Pergamon

Tetrahedron Letters 43 (2002) 8037–8041

TETRAHEDRON LETTERS

Insertion of Fischer carbene complexes into the carbon–carbon bond. Ring expansion of a sulfur heterocycle from five- to six-membered

Alejandro M. Granados,* Jerónimo Kreiker and Rita H. de Rossi

Instituto de Investigaciones en Físico Química de Córdoba (INFIQC), Departamento de Química Orgánica, Facultad de Ciencias Químicas, Universidad Nacional de Córdoba Ciudad Universitaria, 5000 Córdoba, Argentina

Received 17 August 2002; revised 11 September 2002; accepted 12 September 2002

Abstract—The reaction of 4-X-5-alkylthio-3*H*-1,2-dithiole-3-thione (**1**) with Fischer carbene complexes (**2**) gives, as a main product, cyclohexa dithiine derivatives due to insertion of the carbene ligand into the C3–C4 bond of the heterocycle. The reaction takes place with **1** where the alkyl substituents in position 5 are ethyl, butyl, benzyl and dodecyl and the substituents in position 4 are H, O-Me, Ph and Cl. Complexes with Cr and W as metallic center were used, the Cr complexes were more reactive than the W derivatives.

Many of the studies reported in the literature are related to the ability of Fischer carbenes to give reactions similar to those of free carbenes.[1] For instance the cyclopropanation of olefins[2] and insertion into C–H bonds,[3] or other X–H bonds (X = Si, Sn),[4] have been reported. There are only a few examples of the insertion of Fischer carbenes into C–C single bond. Recently, Herndon reported the reaction between cyclobutendiones and Fischer carbenes giving products resulting from the insertion of the carbene ligand into the acyl–acyl bond of the substrate.[5] Cyclopropenones also reacted to give the substituted cyclobutenones.[6] Aumann reported that cyclopentadienyl derivatives react with an alkenyl Fischer carbene to yield an aromatic six-membered ring via cyclopropanation of one of the double bonds and rearrangement.[7] As far as we know, these are the only three examples of ring expansion through Fischer carbene insertion into a C–C bond.

The heterocyclic pseudoaromatic compounds 3*H*-1,2-dithiole-3-thiones (**1**) have been known for several years.[8–10] A wide variety of alkyl and aryl derivatives have been synthesized and a great number of these compounds display biological activity and industrial applications. For instance, oltipraz (4-methyl-5-pyrazinyl-3*H*-1,2-dithiole-3-thione) was originally used as an antischistosomal agent due to its remarkable activity against *Schistosoma mansoni*.[11,12] In addition, recent studies have demonstrated that oltipraz inhibits HIV-1 (AIDS)[13–15] virus replication by irreversibly binding to the viral reverse transcriptase enzyme. This compound has also shown chemoprotective activity against a great variety of carcinogens and investigations are in progress to determine its probable use as a chemoprotective agent.[16–20]

Structural modification of this type of compound is not easy but it represents an alternative to obtain useful derivatives. In this paper we report that Fischer carbenes **2** react with **1** to give a six-membered heterocycle **3** through insertion of the carbene ligand into the C3–C4 bond of **1** (see Scheme 1 and Table 1). As far as we know this is the first example of the ring expansion of a heterocycle through Fischer carbene insertion into a C–C bond.

The 3*H*-1,2-dithiole-3-thiones[21] **1a–f** and carbene complexes **2a–d** were prepared according to the literature.[22–24]

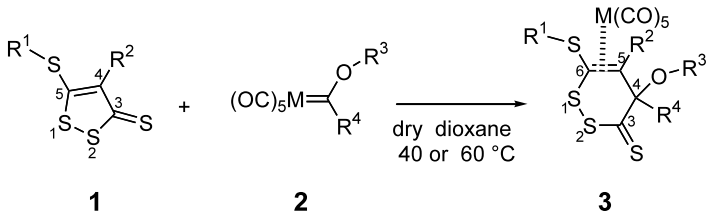
The reaction reported here takes place at room temperature[†] but the optimal reaction temperature for

Keywords: carbene complexes; chromium; 1,2-dithiol-3-thione; insertion in C–C bond; sulfur heterocycles; tungsten.

* Corresponding author. Tel.: 54-351-4334170; fax: 54-3514333030; e-mail: ale@dqo.fcq.unc.edu.ar

[†] For example, the reaction of **1b**+**2a** carried out at room temperature needs 48 h to yield 46% of **3D**.

0040-4039/02/$ - see front matter
PII: S0040-4039(02)01971-8



1 **2** **3**

1: **a**) R^1 = butyl, R^2 = H
b) R^1 = dodecyl, R^2 = H
c) R^1 = benzyl, R^2 = H
d) R^1 = ethyl, R^2 = Ph
e) R^1 = ethyl, R^2 = Cl
f) R^1 = ethyl, R^2 = OMe

2: **a)** R^3 = Me, R^4 = Ph, M = Cr
b) R^3 = Me, R^4 = Me, M = Cr
c) R^3 = Me, R^4 = Ph, M = W
d) R^3 = i-propyl, R^4 = Ph, M = Cr

Scheme 1.

M = Cr is 40–45°C and 57°C for M = W.[‡] A few degrees above this temperature the yield decreased very fast. With M = Cr in refluxing dioxane an untreatable mixture was obtained. In solvents such as hexane, acetonitrile and dichloromethane instead of 1,4-dioxane, colored complexes were formed but they were not stable enough to be isolated.[§]

The characterization of the reaction products was carried out on the bases of NMR spectroscopy and confirmed by high resolution mass spectrometry and elemental analysis.[¶] The ^{1}H and ^{13}C NMR spectra of products **3** have the following common features.

(a) There are signals corresponding to a quaternary carbon (C4) at δ_C = 92–98 ppm, and those corresponding to R^3 and R^4. (b) The signals corresponding to the carbon–carbon double bond and those of the thiocarbonyl group are at higher field than those of **1** namely δ_C = 173, 135 and 212 ppm in **1** and δ_C = 150, 130 and 205 ppm in **3**, which is consistent with the loss of conjugation between the double bond and thiocarbonyl group. (d) There are signals at 215 and 224 ppm which are typical for C=O equatorial and axial, respectively, of the $(CO)_5$Cr moiety.[‖25] (e) The CH_2 bonded to the exocyclic sulfur shows a signal characteristic of diastereotopic protons and clearly indicates that the molecule has an asymmetric center.[26] This is particularly clear in the ^{1}H NMR spectrum of compound **3E**, where the proton signal of the benzilic CH_2 appears as an AB system with coupling constant 12.9 Hz at δ_H = 4.34 ppm. Similar AB systems were obtained for compounds **3A**, **3D** and **3G** when the adjacent protons of the chain were irradiated. The results mentioned above indicate that the carbene ligand and the $M(CO)_5$ moiety were incorporated into structure **1**. Confirmation of the structure of compounds **3** was made on the basis of two-dimensional NMR spectroscopic data. Thus, for **3B**, HSQC experiments show one-bond correlation of the proton signal at δ_H = 7.58 ppm (H-5) with the carbon at δ_C = 127.52 ppm, therefore the last signal was assigned to C5 of **3B**. The signals at δ_C = 33.54 ppm

Table 1. Reaction of **1** with **2**. Reaction conditions and product yields[a]

1+**2**	Temperature (°C)	Time (h)	**3** (%)	Entry
1a+**2a**	45	4	65	A
1a+**2b**	Rt[b]	144	38	B
1a+**2c**	57	27	14	C
1b+**2a**	40	1.5	47	D
1c+**2a**	40	2.5	48	E
1d+**2a**	45	6	18	F
1e+**2a**	45	6	66	G
1e+**2d**	40	4	17	H
1f+**2a**	45	5	45	I

[a] Solvent: dry 1,4-dioxane. The yields of isolated products were calculated on the bases of the weight of **1** which was in slight deficiency.
[b] Room temperature.

[‡] Derivative **1** (0.67 mmol) and derivative **2** (0.9 mmol) were added to 10 mL of dry dioxane contained in a Schlenk tube under a nitrogen atmosphere and the mixture was warmed to 40–45°C for M = Cr and to 57°C for M = W with continuous stirring. Samples were taken every 15 min and checked by thin layer chromatography until all **1** disappeared. The solvent was evaporated at a temperature below 40°C, and the crude product was purified by column chromatography. In some cases final purification was achieved by preparative thin layer chromatography. The products **3** are deeply blue oil and were stored under nitrogen at −18°C.

[§] Dioxane was distilled from sodium and stored on sodium wire. CH_2Cl_2 and hexane were analytical grade and used as received, acetonitrile was dried over silica gel.

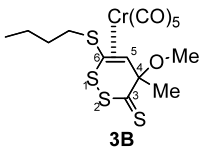
[¶] Nuclear magnetic resonance (^{1}H and ^{13}C) spectra were recorded on a Bruker AC 200 (200 MHz) spectrometer. Chemical shifts are reported in parts per million (δ) downfield from an internal tetramethylsilane reference, spin multiplicities are indicated by the following symbols: s (singlet), d (doublet), dd (double doublet), t (triplet), q (quartet), m (multiplet). HSQC and HMBC spectra were recorded on a Varian Inova 500 (^{1}H frequency 499.957 MHz, ^{13}C frequency 125.72 MHz). Infrared spectra were recorded on a Nicolet FT-IR Avatar 360 spectrometer. Band positions are reported in reciprocal centimeters (cm^{-1}). Band intensities are listed as: vs (very strong), s (strong), m (medium), w (weak).

[‖] For the derivatives containing W instead of Cr the two CO signals appear at 198 and 202 ppm. See Ref. 25.

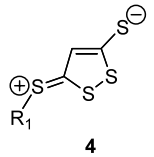
and $\delta_C = 26.05$ ppm show one-bond correlation with the proton signals at $\delta_H = 3.08$ ppm (-CH_2-S) and at $\delta_H = 2.08$ ppm ($R^4 = CH_3$) therefore they were assigned to the α-C of the side chain and the CH_3 bonded to the ring, respectively. The signal at $\delta_C = 53.64$ ppm correlates with the singlet at $\delta_H = 3.32$ ppm and it was assigned to the carbon of OCH_3 group. Finally, the signal at $\delta_C = 148.8$ ppm was assigned to the C6 of the new heterocycle. The loss of conjugation between the double bond and thiocarbonyl group indicates that the carbene insertion took place in the C3–C4 bond of **1**.

To confirm this hypothesis in an unambiguous way, long range correlation experiments (HMBC) were carried out. In this spectrum, the carbon resonance at $\delta_C = 148.8$ ppm showed HMBC correlation with the methylene proton signal of the AB system at $\delta_H = 3.08$ ppm, confirming that it corresponds to C6 of the ring, as stated above. Besides, correlations of the methyl group ($\delta_H = 2.08$ ppm) with the carbon signals at $\delta_C =$ 206.55 ppm (C3), 148.8 ppm (C6) and 92.87 ppm (C4) were observed. The cross correlation between these proton signals and C3 confirm that the insertion did not take place between C5 and S1 in **1** because this would imply five-bonds coupling which as far as we know, has never been observed. For the same reason, the cross correlation between the proton signal of the methyl group bonded to the ring and the signal for C6 confirms that the insertion did not take place within S2 and C3. The cross correlations observed as well as the loss of conjugation between the double bond and the thiocarbonyl group confirm that the insertion reaction took place into the C3–C4 bond of **1**. Unfortunately we were unable to obtain appropriate crystals of any of the derivatives prepared for X-ray structure determination. It is important to note that six-membered rings containing an S–S bond are the constituent of natural products widely used as medicine.[27]

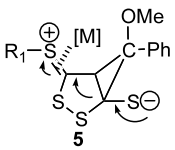
We note that there are only a few reports regarding the interaction of sulfur derived compounds with Fischer carbene complexes. Recently, Aumann[28] described an efficient synthesis of cyclopentadienyl thioacylates from the reaction of 1-alkynyl Fischer carbene complexes (M = Cr and W) with thioacids and thioamides. Besides, it was reported that the reaction of dimethoxy carbene generated by thermolysis of 2,5-dihydro-2,2-dimethoxy-5,5-dimethyl-1,3,4-oxadiazole reacted with 2,2,4,4-tetramethyl-3-thioxocyclobutanone to afford the ring expansion product with the dimethoxycarbene group inserted within C1 and C2 as a major product (50%) and a small amount of the product of insertion in the C2 –C3 bond (5%).[29]



3B



4



5

[M]= $(CO)_5Cr$, $(CO)_5W$

Considering that **4** is one of the resonance forms contributing to the ground state structure of **1**, we can see that there is a certain double bond character in the C3–C4 bond. Therefore we suggest that the reaction reported here may take place via cyclopropanation of this double bond giving the intermediate **5**, which then rearranges to **3**, as indicated by the arrows. A similar mechanism was proposed by Aumann for a five to six member ring expansion.[7]

Conclusions: Fischer carbene complexes with Cr and W as metallic center give an overall C–C σ bond insertion in their reactions with 5-alkylthio-3*H*-1,2-dithiole-3-thiones. A novel type of dithiine ring is formed. The reaction takes place with substrates bearing electron withdrawing as well as electron acceptor substituents.

Insertion reaction of 1a and 2a (entry A of Table 1). 6 - Butylthiovinyliden - [pentacarbonylchromium(0)] - 4-methoxy-4-phenyl-3*H*-1,2-dithiine-3-thione **3A**: ^{1}H NMR ($CDCl_3$): δ 0.97 (t, 3H); 1.48 (m, 2H); 1.74 (m, 2H); 3.12 (m, 2H); 3.29 (s, 3H); 7.49–7.67 (m, 6H). ^{13}C NMR ($CDCl_3$): δ 13.48; 21.83; 30.67; 33.72; 54.20; 97.06; 127.14; 127.59; 129.29; 130.61; 135.36; 148.77; 205.91; 215.02; 223.89. IR (KBr): 742.2 (d); 1045.0 (m); 1406.9 (m); 1492.5 (m); 1933.5 (vs); 2065.1 (s); 2940.4 (w); 2973.3 (w) cm^{-1}. HRMS (FAB) (NBA), calculated for $C_{20}O_6H_{18}S_4Cr$: 533.9391 g/mol; found: 533.9376 g/mol.

Insertion reaction of 1a and 2b (entry B of Table 1). 6 - Butylthiovinyliden - [pentacarbonylchromium(0)] - 4-methoxy-4-methyl-3*H*-1,2-dithiine-3-thione **3B**: ^{1}H NMR ($CDCl_3$): δ 0.96 (t, 3H); 1.47 (m, 2H); 1.69 (m, 2H); 2.08 (s, 3H); 3.08 (m, 2H); 3.32 (s, 3H); 7.58 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 13.51; 21.83; 26.68; 30.63; 33.58; 53.64; 92.87; 127.52; 148.83; 206.53; 214.99; 223.89. HRMS (FAB) (NBA), calculated for $C_{15}O_6H_{16}S_4Cr$: 471.9237 g/mol; found: 471.9235 g/mol.

Insertion reaction of 1a and 2c (entry C of Table 1). 6 - Butylthiovinyliden - [pentacarbonyltungsten(0)] - 4-methoxy-4-phenyl-3*H*-1,2-dithiine-3-thione **3C**: ^{13}C NMR ($CDCl_3$): δ 13.55; 21.87; 30.67; 33.79; 54.23; 97.58; 127.18; 128.01; 129.36; 130.75; 135.29; 151.05; 196.93; 202.30; 203.14. IR (KBr): 748.8 (w); 1045.0 (m); 1406.9 (m); 1492.5 (m); 1933.5 (vs); 2065.1 (s); 2927.2 (w); 2966. 7 (w) cm^{-1}. HRMS (FAB) (NBA), calculated for $C_{20}O_6H_{18}S_4W$: 665.9495 g/mol; found: 665.9517 g/mol.

Insertion reaction of 1b and 2a (entry E of Table 1). 6-Dodecylthiovinyliden-[pentacarbonylchromium(0)]-4-methoxy-4-phenyl-3*H*-1,2-dithiine-3-thione **3D**: ^{1}H NMR ($CDCl_3$): δ 0.97 (t, 3H); 1.27 (s, 18H); 1.74 (m, 2H); 3.12 (m, 2H); 3.29 (s, 3H); 7.49–7.66 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 14.11; 22.70; 28.66; 28.97; 29.56; 31.92; 34.07; 54.23; 97.06; 127.18; 127.63; 129.29; 130.64; 135.39; 148.73; 205.91; 215.02; 223.93. IR (KBr): 1054.0 (m); 1400.1 (m); 1489.8 (m); 1941.9 (vs); 2061.2 (s); 2854.7 (m); 2925.0 (m) cm^{-1}. Elemental

analysis, calculated for $C_{28}O_6H_{34}S_4Cr$, C, 51.99; H, 5.30; found: C, 51.69; H, 5.66%.

Insertion reaction of 1c and 2a (entry E of Table 1). 6-Benzylthiovinyliden-[pentacarbonyl chromium(0)]-4-methoxy-4-phenyl-3*H*-1,2-dithiine-3-thione **3E**: ^{1}H NMR ($CDCl_3$): δ 3.24 (s, 3H); 4.34 (m, 2H); 7.37–7.75 (m, 11H). ^{13}C NMR ($CDCl_3$): δ 38.88; 54.20; 97.23; 127.14; 128.49; 129.01; 129.22; 130.64; 134.31; 135.32; 146.51; 206.32; 214.92; 223.93. IR (KBr): 1044.0 (m); 1410.9 (m); 1495.9 (m); 1940.5 (vs); 2064.7 (s); 2927.8 (w); 2967.0 (w). HRMS (FAB) (NBA), calculated for $C_{23}O_6H_{16}S_4Cr$: 567.9234 g/mol; found: 567.9262 g/mol.

Insertion reaction of 1d and 2a (entry F of Table 1). 6 - Ethylthiovinyliden - [pentacarbonylchromium(0)] - 5-phenyl-methoxy-4-phenyl-3*H*-1,2-dithiine-3-thione **3F**: ^{1}H NMR ($CDCl_3$): δ 1.28 (t, 3H); 2.97 (m, 2H); 3.42 (s, 3H); 7.15–7.78 (m, 10H). ^{13}C NMR ($CDCl_3$): δ 14.59; 29.11; 54.41; 93.94; 127.18; 128.63; 129.33; 130.61; 135.67; 136.98; 164.29; 204.14; 215.16; 224.24. HRMS (FAB) (NBA), calculated for $C_{24}O_6H_{18}S_4Cr$: 581.9391 g/mol; found: 581.9366 g/mol.

Insertion reaction of 1e and 2a (entry G of Table 1). 6-Ethylthiovinyliden-[pentacarbonylchromium(0)]-5-Cl-4-methoxy-4-phenyl-3*H*-1,2-dithiine-3-thione **3G**: ^{1}H NMR ($CDCl_3$): δ 1.43 (t, 3H); 3.12 (m, 2H); 3.32 (s, 3H); 7.52–7.71 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 14.31; 29.04; 54.44; 94.43; 126.93; 129.50; 130.95; 134.52; 146.13; 196.38; 214.88; 224.45. IR (KBr): 1058.1 (m); 1229.3 (w); 1420.1 (s); 1933.5 (vs); 2065.1 (s); 2933.6 (w). HRMS (FAB) (NBA), calculated for $C_{18}O_6H_{13}S_4ClCr$: 539.8688 g/mol; found: 539.8679 g/mol. Elemental analysis, calculated for $C_{18}O_6H_{13}S_4ClCr$: C, 39.96; H, 2.42; found: C, 39.82; H, 2.56%; mp 92–93.5°C.

Insertion reaction of 1e and 2d (entry H of Table 1). 6-Ethylthiovinyliden-[pentacarbonylchromium(0)]-5-Cl-4-i-propoxy-4-phenyl-3*H*-1,2-dithiine-3-thione **3H**: ^{1}H NMR ($CDCl_3$): δ 1.07–1.10 (dd, 6H); 1.44 (t, 3H); 3.13 (m, 2H); 3.91 (m, 1H); 7.50–7.78 (m, 5H). IR (KBr): 1031.4 (m); 1044.2 (m); 1235.8 (w); 1421.1 (s); 1935.6 (vs); 2060.2 (s); 2932.2 (w); 2980.2 (w) cm^{-1}. HRMS (FAB) (NBA), calculated for $C_{20}H_{17}O_6S_4ClCr$: 567.9001 g/mol; found: 567.8986 g/mol.

Insertion reaction of 1f and 2a (entry I of Table 1). 6 - Ethylthiovinyliden - [pentacarbonylchromium(0)] - 5-methoxy-4-methoxy-4-phenyl-3*H*-1,2-dithiine-3-thione **3I**: ^{1}H NMR ($CDCl_3$): δ 1.38 (t, 3H); 3.03 (m, 2H); 3.32 (s, 3H); 3.78 (s, 3H); 7.50–7.69 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 14.62; 27.86; 54.23; 59.46; 94.33; 126.76; 129.29; 130.71; 134.59; 138.99; 153.48; 196.07; 215.02; 224.17. IR (KBr): 1038.4 (m); 1083.4 (m); 1262.2 (m); 1401.9 (s); 1456.1 (m); 1940.0 (vs); 2058.0 (s); 2940.4 (w); 2966.7 (w) cm^{-1}. HRMS (FAB) (NBA), calculated for $C_{19}H_{16}O_7S_4Cr$: 535.9184 g/mol; found: 535.9183 g/mol.

Acknowledgements

This research was supported in part by the Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET), the Agencia Córdoba Ciencia, Agencia Nacional de Ciencia y Tecnología (FONCYT), Fundación Antorchas and the Universidad Nacional de Córdoba, Argentina. J.K. is a grateful recipient of a Fellowship from CONICET. We thank Professor Pelayo Camps, Universidad de Barcelona, Spain, for his help with the HSQC and HMBC NMR spectra.

References

1. (a) Herndon, J. W. *Tetrahedron* **2000**, *56*, 1257; (b) de Meijere, A.; Schirmer, H.; Duetsch, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 3964; (c) Sierra, M. A. *Chem. Rev.* **2000**, *100*, 3591; (d) Aumann, R.; Nienaber, H. *Adv. Organomet. Chem.* **1997**, *41*, 163.
2. Barluenga, J.; Fernandez-Acebes, A.; Travanco, A. A.; Flerez, J. *J. Am. Chem. Soc.* **1997**, *119*, 7591.
3. Sierra, M. A.; Macheño, M. J.; Saez, E.; del Amo, J. C. *J. Am. Chem. Soc.* **1998**, *120*, 6812 and references cited therein.
4. (a) Mak, C. C.; Tse, M. K.; Chan, K. S. *J. Org. Chem.* **1994**, *59*, 3585; (b) Merlic, C. A.; Albaneze, J. *Tetrahedron Lett.* **1995**, *36*, 1007; (c) Nakamura, E.; Tanaka, K.; Aoki, S. *J. Am. Chem. Soc.* **1992**, *114*, 9715.
5. (a) Zora, M.; Herndon, J. W. *Organometallics* **1999**, *18*, 4429; (b) Zora, M.; Herndon, J. W. *Organometallics* **1993**, *12*, 248.
6. (a) Zora, M.; Herndon, J. W. *Organometallics* **1994**, *13*, 3370; (b) Zora, M.; Herndon, J. W.; Li, Y.; Rossi, J. *Tetrahedron* **2001**, *57*, 5097.
7. Wu, H.-P.; Aumann, F. R.; Fröhlich, R.; Saarenketo, P. *Chem. Eur. J.* **2001**, *7*, 700.
8. Landis, P. S. *Chem. Rev.* **1965**, *65*, 237.
9. (a) Pedersen, C. T. *Adv. Heterocyclic Chem.* **1982**, *31*, 63; (b) Pedersen, C. T. *Sulfur Rep.* **1995**, *16*, 173.
10. Breslow, D. S.; Skolnik, H. In *The Chemistry of Heterocyclic Compounds, Multi Sulfur and Sulfur and Oxygen Five- and Six-Membered Heterocycles*; Weissberger, A., Ed.; Wiley: New York, 1966.
11. Barreau, M.; Cotrel, C.; Jeanmart, C. Ger. Offen. Patent 2, 627,211; *Chem. Abstr.* **1977**, *86*, 121373.
12. Barreau, M.; Cotrel, C.; Jeanmart, C. Ger. Offen. Patent 2,705,641; *Chem. Abstr.* **1977**, *87*, 152171.
13. Prochaska, H. J.; Yeh, Y.; Baron, P.; Polsky, B. *Proc. Natl. Acad. Sci. USA* **1993**, *90*, 3953.
14. Prochaska, H. J.; Rubinson, L.; Yeh, Y.; Baron, P.; Polsky, B. *Mol. Pharmacol.* **1991**, *45*, 916.
15. Prochaska, H. J.; Fernandes, C. L.; Pantoja, R. M.; Chavan, S. J. *Biochem. Biophys. Res. Commun.* **1996**, *221*, 548.
16. Kensler, T. W.; Groopman, J. D.; Eaton, D. L.; Curphey, T. J.; Roebuck, B. D. *Carcinogenesis* **1992**, *13*, 95.
17. Prestera, T.; Talalay, P. *Proc. Natl. Acad. Sci. USA* **1995**, *92*, 8965.
18. Begleiter, A.; Leith, M. K.; Curphey, T. J. *Br. J. Cancer* **1996**, *74*, S9–S14.
19. Begleiter, A.; Leith, M. K.; Curphey, T. J.; Doherty, G. P. *Oncology Res.* **1997**, *9*, 371.

20. Kim, W.; Gates, K. S. *Chem. Res. Toxicol.* **1997**, *10*, 296.
21. (a) Aimar, M. L.; de Rossi, R. H. *Synthesis* **2000**, *12*, 1749; (b) Aimar, M. L.; Kreiker, J.; de Rossi, R. H. *Tetrahedron Lett.* **2002**, *43*, 1947.
22. Bao, J.; Wulff, W. D.; Dominy, J. B.; Fumo, M. J.; Grant, E. B.; Rob, A. C.; Whitcomb, M. C.; Yeung, S. M.; Ostrander, R. L.; Rheingold, A. L. *J. Am. Chem. Soc.* **1996**, *118*, 3392.
23. Bernasconi, C. F.; Flores, F. X.; Gandler, J. R.; Leyes, A. E. *Organometallics* **1994**, *13*, 2186.
24. Bernasconi, C. F.; Sun, W. *J. Am. Chem. Soc.* **1993**, *115*, 12526.
25. Wu, H.-P.; Aumann, R.; Fröhlich, R.; Wegelius, E.; Saarenketo, P. *Organometallics* **2000**, *19*, 2373.
26. Friebolin, H. *Basic One- and Two-Dimensional NMR Spectroscopy*; VCH Publisher: New York, 1991.
27. Block, E.; Guo, C.; Thiruvazhi, M.; Toscano, P. J. *J. Am. Chem. Soc.* **1994**, *116*, 9403.
28. Wu, H.-P.; Aumann, R.; Fröhlich, R.; Wegelius, E.; Saarenketo, P. *Chem. Eur. J.* **2001**, *7*, 700.
29. Dawid, M.; Mloston, G.; Warkentin, J. *Chem. Eur. J.* **2002**, *8*, 2184.