1528 *Organometallics* **2005,** *24,* 1528−1532

Functionalization of Primary Carbon−Hydrogen Bonds of Alkanes by Carbene Insertion with a Silver-Based Catalyst

Juan Urbano,[†] Tomás R. Belderraín,[†] M. Carmen Nicasio,[†]
Swiatoslaw Trofimenko,[‡] M. Mar Díaz-Requejo,[*,†] and Pedro J. Pérez[*,†]

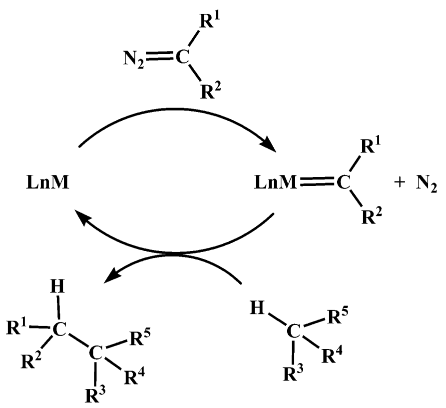
Departamento de Química y Ciencia de Materiales, Universidad de Huelva, Campus de El Carmen, 21071 Huelva, Spain, and Department of Chemistry and Biochemistry, University of Delaware, Newark, Delaware 19716

Received January 12, 2005

The complexes $[Tp^{Br3}Ag]_2 \cdot CH_3COCH_3$ (**1**) and $Tp^{Br3}Ag(thf)$ (**2**) catalyze the insertion of the :$CHCO_2Et$ group from ethyl diazoacetate (EDA) into the saturated C−H bonds of several C5, C6, and C8 linear and branched alkanes. In addition to secondary and/or tertiary sites, the unprecedented insertion into the primary C−H bonds of the substrates studied has been observed with variable regioselectivity, toward the methyl groups, within the range of 40−60% for branched and nearly 25% for linear alkanes.

Introduction

Scheme 1. Transition-Metal-Catalyzed Functionalization of Carbon−Hydrogen Bonds by Carbene Insertion



In the past decade, the intermolecular, metal-catalyzed functionalization of C−H bonds by means of the insertion of carbene units transferred from diazo compounds (Scheme 1) has emerged.[1] After the seminal work by Noels et al.,[2] only a few reports have appeared in the literature,[3,4] until Davies and co-workers developed rhodium-based, chiral catalysts that have provided high conversions as well as asymmetric induction with many substrates.[5] Although first employed in this area,[6] copper-based catalysts were clearly displaced by rhodium on the basis of the observed differences in activity. Only very recently has our group demonstrated the catalytic capabilities of a family of complexes of general formula $Tp^xCu(L)$ (Tp^x = homoscorpionate ligand) to induce the above transformation, leading to the functionalization of several C−H bonds of alkanes and ethers.[7] After this work, related behavior has been described with the analogues $Tp^{(CF3)2}M(THF)$ (M = Cu, Ag).[8] On the basis of the lack of effective catalytic systems reported for the insertion of diazo compounds into the primary C−H bonds, we have focused our efforts on the development of a new catalyst that could enforce the insertion of EDA into such primary, nonactivated sites of regular alkanes. Previous studies have shown that the transient metallocarbene species depicted in Scheme 1, generated in situ from the appropriate transition-metal complex and a diazo compound, is electrophilic in nature.[2−4,9,10] A recent work by Zhou and co-workers[11] has demonstrated with the M(CO)Cl compounds (M = Cu, Ag) that the silver center displays a

---

[†] Universidad de Huelva.

[‡] University of Delaware.

(1) Davies, H. M. L.; Beckwith, R. E. J. *Chem. Rev.* **2003**, *103*, 2861.

(2) (a) Demonceau, A.; Noels, A. F.; Hubert, A.; Teyssié, P. *J. Chem. Soc., Chem. Commun.* **1981**, 688. (b) Demonceau, A.; Noels, A. F.; Hubert, A.; Teyssié, P, *Bull. Soc. Chim. Belg.* **1984**, *93*, 945. (c) Demonceau, A.; Noels, A. F.; Teyssie, P.; Hubert, A. *J. Mol. Catal.* **1988**, *49*, L13. (d) Demonceau, A.; Noels, A. F.; Hubert, A. *J. Mol. Catal.* **1989**, *57*, 149. (e) Demonceau, A.; Noels, A. F.; Costa, J. L.; Hubert, A. *J. Mol. Catal.* **1990**, *58*, 21.

(3) (a) Doyle, M. P. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon Press: Oxford, U.K., 1995; Vol. 12, p 421. (b) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; Wiley: New York, 1998.

(4) (a) Callot, H. J.; Metz, F. *Tetrahedron Lett.* **1982**, *23*, 4321. (b) Callot, H. J.; Metz, F. *Nouv. J. Chem.* **1985**, *9*, 167. (c) Adams, J.; Poupart, M.-A.; Schller, C.; Ouimet, N.; Frenette, R. *Tetrahedron Lett.* **1989**, *14*, 1749. (d) Müller, P.; Tohill, S. *Tetrahedron* **2000**, *56*, 1725

(5) For alkane functionalization see: (a) Davies, H. M. L.; Hansen, T.; Churchill, M. R. J. *J. Am. Chem. Soc.* **2000**, *122*, 3063. (b) Davies, H. M. L.; Antoulinakis, E. G. *J. Organomet. Chem.* **2001**, *617−618*, 39.

(6) (a) Scott, L. T.; DeCicco, G. J. *J. Am. Chem. Soc.* **1974**, *96*, 322. (b) Wulfman, D. S.; McDaniel, R. S.; Peace, B. W. *Tetrahedron* **1976**, *32*, 1241.

(7) (a) Díaz-Requejo, M. M.; Belderrain, T. R.; Nicasio, M. C.; Trofimenko, S.; Pérez, P. J. *J. Am. Chem. Soc.* **2002**, *124*, 896. (b) Caballero, A.; Díaz-Requejo, M. M.; Belderrain, T. R.; Nicasio, M. C.; Trofimenko, S.; Pérez, P. J. *J. Am. Chem. Soc.* **2003**, *125*, 1446. (c) Caballero, A.; Díaz-Requejo, M. M.; Belderrain, T. R.; Nicasio, M. C.; Trofimenko, S.; Pérez, P. J. *Organometallics* **2003**, *22*, 4145.

(8) Dias, H. V. R.; Browning, R. G.; Richey, S. A.; Lovely, C. J. *Organometallics* **2004**, *23*, 1200.

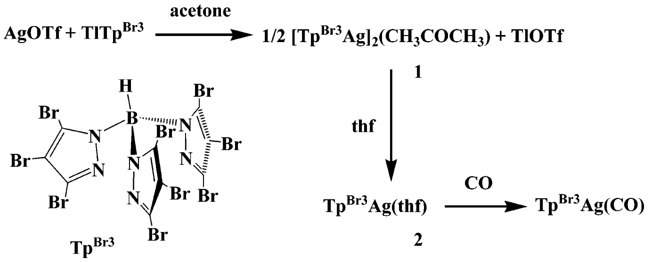
(9) Straub, B. F.; Hofmann, P. *Angew. Chem., Int. Ed.* **2001**, *40*, 1288.

(10) Kirmse, W. *Angew. Chem., Int. Ed.* **2003**, *42*, 1088.

(11) Shao, L.; Zhang, L.; Zhou, M.; Qin, Q. *Organometallics* **2001**, *20*, 1137.

10.1021/om050024k CCC: $30.25

Scheme 2. Preparation of Complexes 1 and 2

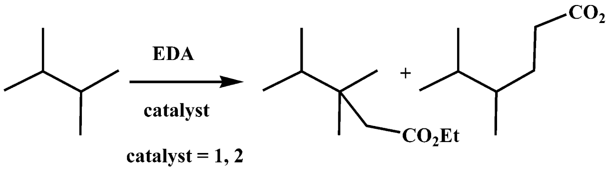


lower electron density, a feature that, when translated into the metallocarbene intermediate shown in Scheme 1, should increase the electrophilicity of such species.

Results and Discussion

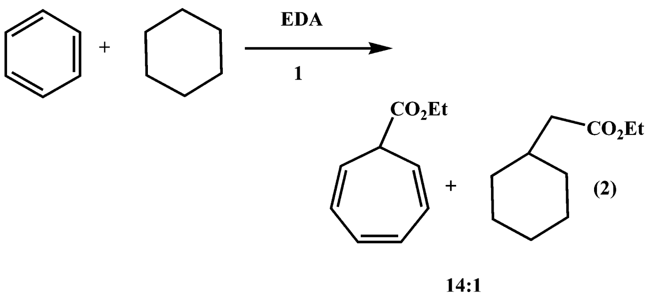
With the above idea in mind, we carried out the reaction of silver triflate and the thallium salt of the Tp^{Br3} ligand in acetone as the solvent (Scheme 2). After several hours of stirring, a white solid precipitated from the originally colorless solution. On the basis of the spectroscopic and elemental analysis data, we propose the formulation $[Tp^{Br3}Ag]_2{\cdot}CH_3COCH_3$ (**1**) for this new compound. This complex displays very low solubility in most common solvents, a fact that could be related to a dinuclear structure similar to that observed for $[TpCu]_2$ and related complexes.[12] However, it readily dissolves in tetrahydrofuran, with the immediate formation of the complex $Tp^{Br3}Ag(thf)$ (**2**), which has also been isolated and characterized. When CO was passed through a solution of **2** in thf, the monocarbonyl adduct $Tp^{Br3}Ag(CO)$ was formed, as inferred from the observation in the IR spectrum of the solution of an absorption centered at 2153 cm^{-1}. This value clearly indicates the absence of back-donation from the metal to the CO ligand,[13] underscoring the extremely low density at the silver center (the copper analogue displayed a ν(CO) value of 2107 cm^{-1}),[7b] a characteristic that we were pursuing to enhance the potential catalytic activity.

As a probe, we ran two experiments, using **1** and **2** as the catalyst, with 2,3-dimethylbutane as the substrate and ethyl diazoacetate as the carbene source in a one-pot experiment in which the catalyst, the substrate and EDA were stirred for a few hours (eq 1). After workup, NMR studies revealed that, in addition to the product derived from the insertion of the :$CHCO_2Et$ unit into the tertiary C−H bond, a second, major product was also obtained, as the result of its insertion into one of the primary C−H bonds of the substrate. A 98% yield, based on EDA, was observed, with a 59:39 primary to secondary ratio of products. After these completely unprecedented results, we extended this study to several C5, C6, and C8 linear and branched alkanes. Table 1 displays the results obtained with **1** as catalyst,[14] demonstrating the general insertion of :$CHCO_2Et$ (from EDA) into the primary carbon−hydrogen bonds in all cases.[15] The yields of the products formed from the functionalization of the primary sites varied from nearly 25% in linear alkanes (entries 1 and 2) to 40−60% in the remaining substrates, with the exception of 2,5-dimethylpentane, which gave a 79% yield. Secondary and tertiary sites were also activated, when available (entries 3−8). The high chemoselectivity induced by these catalysts is also worth mentioning, since overall conversions into the insertion products ranged from 92 to 98%, with diethyl fumarate and maleate (from EDA coupling) accounting for the balance of the initial EDA, despite the absence of any slow addition device, a feature specific to this silver-based system.



(1)

Some comments must be pointed out regarding the regioselectivity obtained with the substrates employed in this study. The primary to secondary ratio of products obtained for *n*-pentane (29:71) is somewhat similar to those obtained in metal-free, photochemical (32:68) and thermal (33:67) processes.[2e] A similar behavior was observed for 2,3-dimethylbutane, where the primary to tertiary ratio of 60:40 compares well with the 61:39 and 59:41 ratios produced under photochemical and thermal conditions, respectively. It could be thought that free carbenes of type :$CHCO_2Et$ might be involved in this process. In fact, Noels et al. reported,[2e] in the case of carbenes generated from diazomalonate, that free carbenes could be formed in the presence of rhodium catalysts. Although this was never proposed with EDA as the carbene source, we decided to investigate this route and carried out several experiments. First, we have prepared the complex $Tp^{Ms}Ag(CH_2Cl_2)$ (**3**; Tp^{Ms} = hydrotris(3-mesityl)pyrazolylborate) and studied its catalytic activity. When 2,3-dimethylbutane was used as the substrate, we found that the Tp^{Ms}-containing catalyst provided a primary to tertiary distribution of products of 35:65, nearly the opposite of that obtained with **1** (Table 1), therefore demonstrating the role of the Tp^x-Ag core in the carbene transfer reaction. Second, in a competition experiment carried out with benzene and cyclohexane using **1** as the catalyst, a 14:1 ratio of ethyl cycloheptatrienecarboxylate and ethyl cyclohexyl acetate (eq 2) was observed, very far from the expected 1:1 described for thermally or photochemically generated free carbenes, and almost double that reported with



(2)

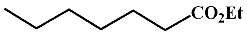
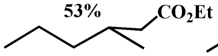
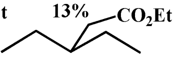
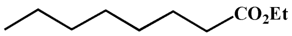
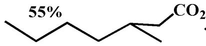
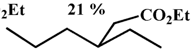
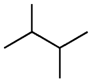
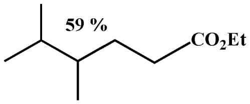
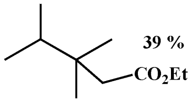
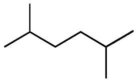
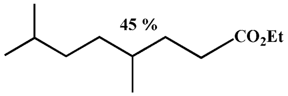
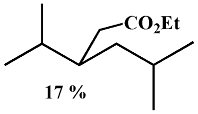
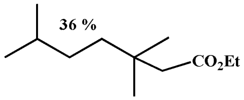
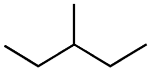
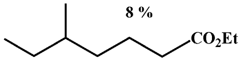
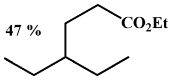
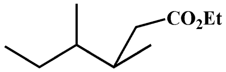
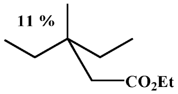
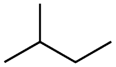
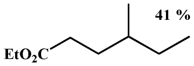
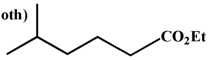
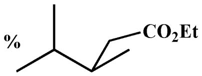
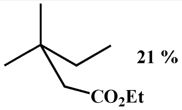
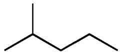
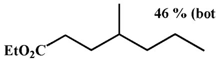
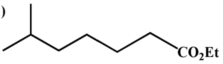
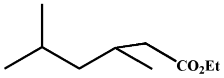
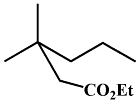
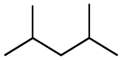
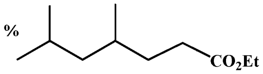
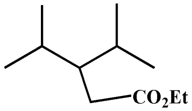
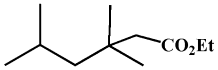
---

[12] (a) Trofimenko, S. *Scorpionates, The Coordination Chemistry of Polypyrazolylborate Ligands*; Imperial College Press: 1999. (b) Mealli, C.; Arcus, C. S.; Wilkinson, J. L.; Marks, T. J.; Ibers, J. *J. Am. Chem. Soc.* **1976**, *98*, 711. (c) Abu Salah, O. M.; Bruce, M. I. *J. Organomet. Chem.* **1975**, *87*, C15.

[13] Weber, L. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1077. (b) Willner, H.; Aubke, F. *Angew. Chem., Int. Ed.* **1997**, *36*, 2402.

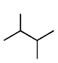
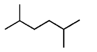
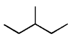
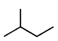
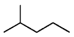
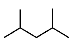
[14] Complex **2** can also be alternatively employed, identical results being obtained, probably due to the formation of a common species of composition $Tp^{Br3}Ag$ acting as the real catalyst.

Table 1. Functionalization of Carbon−Hydrogen Bonds of Hydrocarbons by Insertion of Ethyl Diazoacetate Using 1 as the Catalyst[a]

Entry	Substrate	Primary C-H Products^{b}	Secondary C-H Products^{b}	Tertiary C-H Products^{b}	Others^{c}
1	n-pentane	27% 	53%  13% 	---	7 %
2	n-hexane	22% 	55%  21 % 	---	2 %
3		59 % 	---	39 % 	2%
4		45 % 	 17 %	36 % 	2%
5		8 %  47 % 	 32 %	11 % 	2%
6		41 % (both)  	36 % 	 21 %	2%
7		46 % (both)  	36 % 	19 % 	8 %
8		79 % 	6 % 	13 % 	2%

[a] See Experimental Section. [b] Percentage of products at the end of the reaction, determined by ^{1}H NMR. [c] Diethyl fumarate and maleate and ethyl glycidate as byproducts.

Table 2. Observed Regioselectivity[a] for the Alkane Functionalization by Carbene (from EDA) Insertion Using 1 as the Catalyst

Entry	Substrate	Primary sites	Secondary sites	Tertiary sites
1	n-pentane	1	2.44	---
2	n-hexane	1	2.25	---
3		1	---	3.66
4		1	1.13	4.8
5		1	1.33	1.8
6		1	3.95	4.17
7		1	1.76	3.71
8		1	0.45	0.98

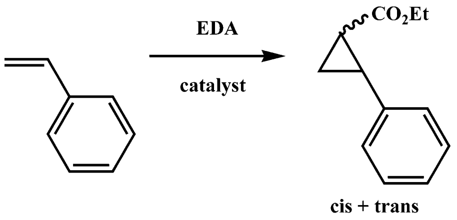
[a] Values normalized for the relative number of C−H bonds of each type.

rhodium (6:1).[16] These results are clearly in disagreement with the involvement of free carbenes in this process.

Table 2 displays the values of the selectivities toward primary, secondary, and tertiary sites, corrected by the number of C−H bonds of each type. It is observable that the tertiary sites are more prone to undergo the insertion of the carbene unit, with the primary sites being the least reactive (2,4-dimethylpentane could be an exception, due to the large number of primary sites). This is in good accord with the sequence of bond energies tertiary < secondary < primary and is in contrast with the steric effect of those sites. This sequence, identical with that already observed with the $Tp^{Br3}Cu(NCMe)$ catalyst,[7b] could be interpreted as the prevalence of the electronic effects in this transformation. The steric hindrance influences the selectivity to a certain degree, although it does not overcome the electronic effect.

An obvious question arises after those results: what makes the difference between the already reported $Tp^{Br3}Cu(NCMe)$[7b,c] and the silver catalyst? We believe that the main factor is the different electronic density located at the metal center. We base this proposal on the following. The effective ionic radii for Cu(I) and Ag(I) in a tetracoordinate environment are 0.74 and 1.14 Å, which would explain the existence of a higher catalytic pocket in the case of silver. The styrene cyclopropanation[17] with EDA in the presence of both the copper and the silver catalysts have provided cis:trans ratios of 58:42 and 50:50 (Scheme 3), respectively, the yield of the more sterically demanding trans isomer being increased with **1** as the catalyst. Therefore, the observation of primary C−H bond functionalization in the silver case, in comparison to copper, is mainly due to the increase in electrophilic character, the steric hindrance of the catalyst, and the substrate contributing in a certain, but not decisive, degree to the selectivity.

Scheme 3. Styrene Cyclopropanation with EDA Using Copper and Silver Catalysts



catalyst	cis:trans
$Tp^{Br3}Cu(NCMe)$	58:42
$Tp^{Br3}Ag(thf)$	50:50

Conclusions

We have developed very highly active silver catalysts (**1** and **2**) for the functionalization of C−H bonds by carbene insertion from ethyl diazoacetate. These catalysts are capable of inserting the :$CHCO_2Et$ fragment not only into tertiary and secondary sites but also into the primary sites of alkanes. Their reactivities are comparable to those of free carbenes, although the carbene transfer proceeds from the metal center. The design of new ligands with defined electronic and steric effects that would enhance the activation of primary sites is currently underway in our laboratory.

Experimental Section

General Considerations. ^1H NMR spectra were run at 400 MHz and ^{13}C NMR at 100 MHz, using $CDCl_3$ as solvent. Mass spectra were carried out in a Varian Saturn 2100T. GC analyses were recorded with a Varian CP-3800. Solvents were dried and degassed before use. All the hydrocarbons were purchased and employed without any further purification.

Synthesis and Characterization of $[Tp^{Br3}Ag]_2 \cdot CH_3COCH_3$ (1). Silver triflate (128.5 mg, 0.5 mmol) was added to a solution of $TlTp^{Br3}$ (563.5 mg, 0.5 mmol) in acetone. After 20 h of stirring in the dark, a white solid precipitated from the initially colorless solution. The solid was filtered off and dried under vacuum to give complex **1** in 80% yield. Anal. Calcd for $C_{21}H_8N_{12}OBr_{18}B_2Ag$: C, 11.90; H, 0.38; N, 7.93. Found for **1**: C, 11.47; H, 0.33; N, 8.02. IR (Nujol mull): ν(B−H) 2552 cm^{-1}, ν(CO) 1704 cm^{-1}. Complex **1** is quite insoluble in most deuterated solvents. A solution of **1** in thf-d_8 was readily achieved, however, due to the exchange of coordinated acetone and the corresponding formation of **2**.

Synthesis and Characterization of $Tp^{Br3}Ag(thf)$ (2). Complex **1** (0.1 mmol) was stirred in thf (20 mL) for 30 min in the dark. After the removal of the volatiles under reduced pressure, a white solid was obtained in quantitative yield. Anal. Calcd for $C_{13}H_9N_6OBr_9BAg$: C, 14.60; H, 0.82; N, 7.62.

---

(15) Pérez Romero, P. J.; Díaz-Requejo, M. M.; Belderraín, T. R.; Nicasio, M. C.; Urbano, J.; Trofimenko, S. Spanish Pat. Appl. P200401787.

(16) Ancieaux, A. J.; Demonceau, A.; Noels, A. F.; Hubert, A.; Warin, R.; Teyssié, P. *J. Org. Chem.* **1981**, *46*, 873.

(17) (a) Díaz-Requejo, M. M.; Caballero, A.; Belderrain, T. R.; Nicasio, M. C.; Trofimenko, S.; Pérez, P. J. *J. Am. Chem. Soc.* **2002**, *124*, 978. (b) Díaz-Requejo, M. M.; Belderrain, T. R.; Trofimenko, S.; Pérez, P. J. *J. Am. Chem. Soc.* **2001**, *123*, 3167−3168.

Found for **2**: C, 14.45; H, 0.76; N, 8.14. IR (Nujol mull): ν(B−H) at 2575 cm^{-1}. $^{13}C\{^1H\}$ NMR (100 MHz, 20 °C, thf-d_8): 130.8, 123.9, and 100.1 ppm. Tetrahydrofuran exchanges rapidly with thf-d_8.

Synthesis and Characterization of Tp^{Ms}Ag(CH$_2$Cl$_2$) (3). Silver nitrate (84.95 mg, 0.5 mmol) was added to a solution of TlTp^{Ms} (386 mg, 0.5 mmol) in acetone. After 8 h of stirring in the dark, the solvent was removed under vacuum and the product was extracted with CH_2Cl_2 from the crude reaction mixture. The solid was dried under vacuum to give complex **3** in 70% yield. Anal. Calcd for $C_{37}H_{42}N_6BCl_2Ag$: C, 58.45; H, 5.57; N, 11.05. Found for **3**: C, 57.74; H, 5.47; N, 11.37. IR (Nujol mull): ν(B−H) at 2397 cm^{-1}. ^1H NMR (400 MHz, 20 °C, $(CD_3)_2CO$): 1.73 (s, 18 H), 2.42 (s, 9 H), 6.45 (br s, 3 H), 6.86 (s, 6 H), 8.18 (br s, 3 H). $^{13}C\{^1H\}$ NMR (100 MHz, 20 °C, $(CD_3)_2CO$): 19.7 (1C), 20.9 (2C), 108.6, 128.5, 154.0 (3C each, pyrazolyl rings), 128.7, 135.5, 136.8, and 138.3 (3 aromatic rings).

Catalytic Experiments. Complex **1** (20 mg, 0.019 mmol) was suspended in 5 mL of the corresponding substrate, and 0.75 mmol of EDA was added in one portion to the stirred mixture. The flask was covered with aluminum foil to avoid exposure to light. After 2−5 h of stirring, depending on the substrate, no EDA was detected by GC. The solvent was removed under vacuum, and the residue was investigated by NMR. The products were characterized by NMR and GC-MS. The representative resonances are given in the Supporting Information. The ratios of products were obtained from the comparison of the integral of the CH_2CO$_2$Et fragments and double-checked by GC.

Acknowledgment. We thank the MCYT (Proyecto BQU2002-01114) for financial support and the Universidad de Huelva for the Servicio de Resonancia Magnética Nuclear. M.M.D.-R. thanks the MEC for a research fellowship (Ramón y Cajal Program).

Supporting Information Available: Text and tables giving spectroscopic data for the ester compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OM050024K