*Pure Appl. Chem.*, Vol. 71, No. 8, pp. 1385–1391, 1999.
Printed in Great Britain.


# Recent advances in selective organic synthesis mediated by transition metal complexes*

José Barluenga

*Instituto Universitario de Química Organometálica 'E. Moles', Universidad de Oviedo, 33071 Oviedo, Spain*

*Abstract:* This short review covers some useful synthetic transformations mediated by group 6 Fischer alkoxy carbene complexes. Alkenyl carbene complexes derived from (–)-8-phenylmenthol are suitable Michael acceptors towards organolithium reagents -alkyllithium and lithium enolate derivatives-yielding ultimately β-alkyl substituted aldehydes with 80–98% enantiomeric excess. The reaction of (menthyloxy)aryl carbene complexes with *s*BuLi and *t*BuLi resulted in clean dearomatization leading to 1,4-cyclohexadiene derivatives. If alkynyl lithium, instead of alkyllithium, compounds are reacted with aryl carbene complexes different products -furans, propargyl ethers, alkoxyindenes are selectively produced. Enamines derived from (S)-methoxymethylpyrrolidine and both aldehydes and ketones react with alkenyl carbenes to afford with very high selectivity [3+2] cycloadducts which are elaborated into useful, enantiopure 3,4-disubstituted cyclopentanones and 2,3-disubstituted 2-cyclopentenones, respectively. The [4+3] carbocyclization occurs from alkenyl carbene complexes and 2-aminobutadiene derivatives, while the analogous heterocyclization can be accomplished from various types of azabutadienes and both alkenyl and alkynyl derivatives. Efficient structural modifications of terpenes can be done using boroxycarbene complexes via C–H insertion reactions. Finally, representative examples of cyclopropanation of electronically neutral alkenes with Fischer carbene complexes are provided.

## INTRODUCTION

Since their discovery by Fischer & Maasböl [1], group 6 Fischer carbene complexes have been demonstrated as highly valuable building blocks for the construction of organic molecules [2]. For instance, organotransition-metal compounds, in general, and Fischer carbene complexes, in particular, offer many interesting possibilities to build carbocyclic and heterocyclic frameworks not readily accessible through conventional routes. Following, some recent examples are described that reflect the potential of Fischer carbene complexes for making carbon-carbon and carbon-heteroatom bonds. These processes resulted in the selective formation of various types of acyclic and cyclic molecules.

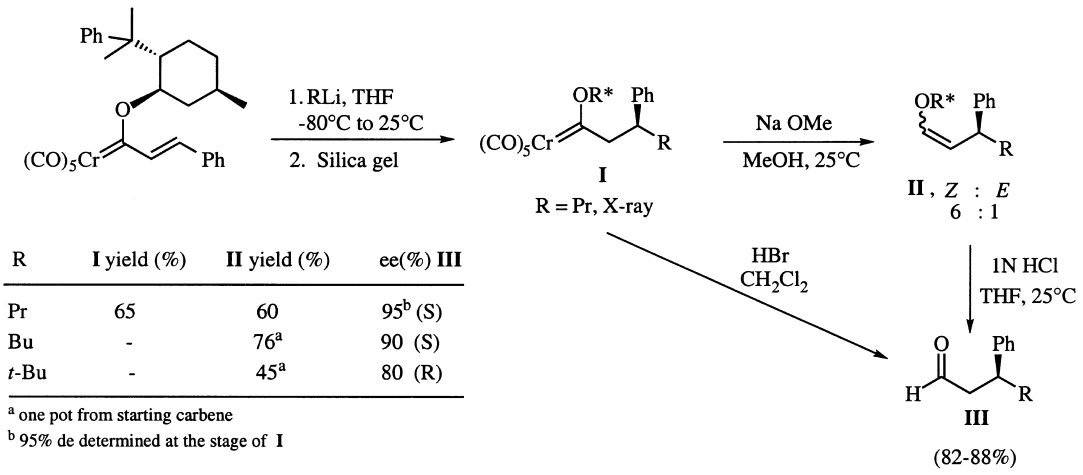
## RESULTS AND DISCUSSION

### 1. Addition of organolithium derivatives to Fischer alkenyl carbene complexes

We found that chiral, nonracemic chromium carbene complexes derived from (–)-8-phenylmenthol are suitable substrates for the efficient Michael-type addition of organolithium reagents. For instance, alkyl and aryl lithiums smoothly react with carbene complexes affording the addition compounds with excellent diastereoselectivity. Removal of the metal fragment leading to enantiopure aldehydes can be

*Lecture presented at the 10th IUPAC Symposium on Organo-Metallic Chemistry Directed Towards Organic Synthesis (OMCOS 10), Versailles, France, 18–22 July 1999, pp. 1381–1547.
*Correspondence*: E-mail: barluenga@sauron.quimica.uniovi.es

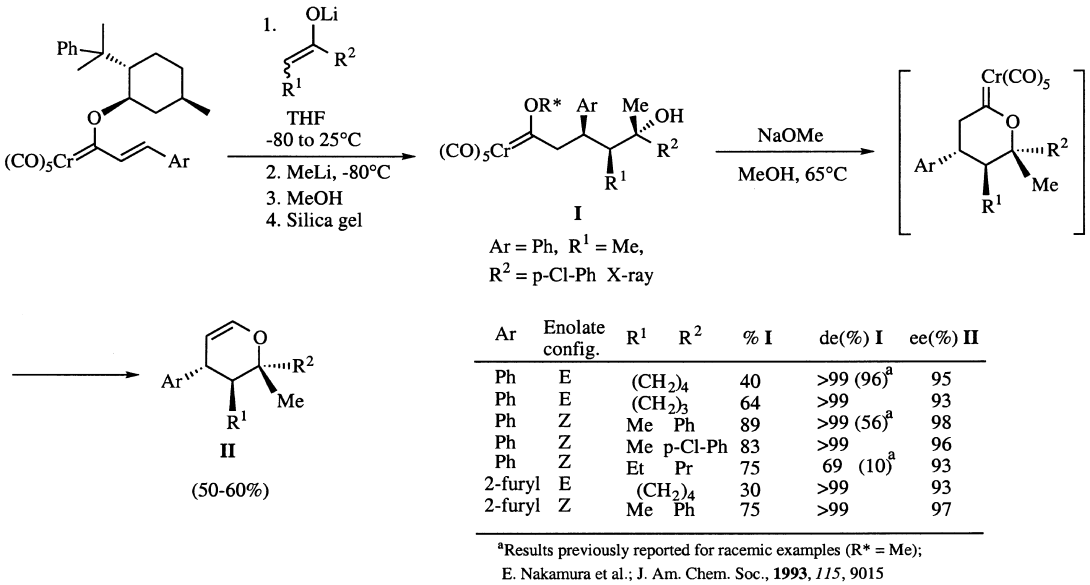
accomplished via: (i) treatment with HBr, or (ii) formation of the enol ether followed by acid hydrolysis [3] (Scheme 1).




| R | I yield (%) | II yield (%) | ee(%) III |
|---|---|---|---|
| Pr | 65 | 60 | 95[b] (S) |
| Bu | - | 76[a] | 90 (S) |
| *t*-Bu | - | 45[a] | 80 (R) |

[a] one pot from starting carbene
[b] 95% de determined at the stage of **I**

Interestingly, lithium ketone enolates behaved similarly leading to the corresponding functionalized adducts as a sole diastereoisomer in most cases [3]. The sequence presented in Scheme 2 illustrates the Michael addition, methyllithium-to-carbonyl addition and lactone formation. Chemical yields as well as diastereo and facial selectivity for representative examples are given in the Table.



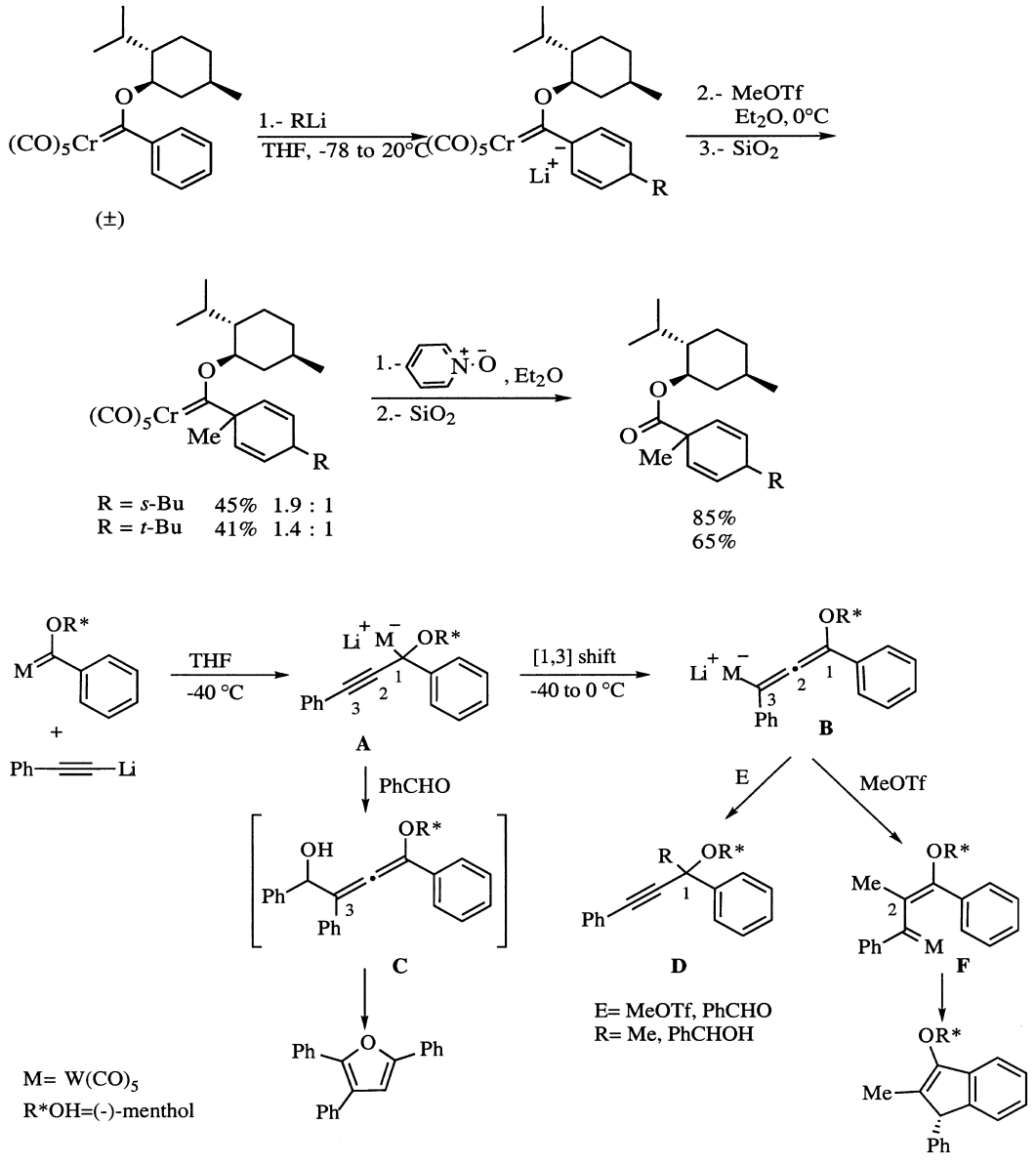

| Ar | Enolate config. | $R^1$ | $R^2$ | % I | de(%) I | ee(%) II |
|---|---|---|---|---|---|---|
| Ph | E | $(CH_2)_4$ | | 40 | >99 (96)[a] | 95 |
| Ph | E | $(CH_2)_3$ | | 64 | >99 | 93 |
| Ph | Z | Me | Ph | 89 | >99 (56)[a] | 98 |
| Ph | Z | Me | p-Cl-Ph | 83 | >99 | 96 |
| Ph | Z | Et | Pr | 75 | 69 (10)[a] | 93 |
| 2-furyl | E | $(CH_2)_4$ | | 30 | >99 | 93 |
| 2-furyl | Z | Me | Ph | 75 | >99 | 97 |

[a] Results previously reported for racemic examples (R* = Me); E. Nakamura et al.; J. Am. Chem. Soc., **1993**, *115*, 9015

## 2. Addition of organolithium derivatives to Fischer aryl carbene complexes

In spite that aryl(methoxy) carbene complexes undergo methoxy displacement processes when reacted with organolithium compounds, the use of bulky alkoxy groups, e.g. menthyloxy and 8-phenylmenthyloxy, resulted in the nucleophilic attack onto the aryl group affording ultimately dearomatized adducts [4] (Scheme 3). Thus, we found that *s*BuLi and *t*BuLi add regioselectively to the phenyl(menthyloxy)carbene complex of chromium at the *para* position. The resulting intermediate was regioselectively trapped with methyl triflate yielding 1,4-cyclohexadiene derivatives after oxidation of the carbene functionality.

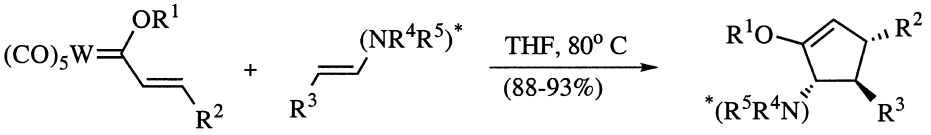
Unexpectedly, the reaction followed a different reactivity pattern when lithium acetylides are involved [5] (Scheme 4). Thus, phenylalkynyllithium is capable to add at low temperature to the carbene function of the aryl carbene complex forming **A**. This propargyl carbanion-type intermediate could be



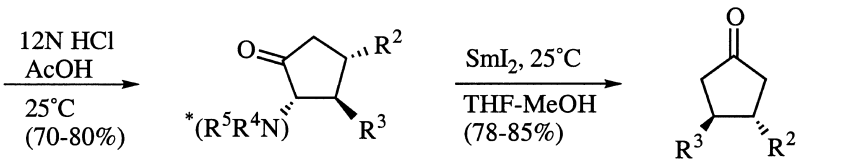

regioselectively trapped with electrophiles. At –40 °C this species reacts with benzaldehyde at C-3 giving ultimately 2,3,5-triphenylfuran (via allene **C**). Upon warming to 0 °C, the intermediate **A** suffers [1,3]-$W(CO)_5$ migration to form the allene carbanion-type intermediate **B** which could be quenched again with various electrophiles at C-1 and C-2 to afford propargyl ether **D** and indene (via **F**) derivatives, respectively.

## 3. Reaction of Fischer alkenyl carbene complexes with enamines: [3+2] carbocyclization

The strong electron-withdrawing character of the $M(CO)_5$ group makes Fischer alkenyl carbene complexes more suitable substrates to react with much less nucleophilic reagents, e.g. enamines, than organolithium systems [6]. Aldehyde enamines derived from (*S*)-2-methoxymethylpyrrolidine were found to undergo regio-, diastereo- and enantioselective [3+2] cycloaddition furnishing substituted 1-alkoxy-5-aminocyclopentenes. Enol ether hydrolysis and $SmI_2$-mediated deamination gave 3,4-disubstituted cyclopentanones with excellent *enantiomer excess* and good overall yield (Scheme 5). Regarding the reaction pathway, the whole process involves conjugated addition of the Cβ-enamine followed by ring closure and reductive metal elimination.



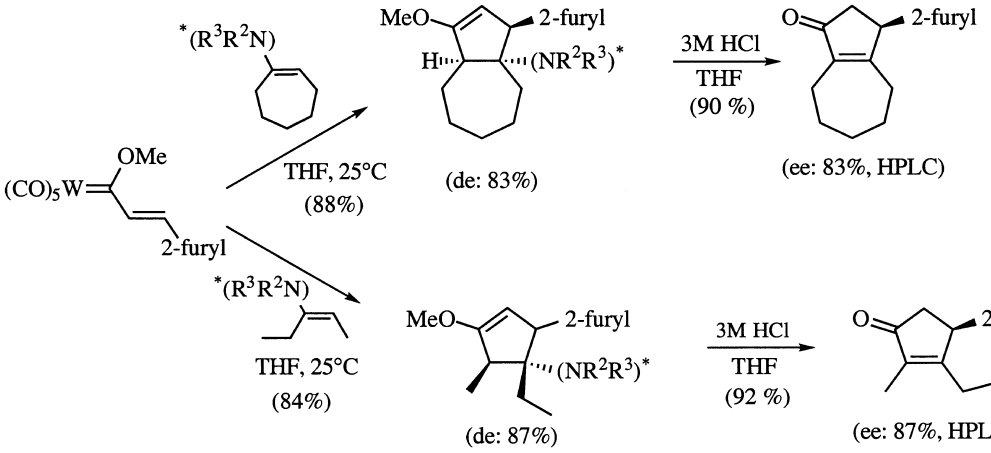

[*(R$^5$R$^4$NH): (*S*)-2-methoxymethylpyrrolidine] (de > 92%)




(ee > 92-98%, HPLC)

(R$^1$ = Me, *t*Bu; R$^2$ = Ph, 2-furyl; R$^3$ = $n$C$_6$H$_{13}$, *i*Pr)

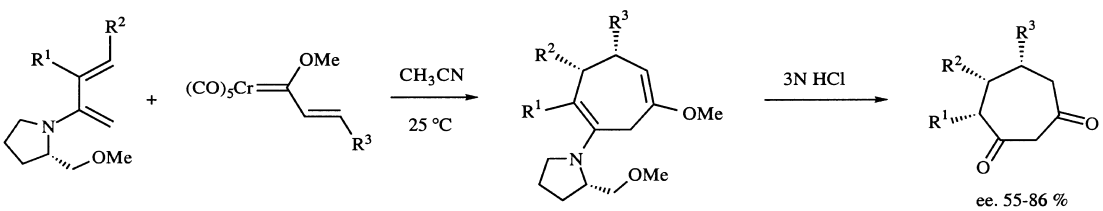
In turn, the ketone enamines analogs provided 1-methoxy-4-aminocyclopentenes on reaction with (*E*)-(3-furyl-1-methoxy-2-propenylidene)pentacarbonyltungsten (Scheme 6). In this case, addition of the Cβ-enamine to the carbene carbon followed by [1,2]-W(CO)$_5$ migration-induced cyclization and reductive metal elimination accounts well for the observed product. Acid hydrolysis readily converted the cycloadducts thus obtained into 2-cyclopentenones with high enantiomeric purity.




*(R$^3$R$^2$NH): (*S*)-2-methoxymethylpyrrolidine

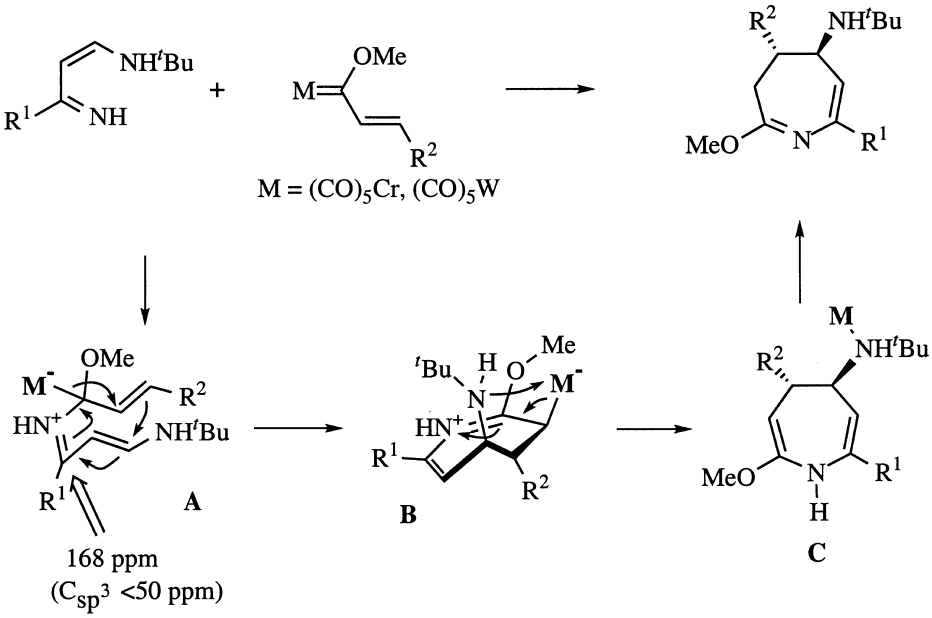
## 4. [4+3] Carbo- and heterocyclization reactions of Fischer alkenyl carbene complexes

Although a few examples of the [4+3] carbocyclization of alkenyl carbene complexes and 1,3-dienes had been reported, we brought about in 1994 the first enantioselective version employing homochiral 2-aminodienes [7]. The treatment of (*S*)-2-methoxymethylpyrrolidine-derived 1,3-butadienes with alkenyl carbene complexes in acetonitrile at room temperature resulted in the formation of the corresponding 1-amino-6-methoxycycloheptadiene in a totally regio and stereoselective manner. Hydrolysis of the latter was accomplished by treatment of its solution in THF with 3N HCl (Scheme 7).

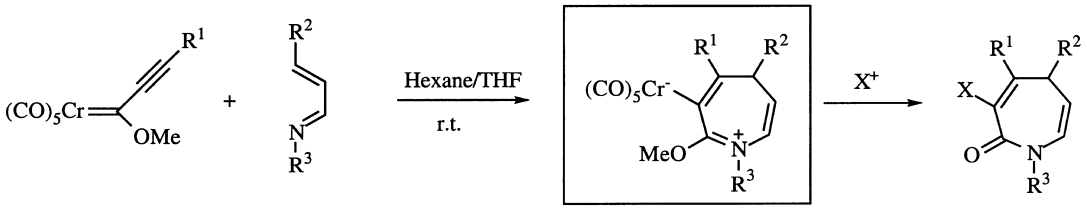



ee. 55-86 %

Moreover, the analogous [4+3] heterocyclization has been successfuly effected in our laboratory starting from either 1-azadiene [8,9] or 2-azadiene derivatives [10]. The cycloaddition of reactive 4-amino-1-aza-1,3-butadienes towards alkenyl carbene complexes went to completion in THF at a temperature as low as –40 °C to produce substituted 4,5-dihydro-3*H*-azepines in 52–91% yield [8]. Monitoring the reaction by NMR allowed to determine various intermediates and to establish the reaction course outlined in Scheme 8. This mechanism features the following points in the chemistry of Fischer carbene complexes: (i) the reaction initiates at –78 °C by nucleophilic 1,2-addition, (ii) the key step cyclization is triggered by a novel [1,2]-W(CO)5 shift.

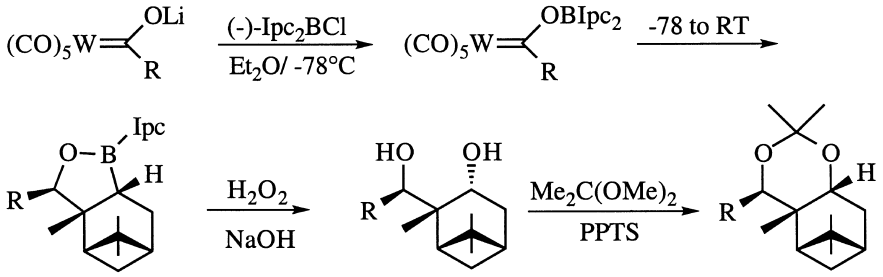



Unexpectedly, Fischer alkynyl carbene complexes also were found to react in the same way with simple 1-azadienes (α,β-unsaturated imines) leading to 2-azepinones after acid hydrolysis [9]. Interestingly, we were able in this case to crystallize the metallated zwitterionic intermediate shown in Scheme 9 and determine unambiguously its structure by an X-ray analysis.




## 5. Intramolecular C–H insertion of Fischer-type carbene complexes

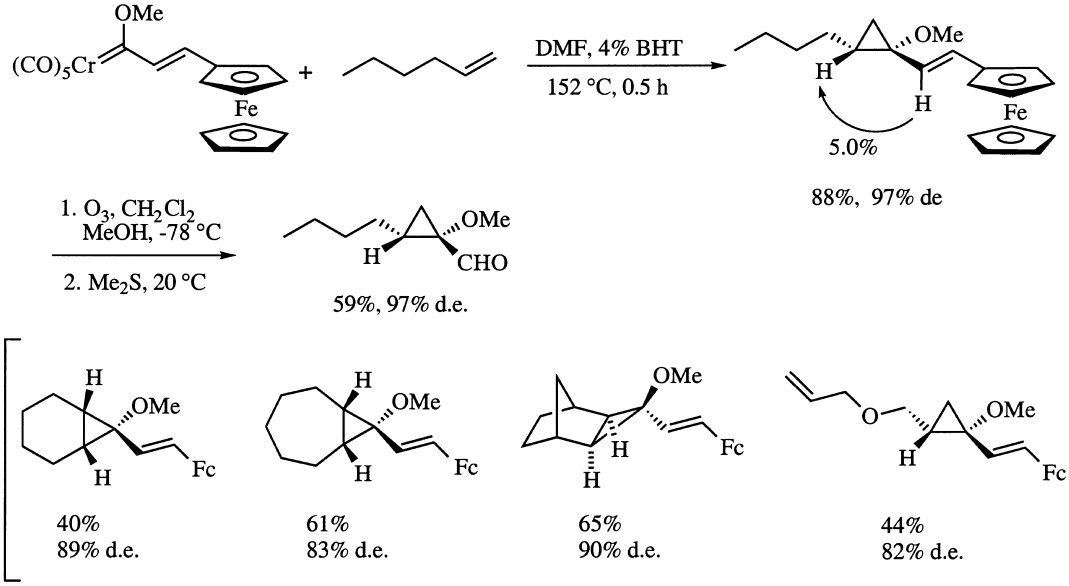
Recently we became interested on the behaviour of bimetallic carbene complexes in which the carbene heteroatom is bound to a second, electron-deficient, metal [11]. Thus, the treatment of lithium pentacarbonylmetal acylate intermediates, resulting from addition of organolithium reagents to hexacarbonylmetal, with chloroborane compounds at –78 °C gave new boroxycarbene complexes (Scheme 10). These compounds were then transformed into oxaborolane derivatives which in turn produced 1,3-diols with acceptable to high yields. Although the diastereoisomeric ratios varied depending on the structure of the carbene complex and, primarily, on the borane, the combination of (–)-Ipc$_2$-BCl and alkenyl carbene complexes led to de's higher than 97% in most instances.




| R | Ph | 2-Naph | (*E*)-PhCH=CH | $CH_2$=C(Ph) | $CMe_2$=CH | $CH_2$=C(Me) |
|---|---|---|---|---|---|---|
| de | 51 | 72 | >99 | >99 | 97 | 86 |

## 6. Diastereoselective cyclopropanation of unactivated alkenes

Contrary to previous belief, we have reported that electronically neutral alkenes can be efficiently cyclopropanated with Fischer carbene complexes [12]. Although other carbene derivatives are capable of effecting the [2+1] cycloaddition (2-ferrocenylalkenyl)carbene complexes showed to be superior in terms of diastereoselectivity (Scheme 11). As a representative example, the cyclopropanation of 1-hexene with the (methoxy)(2-ferrocenylethenyl)carbene was carried out in DMF at 152 °C to furnish the corresponding cyclopropane in high yield and 97% de. The ozonolysis of the alkenyl function permitted to obtain cylopropane aldehydes. Some other cycloadducts prepared are given in Scheme 11.




## ACKNOWLEDGEMENTS

The contribution of the members of my group whose names appear throughout the references is greatly acknowledged. This research was supported by the Ministerio de Education y Cultura of Spain (DGICYT, Grants PB92-1005; PB94-1313; PB97-1271). Thanks are also given to MEC, FICYT and the European Community for a number of doctoral and postdoctoral fellowships.

## REFERENCES

1 E. O. Fischer, A. Maasböl. *Angew. Chem. Int. Ed. Engl.* **3**, 580 (1964).

2 For a leading review see: W. D. Wulff. In *Comprehensive Organometallic Chemistry II* (E. W. Abel, F. G. A. Stone, G. Wilkinson, eds), Vol. 12, p. 469. Pergamon, New York (1995).

3 J. Barluenga, J. M. Montserrat, J. Flórez, S. García-Granda, E. Martín. *Chem. Eur. J.* **1**, 236 (1995).

4 J. Barluenga, A. A. Trabanco, J. Flórez, S. García-Granda, E. Martín. *J. Am. Chem. Soc.* **118**, 13099 (1996).

5 J. Barluenga, A. A. Trabanco, J. Flórez, S. García-Granda, M. A. Llorca. *J. Am. Chem. Soc.* **120**, 12129 (1998).

6 J. Barluenga, M. Tomás, A. Ballesteros, J. Santamaría, C. Brillet, S. García-Granda, A. Piñera-Nicolás, J. T. Vázquez. *J. Am. Chem. Soc.* **121**, 4516 (1999).

7 J. Barluenga, A. Aznar, C. Valdés, A. Martín, S. García-Granda, E. Martín. *J. Am. Chem. Soc.* **115**, 4403 (1993).

8 J. Barluenga, M. Tomás, A. Ballesteros, J. Santamaría, F. López-Ortiz, R. J. Carbajo, S. García-Granda, P. Pertierra. *Chem. Eur. J.* **2**, 88 (1996).

9 J. Barluenga, M. Tomás, E. Rubio, J. A. López-Pelegrín, S. García-Granda, P. Pertierra. *J. Am. Chem. Soc.* **118**, 695 (1996).

10 J. Barluenga, M. Tomás, A. Ballesteros, J. Santamaría, A. Suárez-Sobrino. *J. Org. Chem.* **62**, 9229 (1997).

11 J. Barluenga, F. Rodríguez, J. Vadecard, M. Bendix, F. J. Fañanás, F. López-Ortiz. *J. Am. Chem. Soc.* **118**, 6090 (1996).

12 J. Barluenga, A. Fernández-Acebes, A. A. Trabanco, J. Flórez. *J. Am. Chem. Soc.* **119**, 7591 (1997).