Diastereoselective Intermolecular Cyclopropanation of Simple Alkenes by Fischer Alkenyl and Heteroaryl Carbene Complexes of Chromium: Scope and Limitations

José Barluenga,* Salomé López, Andrés A. Trabanco, Alvaro Fernández-Acebes, and Josefa Flórez

Contribution from the Instituto Universitario de Química Organometálica "Enrique Moles", Unidad Asociada al CSIC, Universidad de Oviedo, Julián Clavería 8, 33071 Oviedo, Spain

Received February 25, 2000

Abstract: The intermolecular cyclopropanation of simple alkyl-substituted alkenes with Fischer methoxycarbene complexes under thermal conditions is reported. The scope and limitations of this [2 + 1] cycloaddition with respect to the nature of the carbene complex, substitution pattern of the electron neutral olefin, and functional group tolerance in the electron neutral olefin are described in detail. This methodology provides functionalized cyclopropanes in good to excellent yields and generally with high diastereoselectivity. A mechanism involving the initial formation of a chelated tetracarbonyl complex intermediate is proposed to account for the observed results.

Introduction

The formal [2 + 1] cycloaddition of group 6 metal heteroatom-stabilized pentacarbonyl carbene complexes with olefins is one of the first and longest studied reactions of Fischer carbene complexes, and represents a valuable route toward functionalized cyclopropanes.[1] Since Fischer and Dötz showed that electron-deficient alkenes are readily cyclopropanated with group 6 metal (alkoxy)(aryl)carbene complexes,[2] many efforts have been made to explore the scope and limitations of this process. The success of this cyclopropanation reaction is not only highly dependent on the electronic nature of the alkene but is also influenced by the intra- or intermolecular nature of the process and the nature of the heteroatom directly bonded to the carbene carbon. Alkenes substituted with either electron-withdrawing[2,3] or electron-donating[4,5] groups can be smoothly cyclopropanated under thermal conditions in an intermolecular fashion with alkoxycarbene complexes. The reaction with electron-rich olefins must be carried out under high pressures of carbon monoxide in order to avoid the corresponding olefin metathesis process.[4a−c] Otherwise, in the cyclopropanation reactions of electron-deficient olefins, a common side reaction is the insertion of the carbene ligand into the olefinic β-C−H bond.[3,6] Steric hindrance, caused by either the number or the size of the substituents on the alkene, seems to be a limitation of these routes to cyclopropane derivatives.[3c] The diastereoselectivity of these carbene transfer reactions is generally low, leading to the corresponding cyclopropanes as a nearly equimolecular mixture of cis and trans isomers. However, much higher stereoselectivities are attained when these carbene transfer reactions involve a conjugated system either in the alkene or in the carbene ligand. Thus, better diastereoselectivities have been observed in the cyclopropanation of either electron-deficient[3e] or electron-rich alkenes[4d] with (alkoxy)(alkenyl)carbene complexes and in the cyclopropanation of 1-azadienes, an electron-poor alkene type, with (alkoxy)(aryl)carbene complexes.[7] In addition, the cyclopropanation reactions of electron-deficient 1,3-dienes[8] and electronically neutral 1,3-dienes[3f,9] with Fischer alkoxycarbene complexes occur regioselectively and with much higher diastereoselectivity than do similar carbene transfer reactions to analogous olefins. Otherwise, the reaction of electron-rich 1,3-dienes with (alkoxy)(alkenyl)carbene complexes of chromium has been reported to produce regio- and diastereoselectively cycloheptadiene derivatives via in situ Cope

(1) Reviews: (a) Brookhart, M.; Studabaker, W. B. *Chem. Rev.* **1987**, *87*, 411. (b) Reissig, H.-U. In *Organometallics in Organic Synthesis*; Werner, H., Erker, G., Eds.; Springer: Berlin, 1989; Vol. 2, pp 311−322. (c) Doyle, M. P. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon: Oxford, 1995; Vol. 12, pp 387−420. (d) Harvey, D. F.; Sigano, D. M. *Chem. Rev.* **1996**, *96*, 271.

(2) (a) Fischer, E. O.; Dötz, K. H. *Chem. Ber.* **1970**, *103*, 1273. (b) Dötz, K. H.; Fischer, E. O. *Chem. Ber.* **1972**, *105*, 1356.

(3) (a) Wienand, A.; Reissig, H.-U. *Tetrahedron Lett.* **1988**, *29*, 2315. (b) Herndon, J. W.; Tumer, S. U. *Tetrahedron Lett.* **1989**, *30*, 4771. (c) Wienand, A.; Reissig, H.-U. *Organometallics* **1990**, *9*, 3133. (d) Harvey, D. F.; Brown, M. F. *Tetrahedron Lett.* **1990**, *31*, 2529. (e) Wienand, A.; Reissig, H.-U. *Chem. Ber.* **1991**, *124*, 957. (f) Herndon, J. W.; Tumer, S. U. *J. Org. Chem.* **1991**, *56*, 286.

(4) (a) Fischer, E. O.; Dötz, K. H. *Chem. Ber.* **1972**, *105*, 3966. (b) Dorrer, B.; Fischer, E. O.; Kalbfus, W. *J. Organomet. Chem.* **1974**, *81*, C20. (c) Wulff, W. D.; Yang, D. C.; Murray, C. K. *Pure Appl. Chem.* **1988**, *60*, 137. For in situ cyclopropanations with acyloxy chromium carbene complexes, see: (d) Murray, C. K.; Yang, D. C.; Wulff, W. D. *J. Am. Chem. Soc.* **1990**, *112*, 5660.

(5) For an in situ generated nonheteroatom-stabilized chromium carbene complex involved in a catalytic synthesis of spirocyclopropanes from diaryl diazo compounds and electron-rich alkenes, see: (a) Pfeiffer, J.; Dötz, K. H. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2828. (b) Pfeiffer, J.; Nieger, M.; Dötz, K. H. *Eur. J. Org. Chem.* **1998**, *1011*, 1.

(6) (a) Cooke, M. D.; Fischer, E. O. *J. Organomet. Chem.* **1973**, *56*, 279. (b) Wienand, A.; Reissig, H.-U. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1129. See also: (c) Barluenga, J.; González, R.; Fañanás, F. J. *Organometallics* **1997**, *16*, 4525.

(7) Barluenga, J.; Tomás, M.; López-Pelegrín, J. A.; Rubio, E. *J. Chem. Soc., Chem. Commun.* **1995**, 665.

(8) (a) Buchert, M.; Reissig, H.-U. *Tetrahedron Lett.* **1988**, *29*, 2319. (b) Buchert, M.; Reissig, H.-U. *Chem. Ber.* **1992**, *125*, 2723. (c) Buchert, M.; Hoffmann, M.; Reissig, H.-U. *Chem. Ber.* **1995**, *128*, 605.

(9) (a) Harvey, D. F.; Lund, K. P. *J. Am. Chem. Soc.* **1991**, *113*, 8916. See also: (b) Merlic, C. A.; Bendorf, H. D. *Tetrahedron Lett.* **1994**, *35*, 9529.

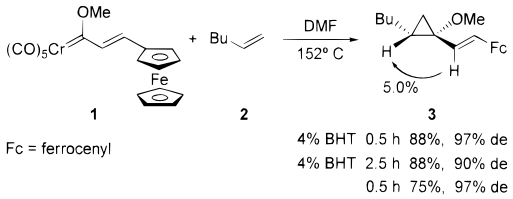
10.1021/ja000694b CCC: $19.00
Published on Web 08/15/2000

rearrangement of an initially formed *cis*-divinylcyclopropane intermediate.[10]

On the other hand, simple alkyl-substituted alkenes fail to undergo intermolecular cyclopropanation by heteroatom-stabilized group 6 metal carbene complexes even under forcing conditions.[11] Nevertheless, these unactivated alkenes can be easily cyclopropanated if the carbene transfer reaction is carried out in an intramolecular fashion. Thus, (alkoxy)(alkyl)- or (alkoxy)(aryl)carbene complexes with a pendent olefin in either the alkyl group[12] or the alkoxy group[13] readily undergo intramolecular cyclopropanation reaction. Furthermore, the intermolecular reaction of nonheteroatom-stabilized group 6 metal carbene complexes with simple alkenes provides the corresponding cyclopropanation products.[14,15]

In contrast, group 6 aminocarbene complexes have been much less studied and are scarcely able to effectively transfer their carbene ligands to alkenes. In general, the reaction of this type of carbene complexes with electron-deficient olefins results in the formation of formal C−H insertion/hydrolysis products, which could arise via the corresponding aminocyclopropanes.[3c,16] However, two examples of intramolecular cyclopropanation of (3-butenylamino)(aryl)carbene complexes of tungsten[13a,c] and chromium[13d] are known and only one example of intermolecular cyclopropanation of electron-deficient alkenes by group 6 pyrrolocarbene complexes has been reported.[17] In these latter complexes, the electron-donating ability of the amino group is limited and in their reactivity pattern they resemble alkoxycarbene complexes more than aminocarbene complexes.[18]

Scheme 1



In a preceding paper, we described the first examples of the intermolecular cyclopropanation of electronically neutral alkenes by 2-phenyl- and 2-ferrocenylalkenyl Fischer carbene complexes of chromium.[19] These reactions occurred with good yields affording vinylcyclopropanes with high diastereoselectivity. Herein, we report a thorough study of the cyclopropanation reaction of simple alkenes with group 6 heteroatom stabilized carbene complexes, which allows the more accurate assessment of the scope of this process. In addition, a mechanism that accounts for the structural requirements of the carbene complex and the high diastereoselectivity observed for this reaction is suggested.

Results and Discussion

Preliminary Results. The initial studies were carried out with chromium carbene complex **1**, in which the carbene ligand contains a ferrocenyl group attached at the β carbon to the carbene carbon atom.[20] This novel heterobimetallic organometallic complex may be regarded as a push−pull π-system in which the $(CO)_5Cr$ fragment acts as the acceptor and the ferrocenyl substituent acts as the electron donor group.[21] The preliminary experiment of our study is shown in Scheme 1 and involves treatment of carbene complex **1** with a 20-fold molar excess of 1-hexene (**2**) and a catalytic amount (4 mol %) of 2,6-di-*tert*-butyl-4-methylphenol (BHT) in dimethylformamide (DMF) at reflux for 0.5 h. After chromatographic purification (*Z*)-vinylcyclopropane **3** was isolated with very high diastereoselectivity (97% diastereomeric excess (de)) and good chemical yield (88%).[22] When this reaction was refluxed for a longer period of time (2.5 h), a slightly lower diastereoselectivity (90% de) was observed, whereas in the absence of BHT, compound **3** was obtained in 75% yield. This additive was initially used in order to prevent polymerization of the alkene. Acetonitrile

(10) Alkoxydienes: (a) Wulff, W. D.; Yang, D. C.; Murray, C. K. *J. Am. Chem. Soc.* **1988**, *110*, 2653. (b) Takeda, K.; Okamoto, Y.; Nakajima, A.; Yoshii, E.; Koizumi, T. *Synlett* **1997**, 1181. (c) Hoffmann, M.; Buchert, M.; Reissig, H.-U. *Chem. Eur. J.* **1999**, *5*, 876. Aminodienes: (d) Barluenga, J.; Aznar, F.; Martín, A.; Vázquez, J. T. *J. Am. Chem. Soc.* **1995**, *117*, 9419. (e) Barluenga, J.; Aznar, F.; Fernández, M. *Chem. Eur. J.* **1997**, *3*, 1629. Moreover, we demonstrated that the later reactions with aminodienes take place by nucleophilic addition to the carbene carbon followed by cyclization to the seven-membered ring with 1,2-migration of the $M(CO)_5$ fragment: (f) Barluenga, J.; Tomás, M.; Ballesteros, A.; Santamaría, J.; Carbajo, R. J.; López-Ortiz, F.; García-Granda, S.; Pertierra, P. *Chem. Eur. J.* **1996**, *2*, 88. (g) Barluenga, J.; Tomás, M.; Rubio, E.; López-Pelegrín, J. A.; García-Granda, S.; Pertierra, P. *J. Am. Chem. Soc.* **1996**, *118*, 695.

(11) See, for example: (a) Fischer, E. O.; Heckl, B.; Dötz, K. H.; Müller, J.; Werner, H. *J. Organomet. Chem.* **1969**, *16*, P29. (b) Hegedus, L. S. In *Transition Metals in the Synthesis of Complex Organic Molecules*, 2nd ed.; University Science Books: Sausalito, CA, 1999; pp 151−157.

(12) (a) Toledano, C. A.; Rudler, H.; Daran, J.-C.; Jeannin, Y. *J. Chem. Soc., Chem. Commun.* **1984**, 574. (b) Barluenga, J.; Montserrat, J. M.; Flórez, J. *J. Chem. Soc., Chem. Commun.* **1993**, 1068.

(13) (a) Casey, C. P.; Vollendorf, N. W.; Haller, K. J. *J. Am. Chem. Soc.* **1984**, *106*, 3754. (b) Casey, C. P.; Shusterman, A. J. *Organometallics* **1985**, *4*, 736. (c) Casey, C. P.; Hornung, N. L.; Kosar, W. P. *J. Am. Chem. Soc.* **1987**, *109*, 4908. (d) Söderberg, B. C.; Hegedus, L. S. *Organometallics* **1990**, *9*, 3113.

(14) (a) Casey, C. P.; Burkhardt, T. J. *J. Am. Chem. Soc.* **1974**, *96*, 7808. (b) Casey, C. P.; Tuinstra, H. E.; Saeman, M. C. *J. Am. Chem. Soc.* **1976**, *98*, 608. (c) Casey, C. P.; Albin, L. D.; Burkhardt, T. J. *J. Am. Chem. Soc.* **1977**, *99*, 2533. (d) Harvey, D. F.; Brown, M. F. *J. Am. Chem. Soc.* **1990**, *112*, 7806. (e) Fischer, H.; Hofmann, J. *Chem. Ber.* **1991**, *124*, 981. (f) Fischer, H.; Volkland, H.-P.; Stumpf, R. *Anal. Quím. Int. Ed.* **1996**, *92*, 148. See also: (g) Rudler, H.; Audouin, M.; Parlier, A.; Martín-Vaca, B.; Goumont, R.; Durand-Réville, T.; Vaissermann, J. *J. Am. Chem. Soc.* **1996**, *118*, 12045. (h) Gunnoe, T. B.; White, P. S.; Templeton, J. L.; Casarrubios, L. *J. Am. Chem. Soc.* **1997**, *119*, 3171.

(15) For intramolecular cyclopropanations of simple alkenes by non-heteroatom-stabilized carbene complexes in situ generated by previous reaction of an alkoxycarbene complex with an alkyne, see for instance: (a) Parlier, A.; Rudler, H.; Platzer, N.; Fontanille, M.; Soum, A. *J. Chem. Soc., Dalton Trans.* **1987**, 1041. (b) Hoye, T. R.; Suriano, J. A. *Organometallics* **1992**, *11*, 2044. (c) Harvey, D. F.; Brown, M. F. *J. Org. Chem.* **1992**, *57*, 5559. (d) Harvey, D. F.; Sigano, D. M. *J. Org. Chem.* **1996**, *61*, 2268.

(16) (a) Sierra, M. A.; Soderberg, B.; Lander, P. A.; Hegedus, L. S. *Organometallics* **1993**, *12*, 3769. (b) Barluenga, J.; Aznar, F.; Martín, A. *Organometallics* **1995**, *14*, 1429.

(17) Merino, I.; Hegedus, L. S. *Organometallics* **1995**, *14*, 2522.

(18) For intramolecular cyclopropanation of simple alkenes with non-heteroatom-stabilized carbene complexes in situ generated by previous reaction of an aminocarbene complex with an alkyne, see: (a) Parlier, A.; Rudler, H.; Yefsah, R.; Alvarez, C. *J. Organomet. Chem.* **1987**, *328*, C21. (b) Hoye, T. R.; Rehberg, G. M. *Organometallics* **1989**, *8*, 2070. (c) Hoye, T. R.; Vyvyan, J. R. *J. Org. Chem.* **1995**, *60*, 4184.

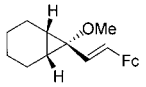
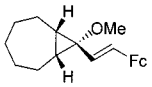
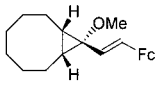
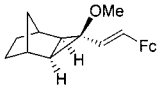
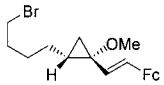
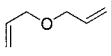
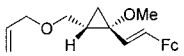
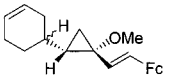
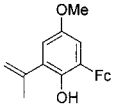
(19) Preliminary communication: Barluenga, J.; Fernández-Acebes, A.; Trabanco, A. A.; Flórez, J. *J. Am. Chem. Soc.* **1997**, *119*, 7591.

(20) Ferrocenylcarbene complexes of Cr, W, and Mn were previously described: (a) Connor, J. A.; Lloyd, J. P. *J. Chem. Soc., Dalton Trans.* **1972**, 1470. Cyclopropanation of dimethyl fumarate with the Cr derivative was reported: (b) Connor, J. A.; Lloyd, J. P. *J. Chem. Soc., Perkin Trans. 1* **1973**, 17.

(21) Complexes of these characteristics are attractive synthetic goals due to their physical and chemical properties. See, for example: (a) Togni, A.; Rihs, G. *Organometallics* **1993**, *12*, 3368. (b) Wong, W.-Y.; Wong, W.-T.; Cheung, K.-K. *J. Chem. Soc., Dalton Trans.* **1995**, 1379. (c) Sato, M.; Mogi, E.; Katada, M. *Organometallics* **1995**, *14*, 4837. (d) Behrens, U.; Brussaard, H.; Hagenau, U.; Heck, J.; Hendrickx, E.; Körnich, J.; van der Linden, J. G. M.; Persoons, A.; Spek, A. L.; Veldman, N.; Voss, B.; Wong, H. *Chem. Eur. J.* **1996**, *2*, 98. (e) Fischer, H.; Leroux, F.; Roth, G.; Stumpf, R. *Organometallics* **1996**, *15*, 3723. (f) Jayaprakash, K. N.; Ray, P. C.; Matsuoka, I.; Bhadbhade, M. M.; Puranik, V. G.; Das, P. K.; Nishihara, H.; Sarkar, A. *Organometallics* **1999**, *18*, 3851.

(22) Vinylcyclopropanes are recognized to have high synthetic potential: (a) Reissig, H.-U. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 971. (b) Tang, Y.; Huang, Y.-Z.; Dai, L.-X.; Chi, Z.-F.; Shi, L.-P. *J. Org. Chem.* **1996**, *61*, 5762.

Table 1. Cyclopropanation Reactions of Electronically Neutral Alkenes with 2-Ferrocenylalkenyl Carbene Complex **1**[a]

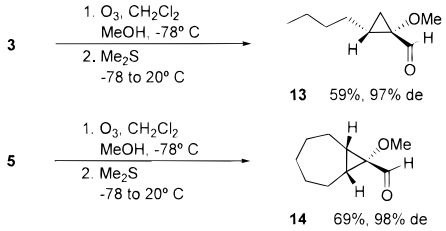
entry	alkene[b]	product[c]		yield[d] (%)	de[e] (%)
1			**4**	40[f]	89[g]
2			**5**	61	83
3			**6**	34	74
4			**7**	65	90[g]
5			**8**	56	94
6			**9**	44	82
7			**10**	45	-[h]
8			**11**	62	-[g]

[a] Reactions were carried out in DMF at reflux for 25−35 min in the presence of 4 mol % of BHT. [b] 20 equiv of alkene was used. [c] Only the major diastereoisomer is shown; Fc = ferrocenyl. [d] Isolated yield based on carbene complex **1**. [e] Determined by ^{1}H NMR at 300 MHz; integration of MeO signal. [f] 40 equiv of cyclohexene was used. [g] Mixture refluxed for 2−2.5 h. [h] A 1:1 mixture of diastereoisomers was formed.

and tetrahydrofuran (THF) were found to be poor solvents for this cyclopropanation. Thus, when the reaction of Scheme 1 using 20 equiv of **2** and 4 mol % of BHT was conducted in refluxing acetonitrile (4 h) or in THF at reflux (7 h), cyclopropane **3** was isolated with 50% yield, 82% de and 20% yield, 90% de, respectively. Procedures employing a lower amount of alkene gave either lower chemical yields and somewhat lower stereoselectivities when 5−10 equiv of **2** was used, or an unidentified mixture of products when 2−3 equiv of **2** was present. The relative stereochemistry of the major isomer **3** was elucidated by nuclear Overhauser effect (NOE) studies (the arrow in Scheme 1 indicates the observed NOE enhancement).

A number of other simple alkyl-substituted alkenes were surveyed in the reaction with carbene complex **1**, and the results are summarized in Table 1. Cyclic olefins such as cyclohexene, cycloheptene, cyclooctene, and norbornene provided the corresponding bicyclic or tricyclic vinylcyclopropane containing products **4**−**7**, with good diastereoselectivity and moderate yields (Table 1, entries 1−4). The reaction with cyclohexene required a larger excess of this alkene (40 equiv) in order to obtain the corresponding cyclopropanation product **4**. A terminal alkene containing a remote bromine atom such as 6-bromo-1-hexene was also readily cyclized to the corresponding vinylcyclopropane **8** with a high level of diastereoselectivity (Table 1, entry 5). Unconjugated dienes with either structurally equivalent or nonequivalent double bonds afforded exclusively the corresponding monocyclopropanated adducts. Diallyl ether was converted to cyclopropane **9** (Table 1, entry 6), whereas the reaction of 4-vinylcyclohexene with carbene complex **1** occurred regio- and stereoselectively at the terminal double bond producing compound **10** as a nearly equimolecular mixture of diastereoisomers, which is due to the presence of a stereogenic carbon atom in the starting diene (Table 1, entry 7). On the other hand, the reaction of carbene complex **1** with 2-methyl-1-buten-3-yne, a conjugated enyne, provided the phenol derivative **11**, which demonstrated that in this case the Dötz benzannulation reaction[23] is highly favored over the cyclopropanation process (Table 1, entry 8).[24,25] The relative configuration of vinylcyclopropanes **4**−**7** and **9** was likewise determined by difference NOE experiments (see the Supporting Information). The same stereochemistry was assumed for compounds **8** and **10**.

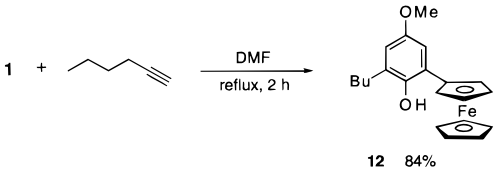
Scheme 2



In addition, the ferrocenyl group can be removed by oxidative cleavage of the vinyl portion with ozone.[26] Two examples are shown in Scheme 2, where vinylcyclopropanes **3** and **5**, each as a single diastereoisomer,[27] were subjected to ozonolysis, furnishing the corresponding cyclopropanecarbaldehydes **13** and **14** with high diastereomeric purities.

Optimization of Reaction Conditions. During the development of this intermolecular cyclopropanation reaction, it was found that alkenylcarbene complex **15a**, bearing a phenyl substituent instead of the ferrocenyl group, afforded also the corresponding vinylcyclopropane **16** when treated with 1-hexene (**2**) as shown in Table 2. The first reaction was carried out in DMF at reflux for 1.5 h using 20 equiv of **2** and produced compound **16** with high diastereoselectivity (82% de) but moderate chemical yield (54%) (Table 2, entry 1). In addition to DMF, acetonitrile and THF were found to serve as effective solvents for this cyclopropanation reaction (Table 2, entries 2 and 3). Although the reaction run in CH_3CN at reflux temperature, using the former conditions (20 equiv of **2**), provided compound **16** with a slightly lower chemical yield (Table 2, entry 2 vs entry 1), the reaction conducted in THF at reflux was slower (6 h), giving vinylcyclopropane **16** with lower

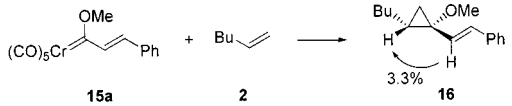
(23) Dötz, K. H. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 587.
(24) This preference has precedents. For example, see ref 1b.
(25) Indeed, carbene complex **1** reacted smoothly with 1-hexyne following the Dötz reaction pathway to give regioselectively 2-butyl-6-ferrocenyl-4-methoxyphenol (**12**).



The structure of phenols **11** and **12**, which corresponds to the expected regioisomer in the Dötz benzannulation reaction with terminal alkynes, was clearly established from the value of the coupling constant between the aromatic protons (J = 3.0−3.1 Hz), which indicates a meta relative disposition of these hydrogens.

(26) (a) Veysoglu, T.; Mitscher, L. A.; Swayze, J. K. *Synthesis* **1980**, 807. (b) Hanessian, S.; Andreotti, D.; Gomtsyan, A. *J. Am. Chem. Soc.* **1995**, *117*, 10393.
(27) The major diastereoisomer was previously separated by column chromatography.

Table 2. Cyclopropanation Reaction of 1-Hexene (2) with 2-Phenylalkenyl Carbene Complex **15a**: Optimization of Reaction Conditions for the Synthesis of **16**



15a **2** **16**

entry	equiv of **2**	solvent	*T* (°C)	*t* (h)[a]	yield[b] (%)	de[c] (%)
1	20	DMF	152	1.5	54	82
2	20	CH_3CN	81	1.5	45	82
3	20	THF	65	6	75	72
4	20	THF	65	18	73	72
5	20	THF	65	24	75	72
6	10	THF	65	6	55	72
7	5	THF	140[d]	1	30	58
8	5	THF	95[d]	3	60	70

[a] Reaction time required for complete disappearance of starting carbene complex **15a**. [b] Isolated yield of product **16** (only the major diastereoisomer is shown) based on carbene complex **15a**. [c] Diastereomeric excess determined from the ^{1}H NMR spectrum of the crude product. [d] Reaction carried out in a sealed flask. Bath temperature.

diastereoselectivity but better chemical yield (Table 2, entry 3 vs entry 1). Under these latter conditions, longer reaction times (18 and 24 h) did not produce any change in the yield and diastereoselectivity of the cyclopropanation reaction (Table 2, entries 4 and 5). Attempts to reduce the number of equivalents of alkene were performed in THF. Treatment of carbene complex **15a** with 10 equiv of **2** in THF at reflux furnished cyclopropane **16** with similar reaction time and diastereoselectivity but lower chemical yield (Table 2, entry 6 vs entry 3). When 5 equiv of **2** was used, the reactions were run in a resealable Schlenk flask in order to prevent complete displacement of this alkene (1-hexene, bp 64 °C) from the reaction medium. Heating at 140 °C led to a very fast consumption (1 h) of starting carbene complex **15a**, but provided cyclopropane **16** with both quite low chemical yield and diastereomeric excess (Table 2, entry 7). The same reaction heated at 95 °C needed some more reaction time (3 h) and allowed both chemical yield and diastereomeric excess to increase to levels similar to those observed in the experiment with 10 equiv of **2** (Table 2, entry 8 vs entry 6). The relative configuration of the major isomer **16** was also ascertained from a difference NOE experiment.

Starting from these data, we choose as more convenient reaction conditions to perform the intermolecular cyclopropanation of simple alkenes with alkenylcarbene complexes those which involve combining the carbene complex with 5 equiv of alkene and THF in a resealable flask and heating the flask at 95−100 °C until disappearance of starting carbene complex.

Synthetic Scope: Carbene Complex Survey. The behavior of different group 6 Fischer carbene complexes in the thermal reaction with 1-hexene (**2**) was initially evaluated under the standard reaction conditions above established, unless otherwise noted. Table 3 summarizes our findings. Other chromium alkenylcarbene complexes substituted at the β position by an aryl **17** or heteroaryl group **18** also underwent this intermolecular cyclopropanation reaction, giving the corresponding vinylcyclopropanes **22** and **23** with high yield (remarkably in the case of **22**; Table 3, entry 1) and good diastereoselectivity (especially in the case of **23**; Table 3, entry 2). Under these standard reaction conditions 2-ferrocenylvinylcarbene complex **1** provided **3** with a bit lower yield and diastereoselectivity (see Table 3, entry 3 and Scheme 1). Aliphatic alkenylcarbene complex **19**, which in addition has the C═C double bond inside a six-membered ring, went through a quite fast reaction yielding **24** with moderate yield (Table 3, entry 4), which can be credited to the presumably lower stability of this aliphatic complex **19** in comparison with the 2-aryl-substituted alkenylcarbene complexes **1**, **15a**, **17**, and **18** (particularly, 2-ferrocenylvinylcarbene complex **1** seems to be quite stable). The reactivity of the other group 6 metal-derived complexes **15b**,**c** was compared to the structurally analogous chromium complex **15a**. Although the molybdenum carbene complex **15b** afforded **16** with moderate yield (Table 3, entry 5),[28] the tungsten complex **15c** needed a higher reaction temperature (160 °C; after 24 h at 100 °C no reaction was observed) to produce **16** in rather low yield (Table 3, entry 6).[29] Nevertheless, in both reactions vinylcyclopropane **16** was isolated as a single diastereoisomer. Heteroarylcarbene complexes **20** and **21** were also able to successfully transfer their carbene ligand to 1-hexene (**2**). The 2-furyl derivative **20** led to cyclopropane **25** under the standard conditions (Table 3, entry 7), but the *N*-methyl-2-pyrrolyl complex **21** required 150 °C (no reaction was observed at 100 °C for 15 h) to provide **27** with significantly low yield and roughly as an equimolecular mixture of diastereoisomers. Conducting the reaction in toluene at 180 °C produced only improved yield (Table 3, entry 8). In the experiments with complexes **20** and **21**, in addition to the expected cyclopropane derivatives **25** and **27**, the corresponding heteroaryl ketone **26** or **28** was isolated as a minor component. These ketones presumably arise from hydrolysis of the appropriate methyl enol ethers generated by formal insertion of the carbene ligand into a terminal olefinic C−H bond.

The major diastereoisomer of cyclopropanes **3**, **16**, and **22**−**25** shown in Table 3 was purified by silica gel column chromatography. For **27**, only the slower moving isomer could be completely separated from the 1:1 mixture using this technique. Compounds **23** and above all **25** and **27** must be stored under N_2 at low temperature; they slowly decompose upon standing at room temperature (after 4−6 days they become dark). Stereochemical assignments for cyclopropanes **22**−**25** are based on either 1D NOE experiments or 2D nuclear Overhauser enhancement spectroscopy (NOESY) studies (see the Supporting Information).[30]

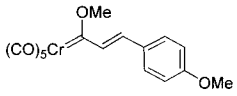
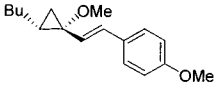
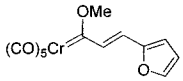
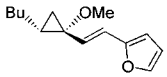
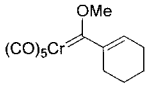
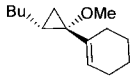
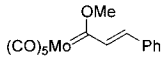
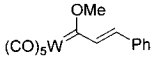
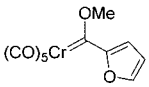
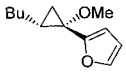
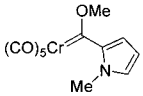
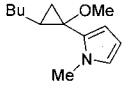
Regarding the structural nature of the chromium carbene complex, some limitations to this intermolecular cyclopropanation reaction of simple alkenes with Fischer carbene complexes under the conditions described above have been identified (Scheme 3). The reaction of (methoxy)methyl complex **I** with 1-hexene (**2**) did not give any isolable product. Treatment of alkynylcarbene complex **II** or arylcarbene complexes **III** and **IV** with the same olefin and using different solvents (THF, toluene, CH_3CN, DMF) provided only polymers or intractable mixtures of many compounds. A similar result was obtained from reaction of **2** with cyclic alkenylcarbene complex **V** fixed into an s-cis conformation. After 57 h at 95 °C (THF, sealed flask) carbene complex **V** was completely consumed, producing a mixture of unidentified products. In contrast, bicyclic alkenylcarbene complex **VI** locked into an s-trans conformation remained perfectly stable in the reaction medium even after being heated at 150 °C for 20 h.

(28) The relative instability of the molybdenum carbene complexes compared to chromium and tungsten derivatives is known: see ref 3d.

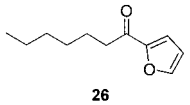
(29) The reduced bias of tungsten carbene complexes to undergo cyclopropanation reactions in relation to chromium carbene derivatives has precedents: see refs 4c, 9, and Barluenga, J.; Aznar, F.; Martín, A.; Barluenga, S.; García-Granda, S.; Paneque-Quevedo, A. A. *J. Chem. Soc., Chem. Commun.* **1994**, 843.

(30) The structural assignments, particularly the cyclopropyl protons, were based on their ^{1}H and ^{13}C NMR spectra including correlated spectrosopy (COSY) and proton-detected heteronuclear (^{1}H to ^{13}C) 2D correlation experiments: heteronuclear multiple quantum coherence (HMQC) and heteronuclear multiple-bond correlation (HMBC).

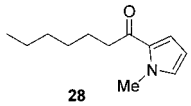
Table 3. Cyclopropanation Reaction of 1-Hexene (**2**) with Different Group 6 Fischer Carbene Complexes **1**, **15b**,**c**, and **17**−**21**

entry	carbene complex		reaction conditions[a] T (°C)	t (h)	product[b]		yield[c] (%)	de[d] (%)
1		**17**	100	6		**22**	90	68
2		**18**	100 65[e]	2 6.5		**23**	68 40	80 80
3	**1**		95	4	**3**		70	82
4		**19**	110	1		**24**	45	80
5		**15b**	95	2	**16**		53	99[f]
6		**15c**	160	4	**16**		20	99[f]
7		**20**	95	7		**25**	56[g]	66
8		**21**	150 180[i]	5 8		**27**	25[h] 45[j]	0 0

[a] All reactions were performed in THF on a sealed flask using 5 equiv of 1-hexene. [b] Only the major diastereoisomer is shown. [c] Isolated yield based on the corresponding carbene complex. [d] Diastereomeric excess determined from the ^{1}H NMR spectrum of the crude products. [e] Mixture refluxed in a normal flask in the presence of 20 equiv of **2** and 4 mol % of BHT. [f] Only one diastereoisomer observed in ^{1}H and ^{13}C NMR spectroscopy. [g] In this experiment compound **26** was also isolated in 7% yield.



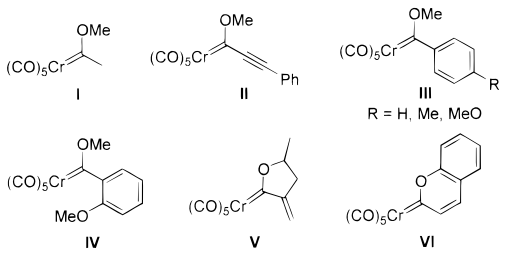
26



28

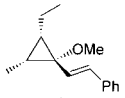
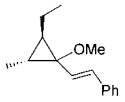
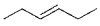
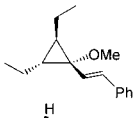
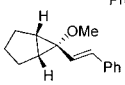
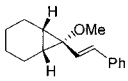
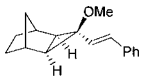
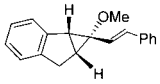
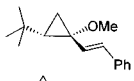
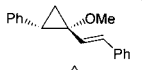
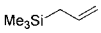
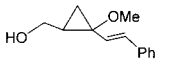
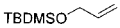
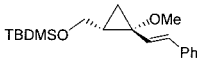
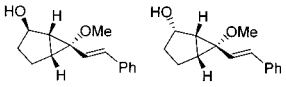
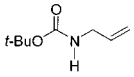
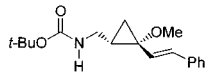
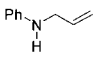
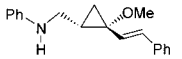
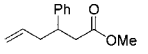
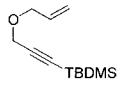
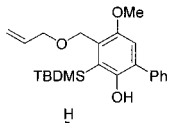
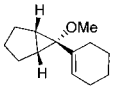
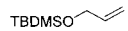
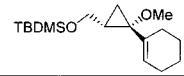
[h] In this reaction compound **28** was also formed in 10% isolated yield. [i] Toluene was used instead of THF. [j] In addition, compound **28** was isolated in 7% yield.

Scheme 3

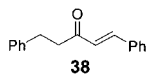


Synthetic Scope: Alkene Survey. Employing chromium carbene complex **15a**, we first screened various alkyl-substituted olefins under the standard reaction conditions previously found. The results are listed in Table 4. 1,2-Disubstituted olefins with either an acyclic structure (*cis*-2-pentene, *trans*-2-pentene, and *trans*-3-hexene) or a cyclic nature (cyclopentene, cyclohexene, norbornene and indene) were readily transformed to the corresponding vinylcyclopropanes **29**−**35** with moderate to good yields and high diastereoselectivity (Table 4, entries 1−7), with the exception of cyclopropane **30**, which was generated without any diastereomeric excess (Table 4, entry 2). It is noteworthy that while the cyclopropanation reaction with *cis*-2-pentene was completely diastereoselective, the same reaction with the trans diastereoisomer was totally nondiastereoselective (Table 4, entries 1 and 2). On the other hand, the reaction with trans equally disubstituted alkene (*trans*-3-hexene) afforded a single diastereoisomer **31**, given that in this case both orientations of the carbene ligand in the cyclopropanation process led to the same diastereoisomer (Table 4, entry 3). Terminal alkenes substituted by a bulky group (3,3-dimethyl-1-butene) or an aromatic ring (styrene) reacted with **15a** to provide cyclopropane derivatives **36** and **37**. *tert*-Butylcyclopropane **36** was isolated as a diastereomerically pure compound (Table 4, entry 8), whereas phenylcyclopropane **37** was formed rather less diastereoselectively and it was accompanied by a significant amount (34%) of ketone **38** when the reaction was run in a sealed flask (Table 4, entry 9). Different monosubstituted olefins bearing a silane, hydroxy, silyl ether, carbamate, amine, or halogen function in the allylic position were next investigated. In all of the successful examples, a fast reaction was observed (1−4 h) leading to the appropriate cyclopropane containing product **39**−**44** with generally good yields and diastereoselectivities (Table 4, entries 10−15). From allyltrimethylsilane cyclopropane, **39** was obtained (Table 4, entry 10). Cyclopropanation of allyl alcohol produced cyclopropylmethyl alcohol **40** as a 1:1 mixture of diastereoisomers (Table 4, entry 11). However, the diastereoselectivity of this cyclopropanation was clearly improved (70−73% de) by previous protection of the hydroxyl group as its *tert*-butyldimethylsilyl (TBDMS) ether (Table 4, entry 12). In addition, the reaction of carbene complex **15a** with only a stoichiometric amount of allyl *tert*-butyldimethylsilyl ether allowed an increase in the chemical yield (95%), presumably due to the formation of a cleaner reaction crude (no excess of alkene was present) which would minimize loss of product in the purification step. By contrast, the reaction with unprotected cyclic allylic alcohol 2-cyclopentenol produced a 2:1 mixture

Table 4. Cyclopropanation Reactions of Simple Alkenes by Alkenyl Carbene Complexes **15a**, **19**

entry	alkene	carbene complex	reaction conditions[a] T(°C)	t (h)	product[b]		yield[c] (%)	de[d] (%)
1		**15a**	95	8		**29**	40	99[e]
2		**15a**	95	7		**30**	55	0
3		**15a**	95	5		**31**	40	[f]
4		**15a**	110	4		**32**	78	99[e]
5		**15a**	100	3.5		**33**	85	70
6		**15a**	110	7		**34**	50	90
7		**15a**	100	3.5		**35**	73	79
8		**15a**	100 65[g]	3.5 7		**36**	80 65	99[e] 99[e]
9		**15a**	95 65[g]	7 7		**37**	50[h] 48[i]	32 50
10		**15a**	100	3		**39**	40	85
11		**15a**	95	4		**40**	70	0
12		**15a**	100 100	3 3[k]		**41**	85 95	70[j] 73[j]
13		**15a**	110 110	1 1[k]	 **42a** 2 : 1 **42b**		55 60	92, 94[j, l] 92, 94[j, l]
14		**15a**	95	3[k]		**43**	60	74
15		**15a**	105	4		**44**	30	50
16		**15a**	100 65[m]	25 48		**45**	53 50	- -
17		**15a**	140	1.5		**46**	57	-
18		**19**	100	3		**47**	73	81
19		**19**	100	3		**48**	90	33

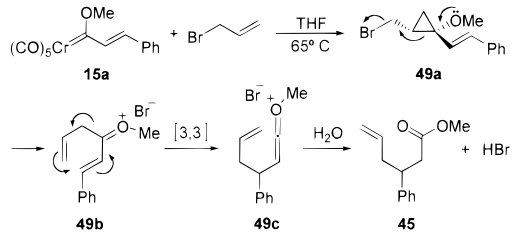
[a] All reactions were conducted in THF on a sealed flask using 5 equiv of the corresponding alkene, unless otherwise noted. [b] Only the major diastereoisomer is shown. [c] Isolated yield based on the corresponding carbene complex **15a** or **19**. [d] Diastereomeric excess determined by ^{1}H NMR analysis of the crude products. [e] Only one diastereoisomer observed in ^{1}H and ^{13}C NMR spectroscopy. [f] Both orientations in the cyclopropanation reaction led to the same diastereoisomer. [g] Mixture refluxed in a normal flask in the presence of 20 equiv of alkene. [h] In this experiment compound **38** was also isolated in 34% yield.



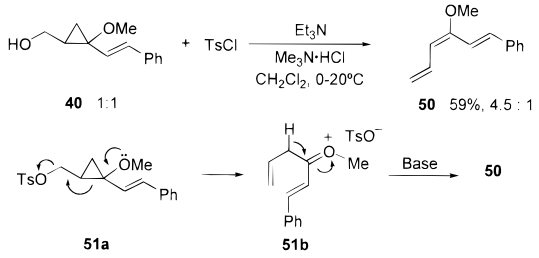
38

[i] A small amount of the formal insertion product, which has not been quantified, seems to be present in the ^{1}H NMR spectrum of the crude reaction mixture. [j] Diastereomeric excess based upon ^{1}H NMR analysis of the products after column chromatography. [k] Reaction run with 1 equiv of alkene. [l] Diastereomeric excesses for **42a** and **42b**, respectively, which refer to the relative configuration at the new stereocenters created in the cyclopropanation reaction. [m] Reaction refluxed in a normal flask in the presence of 5 equiv of alkene.

Scheme 4



Scheme 5



of diastereomeric alcohols **42a** and **42b**, each of which was found to be a diastereomerically highly enriched compound. Comparable results with a bit higher yield were observed when the reaction was conducted with only 1 equiv of this nonvolatile alkene (Table 4, entry 13). The allylamine derivatives *N*-(*tert*-butoxycarbonyl)allylamine and *N*-allylaniline were also cyclopropanated to give compounds **43** and **44**. Both yield and diastereoselectivity were better with the less basic carbamate derivative (Table 4, entries 14,15). On the other hand, the reaction of allyl bromide with carbene complex **15a** was a slower process and afforded the noncyclopropane containing product **45** (Table 4, entry 16). Formation of this methyl ester **45** can be interpreted as resulting from the successive ring opening of vinylcyclopropane **49a**, isomerization of 1,5-diene **49b** in a [3,3] sigmatropic rearrangement, and addition of water to ionic ketene intermediate **49c** (Scheme 4). In an attempt to find some evidence for the initial formation of cyclopropane **49a**, an aliquot of the reaction of **15a** with allyl bromide in THF at reflux was worked up after 4 and 10 h of reaction. The ^{1}H NMR analysis of both crude reaction mixtures showed the signals of **45** (estimated yield 17 and 30%, respectively) without any indication of the presence of **49a**. To rule out an alternative reaction pathway which could involve an initial alkylation of the metal by the highly reactive allyl bromide, two reactions were carried out. A mixture of carbene complex **15a** and benzyl bromide (5 equiv) in THF and otherwise a THF solution of allyl bromide (5 equiv) and pentacarbonyl[(methoxy)(phenyl)-methylene]chromium were heated for 9−10 h at 100 °C (sealed flask). Both experiments produced complex reaction mixtures. In addition, indirect evidence of the intermediacy of cyclopropane **49a** could be attained by alternative synthesis and subsequent heating (reflux of THF) of cyclopropane **51a** (Scheme 5), whose unique difference with **49a** is the presence of a tosylate group instead of the bromine atom (both of comparable leaving group ability). However, tosylation of cyclopropylmethyl alcohol **40** as summarized in Scheme 5[31] afforded triene derivative **50** (4.5:1 mixture of diastereoisomers; only the major isomer is shown), indicating that tosylated cyclopropane **51a** is unstable even at room temperature and undergoes a similar ring opening reaction. In the basic reaction medium, 1,5-diene intermediate **51b**, analogous to **49b**, leads to enol ether **50** by elimination of *p*-toluenesulfonic acid. A final experiment with carbene complex **15a** was performed with the 1,6-enyne allyl 3-(*tert*-butyldimethylsilyl)-2-propynyl ether. Even in this case the thermal reaction with the internal alkyne was faster than that with the terminal alkene, giving the Dötz benzannulation reaction product **46** as a single regioisomer (Table 4, entry 17). Finally, two other reactions with cyclohexenylcarbene complex **19** were successfully performed as given in Table 4, entries 18, 19. With this carbene complex, however, the diastereoselectivity of the cyclopropanation reaction of allyl *tert*-butyldimethylsilyl ether was low (Table 4, entry 19).

Chromatographic purification on a silica gel column allowed the major diastereoisomer of cyclopropanes **33**−**35**, **37**, **39**, **41**−**44**, **47**, and **48** to be isolated. For phenylcyclopropane **37** it was also possible to isolate the minor diastereoisomer in pure form. From the 1:1 mixture of diastereoisomers **40**, only the isomer with the higher R_f value was obtained in pure form from the column. Likewise, diastereomeric alcohols **42a**,**b** were easily separated. Conversely, column chromatography of the roughly 1:1 mixture of isomers **30**, led scarcely to enriched fractions in one of the two diastereoisomers. The relative configuration shown for compounds **29**, **32**, **33**, **37**, **41**, **42a**,**b**, **44**, and **50** and the structure of **46** were ascertained by either 2D NOESY or difference NOE experiments (see the Supporting Information).[30] In addition, the observed coupling constant (J = 10.0 Hz)[9a] between the cyclopropane protons of compound **29** is in agreement with a cis disposition of these hydrogens, proving that the stereochemistry of the alkene is retained in the cyclopropanation reaction. The stereochemistry assigned to cyclopropanes **31**, **34**−**36**, **39**, **43**, **47**, and **48** has been assumed by analogy.

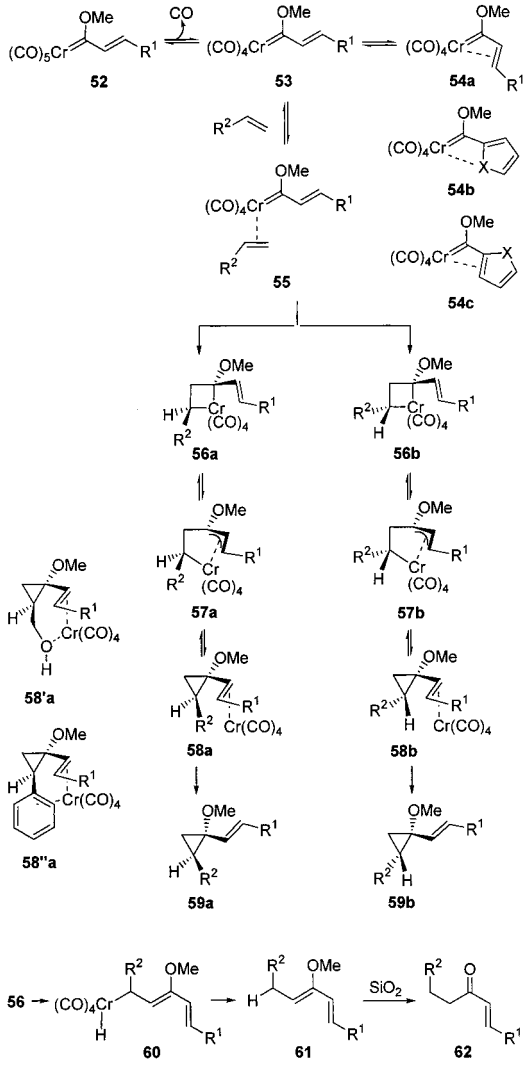
Regarding the nature of the alkyl-substituted alkene, some limitations of this route to cyclopropanes have been found. 1,1-Disubstituted olefins (2-methyl-1-pentene and methylenecyclopentane) and trisubstituted olefins (2-methyl-2-butene and 1-methyl-1-cyclopentene) failed to undergo cyclopropanation with carbene complexes **15a** or **18**. After 6−13 h at 95−100 °C in THF (sealed flask) unidentified mixtures of products were obtained. Similarly, no cyclopropanes could be detected in the complex reaction mixtures that originated when carbene complex **15a** was treated with diallylamine or allyl chloride.

Proposed Reaction Mechanism. For this thermal intermolecular cyclopropanation reaction of electronically neutral alkenes, we assume a mechanism analogous to the one which was initially proposed by Casey and Cesa to explain the cyclopropanation of electron-deficient olefins with Fischer carbene complexes.[32] This mechanistic proposal involves initial CO dissociation from the carbene complex, followed by coordination of the alkene and generation of a metallacyclobutane from which reductive elimination of the metal fragment leads to the cyclopropane derivative. On the other hand, our results demonstrate that only methoxy carbene complexes containing either an alkenyl group or a heteroaryl group directly bonded to the carbene carbon were able to transfer their carbene ligand to simple alkenes. In addition, this process showed generally a high degree of diastereoselectivity. The major diastereoisomer in each of these transformations was that in which the alkenyl or the heteroaryl group is *cis*-positioned with respect to the vicinal cyclopropane methine proton. Accordingly, a plausible mechanism to explain all of these results is presented in Scheme 6. Dissociation of a CO ligand from alkenyl carbene complex **52** generates a coordinatively unsaturated intermediate **53** which would be in equilibrium with chelated carbene−alkene π complex **54a**.[33,34] This intramolecular coordination of the C=

(31) Yoshida, Y.; Sakakura, Y.; Aso, N.; Okada, S.; Tanabe, Y. *Tetrahedron* **1999**, *55*, 2183.

(32) Casey, C. P.; Cesa, M. C. *Organometallics* **1982**, *1*, 87.

Scheme 6



C double bond to the metal center helps to stabilize reactive tetracarbonyl intermediate **53**, promoting its formation and therefore the cyclopropanation by increasing the probability of alternative stabilization by intermolecular coordination with the alkyl-substituted olefin to give carbene−alkene π complex **55**. For 2-heteroaryl carbene complexes **20** and **21**, either the heteroatom or the adequately positioned ring unsaturation could be playing a similar role, giving rise to chelate structures **54b** or **54c**. Formation of chelated carbene complexes **54a** is only possible if alkenylcarbene complexes **52** can readily adopt an s-cis conformation of the vinylcarbene functionality. This would explain why cyclic alkenylcarbene complex **VI**, which is locked in an s-trans conformation, failed to react.[35] However, cyclic alkenylcarbene complex **V**, locked in an s-cis conformation, did not undergo the cyclopropanation process either, which in this case could be due to the formation of a too stable chelate tetracarbonyl structure which would prevent the subsequently required intermolecular coordination of the olefin. As presented in Scheme 6, carbene−alkene π complex **55** undergoes a formal [2 + 2] cycloaddition to provide 16 electron metallacyclobutanes **56**[36] which could be in rapid equilibrium with the 18 electron π-allyl complexes **57**. A similar equilibrium was proposed by Harvey and Lund to explain the cyclopropanation of simple 1,3-dienes[9a] and later applied by Reissig and co-workers for the same reactions of electron-deficient 1,3-dienes[8b] and also to explain a formal [3 + 2] cycloaddition of chromium alkenylcarbene complexes to electron-deficient olefins.[37] Finally, reductive elimination from one of these intermediates **56** or **57** followed by decomplexation of the metal fragment from **58** leads to cyclopropanes **59**, where **59b** has the relative configuration of the major diastereoisomer isolated in these cyclopropanations. This cyclopropane stereochemistry would be determined by steric interactions between the alkenyl (or heteroaryl) substituent of the carbene ligand and the olefin alkyl chain in the initial π-complex **55** and at the subsequent cyclopropane forming stages **56**−**58**,[38] which would significantly disfavor the formation of the corresponding minor isomer **59a**. This proposal accounts for the observation of higher diastereoselectivity by increasing the size of either the R^1 (see for example ferrocenyl vs Ph) or R^2 (see for example *t*-Bu vs Bu) group. Similarly, cis-disubstituted olefins are predicted by this model to produce cyclopropane products with a high degree of diastereoselectivity (for example: *cis*-2-pentene, 99% de), whereas the corresponding trans isomers will generate diastereoisomeric intermediates **55**−**58** of comparable stability and, therefore, nearly equimolecular diastereoisomeric mixtures of cyclopropanes (trans-2-pentene, 0% de).[39] The lack of diastereoselectivity observed in the cyclopropanation of allyl alcohol could be justified by the presence of electronic interactions working in opposite direction to the steric effects which would deteriorate the diastereoselectivity of the cyclopropanation reaction. Intermediate **58′a**, which has the alkenyl and hydroxymethyl groups relatively cis-positioned, allows the simultaneous coordination of both of these groups to the metal center (18-electron configuration) which increase its stability in relation with the corresponding isomeric 16-electron complex containing the alkenyl and hydroxymethyl groups relatively trans-positioned and which do not have this ability.[8b,9a] This electronic stabilization makes the formation of the corresponding minor diastereoisomer **59a** less unfavorable. Silylation of the alcohol with the bulky TBDMS group or the rigidity imposed by the ring in 2-cyclopenten-1-ol hampers this bidentate coordination. In addition, the observation of considerably lower diastereoselectivity with an aromatic amine (*N*-allylaniline) than with a carbamate [*N*-(*tert*-butyloxycarbonyl)-allylamine] supports this interpretation. A similar argument

(33) A group 6 C−C double-bond chelated amino vinylcarbene complex analogous to **54a** has been isolated: (a) Barluenga, J.; Aznar, F.; Martín, A.; García-Granda, S.; Pérez-Carreño, E. *J. Am. Chem. Soc.* **1994**, *116*, 11191. For examples of the corresponding nonheteroatom stabilized derivatives, see: (b) Garrett, K. E.; Sheridan, J. B.; Pourreau, D. B.; Feng, W. C.; Geoffroy, G. L.; Staley, D. L.; Rheingold, A. L. *J. Am. Chem. Soc.* **1989**, *111*, 8383. (c) Mayr, A.; Asaro, M. F.; Glines, T. J.; Van Engen, D.; Tripp, G. M. *J. Am. Chem. Soc.* **1993**, *115*, 8187. For a review about the chemistry of η^3-allylidene complexes, see: (d) Mitsudo, T. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 1525.

(34) This equilibrium has been previously identified by a density functional study and by NMR analysis; see, respectively: (a) Gleichmann, M. M.; Dötz, K. H.; Hess, B. A. *J. Am. Chem. Soc.* **1996**, *118*, 10551. (b) Barluenga, J.; Aznar, F.; Gutiérrez, I.; Martín, A.; García-Granda, S.; LLorca-Baragaño, M. A. *J. Am. Chem. Soc.* **2000**, *122*, 1314.

(35) In addition, the aromatic nature of carbene complex **VI** will decrease its reactivity as indicated by the high thermal stability of this complex.

(36) This regioselectivity could be predicted based on the polarization of both the olefin carbon−carbon double bond and metal−carbene carbon bond of the carbene complex and is the one deduced from the constitution of formal insertion−hydrolysis products **26**, **28**, and **38**.

(37) Hoffmann, M.; Reissig, H.-U. *Synlett* **1995**, 625.

(38) Doyle, M. P.; Griffin, J. H.; Bagheri, V.; Dorow, R. L. *Organometallics* **1984**, *3*, 53.

(39) Alternatively, the non existing diastereoselectivity in the cyclopropanation reaction of *trans*-2-pentene could be due to low regioselectivity in the formation of the corresponding metallacyclobutanes **56**. This trans olefin with two similar substituents could form two regioisomeric metallacyclobutane intermediates of comparable stability which finally would lead to two different diastereoisomers. In this case, it can be said that this cyclopropanation reaction of cis and trans olefins is stereospecific. We thank one of the referees for calling our attention to this possibility.

could be invoked to explain the low diastereoselectivity attained with styrene. In this case the ability of complex **58″a** to coordinate the $Cr(CO)_4$ fragment to both the alkenyl and the phenyl (η^2 fashion) substituents would relatively favor formation of the minor diastereoisomer. Finally, the minor insertion-hydrolysis products **26**, **28**, and **38** isolated in some reactions could arise from intermediate **56** through a formal β-hydrogen elimination, giving hydridochromium complex **60** which undergoes reductive elimination affording methyl enol ethers **61**.[6b,40,41] Hydrolysis of enol ethers **61** during workup and mainly at the time of the chromatographic purification finally led to ketones **62**.

Conclusion

The results reported herein represent the first developed intermolecular cyclopropanation of electronically neutral alkenes with heteroatom-stabilized group 6 Fischer carbene complexes. The reaction, which occurs under thermal conditions, is general between alkoxy(alkenyl)- or alkoxy(2-heteroaryl)carbene complexes of chromium and terminal or either acyclic or cyclic 1,2-disubstituted simple olefins, and in addition takes place with a high degree of diastereoselectivity, representing a useful method for the diastereoselective synthesis of functionalized alkoxycyclopropanes. This [2 + 1] cycloaddition reaction can be successfully carried out with only equimolecular amounts of starting materials when nonvolatile alkenes are employed. Unconjugated dienes underwent regioselective cyclopropanation at the less substituted carbon−carbon double bond, while with enynic substrates the reaction with the alkyne is largely favored. The process showed a good functional group tolerance at the olefin allylic position. However, alkenes with a good leaving group at the allylic position seem to generate unstable cyclopropanes which alternatively have been found to undergo spontaneous ring opening due to the 1,2 substitution by an electron-donating group (OMe) and an alkyl chain (CH_2Br, CH_2-OTs) containing a good leaving group at the α position. The ability of the carbene complex to generate a chelated tetracarbonyl complex intermediate is proposed as a key step in the suggested reaction mechanism, whereas the cyclopropane stereochemistry can be explained mainly on the basis of steric interactions.

Experimental Section[42]

Pentacarbonyl[(*E*)-3-ferrocenyl-1-methoxy-2-propenylidene]chromium (1). To a solution of pentacarbonyl[(methoxy)(methyl)methylene]-chromium (6.3 g, 25 mmol) in Et_2O (150 mL) at room temperature were successively added triethylamine (13.94 mL, 100 mmol), ferrocenecarbaldehyde (6.42 g, 30 mmol), and chlorotrimethylsilane (9.52 mL, 75 mmol). The mixture was stirred at room temperature for 48 h. Silica gel (ca. 25 g) was then added, and the solvent was removed under reduced pressure. The residue was loaded onto a silica gel column under N_2. Elution with hexane gave 8.35 g (18.72 mmol, 75%) of carbene complex **1** as a dark violet solid. Melting point 105−107 °C; $R_f = 0.30$ (hexane); ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.22 (s, 5H), 4.60 (br s, 4H), 4.70 (s, 3H), 7.19 (d, $J = 15.0$ Hz, 1H), 7.52 (d, $J = 15.0$ Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 65.6, 69.9, 70.3, 72.6, 78.3, 137.5, 138.0, 217.1, 224.2, 326.0; IR (KBr) υ 3020 (s), 2401 (w), 2361 (w), 2054 (m), 1939 (s), 1575 (m), 1541 (w), 1423 (w), 1217 (s); low-resolution mass spectroscopy (LRMS) (70 eV, EI) *m*/*z* (%) 446 (M^+, 20), 418 (15), 332 (30), 306 (80), 270 (90), 237 (25), 220 (45), 205 (46), 186 (75), 149 (40), 121 (100); high-resolution mass spectroscopy (HRMS) (70 eV, EI) calcd for $C_{19}H_{14}CrFeO_6$ (M^+) 445.9545, found 445.9564. Anal. Calcd for $C_{19}H_{14}CrFeO_6$: C, 51.15; H, 3.16. Found: C, 51.22; H, 3.06.

General Procedure for the Cyclopropanation Reactions in DMF with 20 equiv of Olefin. A mixture of carbene complex **1** (223 mg, 0.5 mmol), the corresponding alkene (10 mmol), and 2,6-di-*tert*-butyl-4-methylphenol (BHT, 5 mg, 0.02 mmol) in DMF (20 mL) was refluxed for a period of 25−35 min (2−2.5 h for compounds **4**, **7**, and **11**). Upon cooling to room temperature the solvent was removed under reduced pressure and the resulting residue was dissolved in hexane and filtered throught a plug of Celite. Evaporation of the volatiles and column chromatography (silica gel) afforded pure compounds **3**−**11**. For compounds **3**, **5**, and **9**, the major diastereoisomer was separated by this procedure. Yields are described in Scheme 1 and Table 1.

(1*S,2*R**)-2-Butyl-1-[(*E*)-2-ferrocenylethenyl]-1-methoxycyclopropane (3).** Orange oil; $R_f = 0.30$ (hexane: CH_2Cl_2, 4:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.60 (dd, $J = 7.01$, 4.58 Hz, 1H), 0.84−1.00 (m, 5H), 1.42−1.50 (m, 5H), 1.64 (m, 1H), 3.39 (s, 3H), 4.13 (s, 5H), 4.21 (t, $J = 1.83$ Hz, 2H), 4.33 (t, $J = 1.83$ Hz, 2H), 5.64 (d, $J = 15.8$ Hz, 1H), 6.21 (d, $J = 15.8$ Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.1, 18.3, 22.5, 27.4, 28.0, 31.9, 55.5, 65.5, 66.2, 66.4, 68.3, 69.0, 83.3, 124.3, 128.8; LRMS (70 eV, EI) *m*/*z* (%) 338 (M^+, 100), 307 (10), 214 (10), 186 (20), 121 (20), 44 (15), 36 (20); HRMS (70 eV, EI) calcd for $C_{20}H_{26}FeO$ (M^+) 338.1333, found 338.1332. Anal. Calcd for $C_{20}H_{26}FeO$: C, 71.01; H, 7.75. Found: C, 70.79; H, 7.97.

***meso*-(1*R*,2*S*,3*S*,4*R*,5*S*)-3-[(*E*)-2-Ferrocenylethenyl]-3-methoxytricyclo[3.2.1.0^{2,4}]octane (7).** Orange solid. Data on the 95:5 mixture of diastereoisomers; $R_f = 0.30$ (hexane/EtOAc, 4:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.81 (d, $J = 5.3$ Hz, 1H), 0.98 (s, 2H), 1.20−1.48 (m, 2H), 1.41−1.62 (m, 2H), 1.92 (d, $J = 5.3$ Hz, 1H), 2.63 (s, 2H), 3.35 (s, 3H), 4.11 (s, 5H), 4.18 (s, 2H), 4.31 (s, 2H), 5.42 (d, $J = 15.6$ Hz, 1H), 6.18 (d, $J = 15.6$ Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 29.7, 30.9, 32.6, 36.9, 54.9, 66.2, 68.3, 68.6, 68.9, 83.6, 123.5, 129.7; LRMS (70 eV, EI) *m*/*z* (%) 349 (20), 348 (M^+, 100), 333 (10), 317 (15); HRMS (70 eV, EI) calcd for $C_{21}H_{24}FeO$ (M^+) 348.1176, found 348.1168.

(1*S,2*S**)-2-(3-Cyclohexenyl)-1-[(*E*)-2-ferrocenylethenyl]-1-methoxycyclopropane (10).** Orange oil. Data on the 1:1 mixture of diastereoisomers; $R_f = 0.56$ (hexane/EtOAc, 9:1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.66, 0.78 (m, 1H), 0.82−0.92 (m, 2H), 1.39−1.60 (m, 2H), 1.82−1.98 (m, 2H), 2.09−2.25 (m, 3H), 3.38 (s, 3H), 4.11 (s, 5H), 4.20 (t, $J = 1.83$ Hz, 2H), 4.33 (t, $J = 1.83$ Hz, 2H), 5.60−5.71 (m, 3H), 6.20, 6.22 (2d, $J = 15.8$ Hz, 1H of each isomer); ^{13}C NMR (50.0 MHz, $CDCl_3$) δ 16.8, 25.0, 28.2, 29.2, 31.3, 31.9, 32.8, 33.0, 33.7, 33.9, 55.5, 65.4, 65.7, 66.3, 66.5, 68.4, 69.0, 83.3, 124.3, 126.5, 126.6, 127.1, 128.9; LRMS (70 eV, EI) *m*/*z* (%) 362 (M^+, 100), 266 (10), 229 (10), 199 (25), 186 (20), 121 (15); HRMS (70 eV, EI) calcd for $C_{22}H_{26}FeO$ (M^+) 362.1333, found 362.1337. Anal. Calcd for $C_{22}H_{26}$-FeO: C, 72.94; H, 7.23. Found: C, 72.66; H, 7.38.

General Procedure for the Cyclopropanation Reactions in THF with 5 or 1 equiv of Olefin. A mixture of the appropriate carbene complex **1**, **15a**,**b**,**c**, **17**−**21**, **I**−**VI** (1 mmol) and the corresponding alkene (5 or 1 mmol) in THF (15 mL) was introduced in a sealed flask and was heated in an oil bath at 95−110 °C (unless otherwise noted in Tables 2−4) until disappearance of the color of the starting carbene complex (reaction times are given in Tables 2−4). Most often an initial dark red solution turned brown. For carbene complexes **1** and **VI**, the initial THF solutions are violet and those of carbene complexes **17** and **21** are orange. When allyl alcohol and 2-cyclopenten-1-ol were used as alkenes, green final solutions were observed. After thermolysis, the reaction mixture was cooled to room temperature, the solvent was removed under reduced pressure, and the residue was dissolved in hexane and exposed to sunlight and air during 0.5−1 h to remove metal species. The resulting mixture was filtered through a short pad of Celite and then the volatiles were evaporated. The remaining oil was purified by column chromatography (silica gel) to give compounds **3**, **16**, and **22**−**48**. Yields are listed in Tables 2−4. The major diastereoisomer of **16**, **22**−**25**, **33**−**35**, **37**, **39**, **41**−**44**, **47**, and **48** was separated by this

(40) It was suggested that enol ethers similar to **61** are formed by acid-catalyzed rearrangement from the corresponding donor−acceptor-substituted cyclopropanes: see ref 3c.

(41) Indeed, ^{1}H NMR analysis of the crude reaction mixtures suggested the presence of **61** (a triplet signal appearing at δ 4.80 (precursor of **26**), 4.92 (precursor of **28**), 5.00 (precursor of **38**) and a multiplet at 2.30 (precursor of **26**), 2.06 (precursor of **28**), or doublet signal at 3.69 (precursor of **38**)).

(42) General information, experimental procedures, and spectral data for compounds not described here are provided in the Supporting Information.

procedure. This technique also allowed the minor diastereoisomer of **37** and diastereomeric alcohols **42a**,**b** to be separated.

(1*S,2*R**)-2-Butyl-1-methoxy-1-[(*E*)-2-phenylethenyl]cyclopropane (16).** Colorless oil; R_f = 0.27 (hexane/CH_2Cl_2, 9:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.70 (dd, J = 6.41, 4.88 Hz, 1H), 0.87−1.00 (m, 4H), 1.03−1.12 (m, 1H), 1.38−1.49 (m, 5H), 1.59−1.75 (m, 1H), 3.41 (s, 3H), 5.99 (d, J = 16.2 Hz, 1H), 6.51 (d, J = 16.2 Hz, 1H), 7.20−7.26 (m, 1H), 7.28−7.43 (m, 4H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.1, 18.8, 22.5, 27.5, 28.5, 31.8, 55.8, 65.5, 125.8, 126.4, 126.8, 128.5, 132.3, 137.1. Anal. Calcd for $C_{16}H_{22}O$: C, 83.43; H, 9.63. Found: C, 83.54; H, 9.59.

(1*S,2*R**)-2-Butyl-1-(1-cyclohexenyl)-1-methoxycyclopropane (24).** Colorless oil; R_f = 0.60 (hexane/EtOAc, 95:5); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.28 (dd, J = 5.6, 4.2 Hz, 1H), 0.75−0.84 (m, 2H), 0.91 (t, J = 7.0 Hz, 3H), 1.24−1.39 (m, 5H), 1.52−1.66 (2m, 5H), 1.94−2.11 (m, 4H), 3.15 (s, 3H), 5.59 (t, J = 1.6 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.1, 15.1, 22.5, 22.6, 22.8, 25.0, 25.2, 25.5, 27.4, 32.2, 54.3, 68.4, 123.3, 136.4.

(1*S,2*R**)-2-Butyl-1-(2-furyl)-1-methoxycyclopropane (25).** Yellow oil; R_f = 0.33 (hexane/EtOAc, 95:5); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.66 (dd, J = 6.7, 5.4 Hz, 1H), 0.91 (t, J = 7.0 Hz, 3H), 1.10 (dd, J = 9.6, 5.4 Hz, 1H), 1.14−1.25 (m, 1H), 1.32−1.49 (m, 5H), 1.61−1.71 (m, 1H), 3.30 (s, 3H), 6.18 (m, 1H), 6.30 (dd, J = 3.2, 1.6 Hz, 1H), 7.32 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 17.4, 22.5, 26.7, 27.1, 31.8, 55.8, 61.4, 106.1, 110.0, 141.5, 155.3; LRMS (70 eV, EI) *m*/*z* (%) 194 (M^+, 17), 163 (13), 137 (100), 95 (16). HRMS (70 eV, EI) calcd for $C_{12}H_{18}O_2$ (M^+) 194.1307, found 194.1310. Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.17; H, 9.38.

(1*R,2*S**,3*R**)-2-Ethyl-1-methoxy-3-methyl-1-[(*E*)-2-phenylethenyl]cyclopropane (29).** Colorless oil; R_f = 0.40 (hexane/EtOAc, 95:5); ^{1}H NMR (300 MHz, d_6−PhH) δ 0.89 (dt, J = 10.0, 7.1 Hz, 1H), 1.00−1.15 (m with t at 1.13, J = 7.4 Hz, 4H), 1.22 (d, J = 6.3 Hz, 3H), 1.52−1.80 (2m, 2H), 3.34 (s, 3H), 6.16 (d, J = 16.1 Hz, 1H), 6.62 (d, J = 16.1 Hz, 1H), 7.10−7.40 (m, 5H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 6.8, 14.0, 15.6, 22.5, 30.7, 55.8, 65.6, 125.7, 126.3, 126.7, 128.3, 133.1, 137.0; LRMS (70 eV, EI) *m*/*z* (%) 216 (M^+, 4), 215 (10), 131 (27), 105 (100), 91 (28), 77 (41); HRMS (70 eV, EI) calcd for $C_{15}H_{20}O$ (M^+) 216.1514, found 216.1509.

***meso*-(1*R*,5*S*,6*S*)-6-Methoxy-6-[(*E*)-2-phenylethenyl]bicyclo[3.1.0]-hexane (32).** Colorless oil; R_f = 0.90 (hexane/EtOAc, 95:5); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.62 (m, 2H), 1.66−1.84 (m, 1H), 1.98−2.05 (m, 5H), 3.46 (s, 3H), 5.95 (d, J = 16.1 Hz, 1H), 6.44 (d, J = 16.1 Hz, 1H), 7.20−7.39 (m, 5H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 24.9, 26.4, 32.9, 55.7, 69.4, 125.7, 126.0, 126.6, 128.3, 131.7, 137.0; LRMS (70 eV, EI) *m*/*z* (%) 214 (M^+, 7), 213 (12), 105 (100), 91 (50), 77(45); HRMS (70 eV, EI) calcd for $C_{15}H_{18}O$ (M^+) 214.1358, found 214.1352. Anal. Calcd for $C_{15}H_{18}O$: C, 84.06; H, 8.46. Found: C, 84.00; H, 8.37.

(1*R,2*S**)-2-(*tert*-Butyldimethylsilyloxymethyl)-1-methoxy-1-[(*E*)-2-phenylethenyl]cyclopropane (41).** Colorless oil; R_f = 0.40 (hexane/EtOAc, 95:5); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.12 (s, 3H), 0.13 (s, 3H), 0.87 (dd, J = 7.1, 5.6 Hz, 1H), 0.95 (s, 9H), 1.01 (dd, J = 9.5, 5.6 Hz, 1H), 1.42 (apparent dq, J = 9.5, 6.9 Hz, 1H), 3.43 (s, 3H), 3.84 (d, J = 6.7 Hz, 2H), 6.05 (d, J = 16.0 Hz, 1H), 6.55 (d, J = 16.0 Hz, 1H), 7.20−7.43 (m, 5H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ −5.24, −5.21, 17.3, 18.3, 25.9, 29.6, 55.7, 61.8, 65.5, 126.0, 127.1, 127.6, 128.4, 130.8, 136.8; LRMS (70 eV, EI) *m*/*z* (%) 318 (M^+, 3), 317 (9), 287 (60), 186 (65), 173 (62), 89 (100), 73 (89); HRMS (70 eV, EI) calcd for $C_{19}H_{30}O_2Si$ (M^+) 318.2015, found 318.2021. Anal. Calcd for $C_{19}H_{30}O_2Si$: C, 71.64; H, 9.49. Found: C, 71.78; H, 9.36.

Acknowledgment. Support for this research by the Dirección General de Investigación Científica y Técnica (DGICYT) of Spain (grants PB92-1005 and PB97-1271) is gratefully acknowledged. A.F.A. thanks the Departamento de Educación, Universidades e Investigación del País Vasco, for a postdoctoral fellowship.

Supporting Information Available: General experimental information; analytical and spectral data for compounds **4**-**6**, **8**, **9**, **11**, **12**, **22**, **23**, **26**−**28**, **30**, **31**, **33**−**40**, **42a**,**b** and **43**−**48**; experimental procedures and spectral data for **13**, **14**, and **50**; and schemes showing observed difference NOE's enhancements for compounds **4**−**7**, **9**, **22**, **23**, **29**, **32**, **37**, **41**, and **44** and NOEs enhancements from 2D NOESY spectra for compounds **24**, **25**, **29**, **33**, **42a**,**b**, **46**, and **50**. This material is available free of charge via the Internet at http://pubs.acs.org. See any current masthead page for ordering information and Web access instructions.

JA000694B