; Fabrissin, S.; Gianferrara, T. *J. Org. Chem.* **1994**, *59*, 1518. (e) Grangier, G.; Aiken, D. J.; Guillaume, D.; Fusson, H.-P. *Tetahedron Lett.* **1994**, *35*, 4355. (f) Burgess, K.; Ho, K.-K. *J. Org. Chem.* **1992**, *57*, 5931. (g) Pirrung, M. C.; Dunlap, S. E.; Trinks, U. P. *Helv. Chim. Acta* **1989**, *72*, 1301.

[3] Berberich, S. M.; Cherney, R. J.; Colucci, J.; Courillon, C.; Geraci, L. S.; Kirkland, T. A.; Marx, M. A.; Schneider, M. F.; Martin, S. F. *Tetrahedron* **2003**, *59*, 6819.

[4] Swain, N. A.; Brown, R. C. D.; Bruton, G. *J. Org. Chem.* **2004**, *69*, 122.

[5] Kazuta, Y.; Tsujita, R.; Yamashita, K.; Uchino, S.; Kohsaka, S.; Matsuda, A.; Shuto, S. *Bioorg. Med. Chem.* **2002**, *10*, 3829.

[6] Brana, M. F.; Guisado, C.; Alguacil, L. F.; Garrido, E.; Pérez-Garcia, C.; Ruiz-Gayo, M. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3561.

[7] Plake, H. R.; Sundberg, T. B.; Woodward, A.; Martin, S. F. *Tetrahedron Lett.* **2003**, *59*, 1571.

[8] (a) Barluenga, J.; Santamaría, J.; Tomás, M. *Chem. Rev.* **2004**, *104*, 2259. (b) Barluenga, J.; Flórez, J.; Fañanás, F. J. *J. Organomet. Chem.* **2001**, *624*, 5. (c) Herndon, I. W. *Tetrahedron* **2000**, *56*, 1257. (d) Sierra, M. A. *Chem. Rev.* **2000**, *100*, 3591. (e) 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 470.

[9] De Meijere, A.; Schirmer, H.; Duetsch, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 3964.

[10] Barluenga, J.; Bernard, P. L., Jr.; Concellón, J. M.; Piñera-Nicolás, A.; García-Granda, S. *J. Org. Chem.* **1997**, *62*, 6870.

[11] For some leading references, see: (a) Luisi, R.; Capriati, V.; Degennaro, L.; Florio, S. *Org. Lett.* **2003**, *5*, 2723. (b) Luisi, R.; Capriati, V.; Degennaro, L.; Florio, S. *Tetrahedron* **2003**, *59*, 9713. (c) Luisi, R.; Capriati, V.; Carlucci, C.; Degennaro, L.; Florio, S. *Tetrahedron* **2003**, *59*, 9707. (d) Capriati, V.; Degennaro, L.; Favia, R.; Florio, S.; Luisi, R. *Org Lett.* **2002**, *4*, 1551. (e) Abbotto, A.; Capriati, V.; Degennaro, L.; Florio, S.; Luisi, R.; Pierrot, M.; Salomone, A. *J. Org. Chem.* **2001**, *66*, 3049.

[12] Florio, S.; Capriati, V.; Luisi, R. *Tetrahedron Lett.* **1996**, *37*, 4781.

10.1021/jo048731v CCC: $27.50

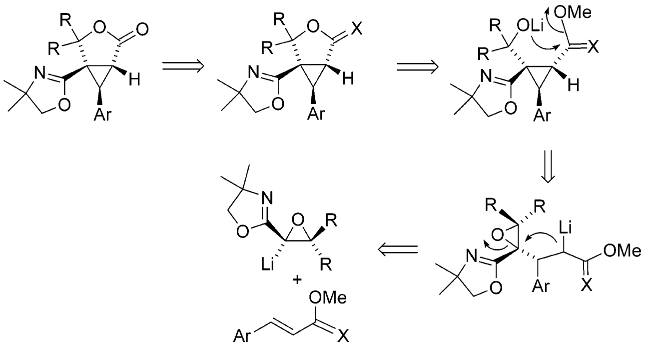
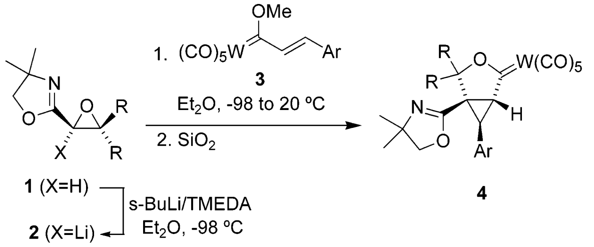


FIGURE 1. Retrosynthetic approach to cyclopropane-γ-lactones.

SCHEME 1



Thus, in the present paper we report a highly stereoselective preparation of cyclopropane-fused bicyclic and cyclopropyl carbene tungsten complexes using a synthetic procedure which combines the chemistry of lithiated oxazolinyloxiranes with that of some Fischer-type carbene complexes. The new complexes can be easily transformed into interesting cyclopropanelactones and cyclopropanecarboxylates.

TABLE 1. Preparation of Cyclic Carbene Complexes 4 from α-Lithiated Oxirane 2 and α,β-Unsaturated Carbene Complexes 3

oxirane	R	carbene complex	Ar	product	yield[a] (%)
2a	Ph	**3a**	Ph	**4a**	80
2a	Ph	**3b**	2-Furyl	**4b**	75
2a	Ph	**3c**	4-MeOC$_6$H$_4$	**4c**	83
2a	Ph	**3d**	4-ClC$_6$H$_4$	**4d**	81
2a	Ph	**3e**	4-BrC$_6$H$_4$	**4e**	76
2b	Me	**3d**	4-ClC$_6$H$_4$	**4f**	61

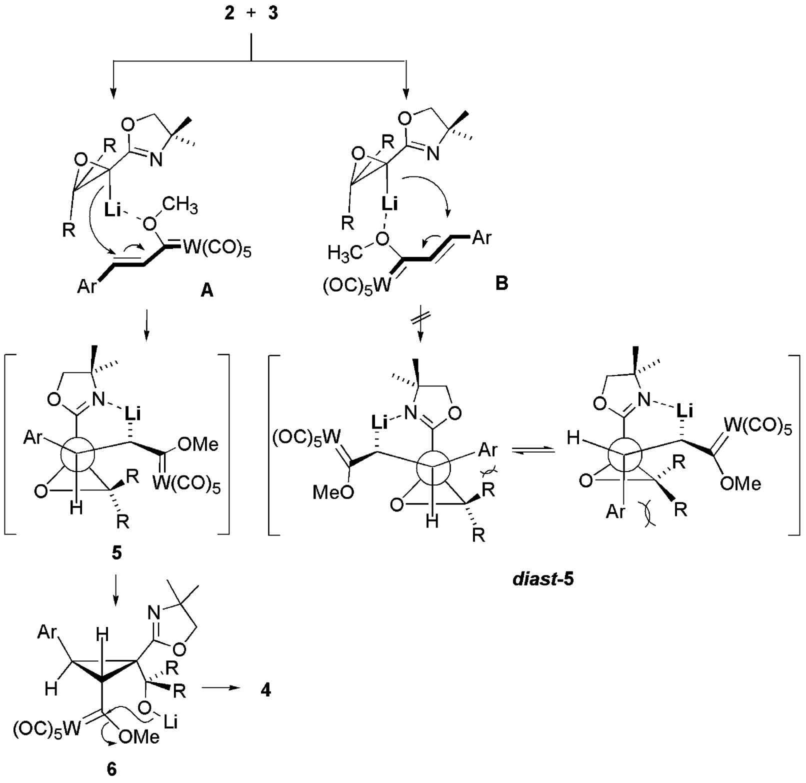
[a] Isolated yield based on starting carbene complexes **3**.

When an Et$_2$O solution of α-lithiated oxazolinyloxiranes **2**, generated by deprotonation of **1** with *s*-BuLi/TMEDA at −98 °C, was treated with carbene complexes **3** at temperatures ranging between −98 and +20 °C, bicyclic carbene complexes **4** formed in high yields and in all cases as single diastereoisomers (Scheme 1 and Table 1). Compounds **4** were fully characterized by ^{1}H and ^{13}C NMR, DEPT, 2D-NOESY, GC−MS, IR, and elemental analysis.[13]

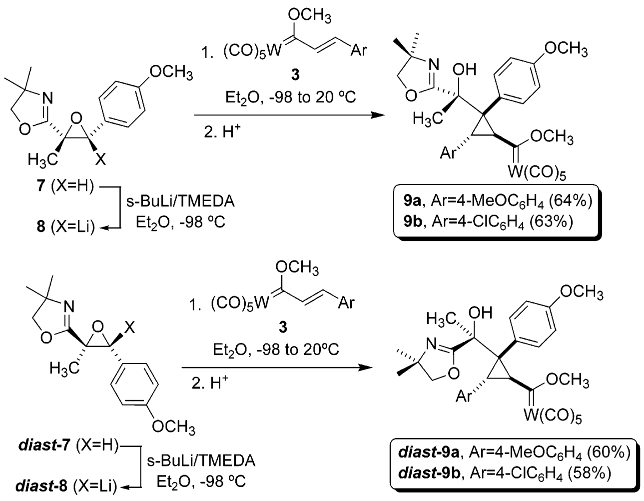
It was particularly remarkable the complete diastereoselectivity of the addition reaction of lithiated oxiranes **2** to carbene complexes **3** as only compounds **4** were obtained.

The observed complete diastereoselectivity can tentatively be explained following the mechanistic proposal showed in Scheme 2. According to this mechanism, lithiated oxirane **2**, after a preliminary coordination of lithium on the oxygen atom of the methoxy group of the carbene complex **3** (complex A), would attack the *re* diastereotopic face of **3**, thus producing the chelated intermediate **5**, which has an ideal arrangement of the groups involved in the cyclopropanation to **6** and subse-

SCHEME 2



SCHEME 3

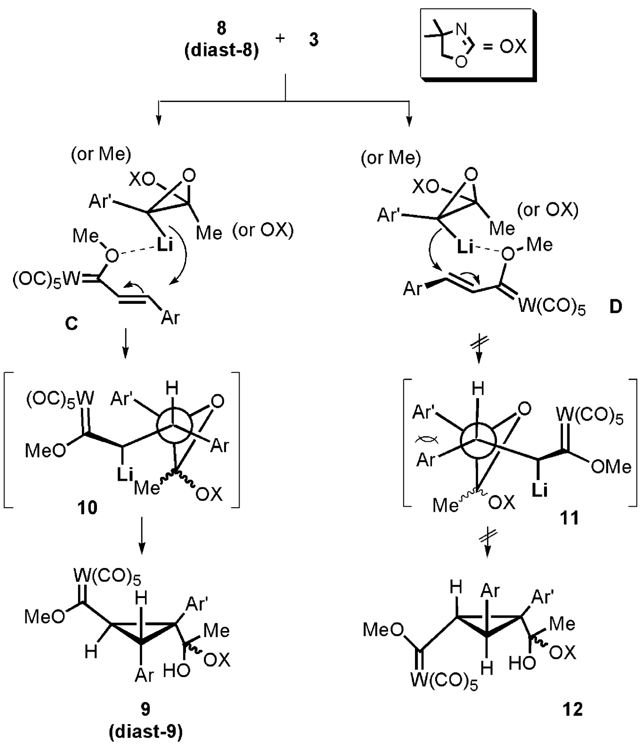


quent lactonization to **4**. In the chelated intermediate **diast-5**, after the attack of **2** on the *si* diastereoface of **3**, both conformations would be disfavored for experiencing the destabilizing steric interaction between the R groups of the oxirane ring and the Ar group.

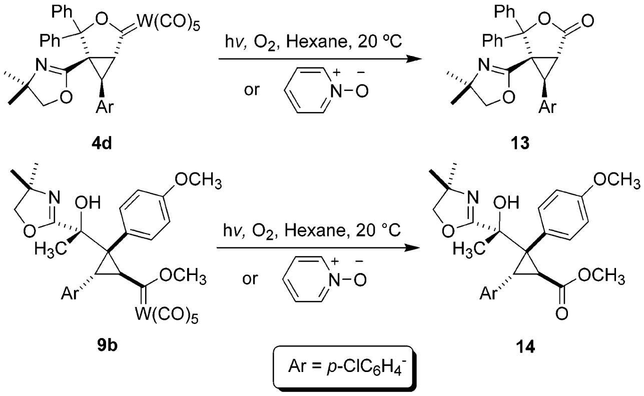
After studying the reaction of α-lithiated oxazolinyloxiranes **2** and alkenylcarbene complexes **3**, we decided to study the behavior of *β*-lithiated oxazolinyloxiranes in their reaction with carbene complexes **3**. We found that lithiated oxirane **8**, promptly generated upon deprotonation of (1*R**,2*R**)-**7**, reacted with complexes **3**, under the same reaction conditions described above, ending up with the formation of cyclopropyl tungsten complexes **9a**,**b** (Scheme 3). In a similar way, lithiated oxirane ***diast*-8**, derived from (1*R**,2*S**)-***diast*-7**, reacted with carbene complexes **3** to give cyclopropyl carbene complexes ***diast*-9a**,**b**, which are diastereomerically related to **9a**,**b**, differing exclusively in the configuration of the alcohol carbon stereocenter. It is interesting to point out that both carbene complexes **9a**,**b** and ***diast*-9a**,**b** do not undergo the kind of intramolecular cyclization which takes place in the conversion of **2** to **4** simply because of the *trans* arrangement of the hydroxyalkyl group and the metal fragment (Scheme 3).

A mechanism that could explain the formation of compounds **9** and ***diast*-9** is shown in Scheme 4, in which we propose a model where *β*-lithiated oxazolinyloxirane **8** (or ***diast*-8**), which proved to be configurationally stable, approaches the alkenylcarbene **3** forming the complex **C**, that then controls the C−C bond formation, on the *re* face of **3** to generate the lithiated intermediate **10**, with the ideal alignment of the groups involved in the cyclopropanation reaction to **9** (or **diast-9**). The formation of lithiated intermediate **11**, that would originate from complex **D** via addition of **8** to the *si* face of **3**, would be disfavored because of the steric hindrance between Ar and Ar′ groups. This hindrance is not observed in **C**, and thus the formation of **10** is preferred over **11**, which actually does not form.

SCHEME 4



SCHEME 5



To check the synthetic utility of the carbene complexes obtained through the methodology described here, we performed the oxidation of the metal fragment in some representative examples of carbene complexes (Scheme 5). Thus, exposure of carbene complex **4d** to the air in the presence of sun light gave rise to cyclopropane-*γ*-lactone **13** in 80% yield. Moreover, carbene complex **9a** led, under similar conditions, to the highly functionalized cyclopropane carboxylate **14** in 81% yield. Alternatively, both oxidations can be performed using pyridine *N*-oxide (see the Supporting Information).

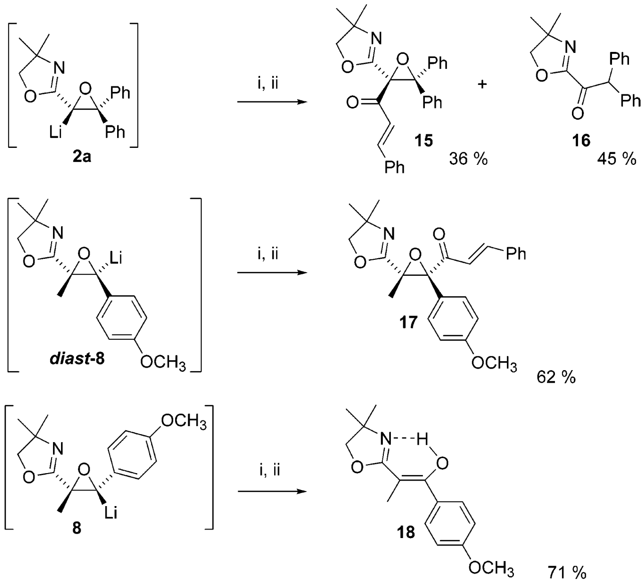
The ability of complexes **3** to act as Michael acceptors is crucial for the formation of complexes **4** and **9**. Indeed, when treated with methylcinnamate, lithiated oxirane **2a** furnished oxazolinyl derivatives **15** and **16**,[14] while **8** and ***diast*-8** generated compounds **18** and **17**, respectively (Scheme 6).

---

[13] The relative configuration of compounds **4a**−**f**, **9a**,**b**, ***diast*-9a**,**b**, **13**, and **14** has been assigned by 2D-NOESY experiments and on the basis of the coupling constant between the vicinal hydrogens of the cyclopropane ring: J_{cis} (8−12 Hz) > J_{trans} (4−7 Hz) ($^3J_{\mathrm{H-H}}$ ranging 3.1−5.8, see the Supporting Information).

[14] Capriati, V.; Florio, S.; Luisi, R.; Russo, V.; Salomone, A. *Tetrahedron Lett.* **2000**, *41*, 8835.

SCHEME 6 [a]



[a] Reagent and conditions: (i) *trans*-methylcinnamate; (ii) −98 °C to rt.

The outcome of the reaction of **2a** is explained with its reported[14] bias to undergo isomerization to give **16** and with a 1,2 addition to *trans*-methylcinnamate to give **15**. The different behavior of **8**, which isomerizes to give **18** after acidic quenching, with respect to **diast-8**, which furnished **17** upon addition to *trans*-methylcinnamate, can be rationalized with the higher stability of ***diast*-8**, which is ascribed to the lithium chelation by the oxazolinyl group (*cis* arrangement).[11d]

In conclusion, in this paper we report an easy and diastereoselective synthesis of functionalized bicyclic and cyclopropylcarbene tungsten complexes by the reaction of lithiated oxirane derivatives and alkenylcarbene complexes. The oxidation of these complexes leads to interesting cyclopropane-γ-lactones and cyclopropane carboxylates, which look like useful synthetic intermediates amenable for elaboration to other kind of substances. It must be mentioned that the compounds obtained through this method are tetrasubstituted cyclopropanes containing a quaternary stereocenter in their structures and up to four chiral centers. Efforts to develop an asymmetric version of the synthesis described here is underway in our laboratories.

Acknowledgment. This work was carried out under the framework of the National Project “Stereoselezione in Sintesi Organica, Metodologie ed Applicazioni” and the FIRB Project “Progettazione, preparazione e valutazione biologica e farmacologica di nuove molecole organiche quali potenziali farmaci innovativi” supported by the MIUR (Rome), by the University of Bari, and consorzio CINMPIS. We also thank Principado de Asturias (Grant No. PR-01-GE-9) and Spanish DGI (Grant No. BQU-2001-3853).

Supporting Information Available: Spectroscopic and physical data for compounds **4a**−**f**, **9a**,**b**, ***diast*-9a**,**b**, **13**, **14**, **15**, **17**, and **18** and spectra for **7**, ***diast*-7**, **17**, and **18**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO048731V