Palladium-Catalyzed C–H Activation at Methoxy Groups for Cross-Coupling Reactions: A New Approach to Substituted Benzo[*b*]furans[1]

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Palladium catalyzed C–H activation of methoxy groups as the key step in a cross-coupling reaction of *o*-iodomethoxybenzenes with bromo olefins is described. By this method, substituted benzofurans are synthesized in moderate to good yields.

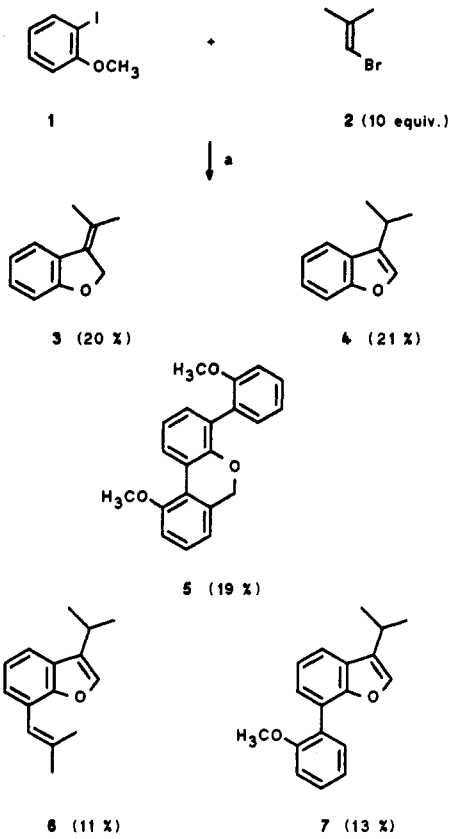
Introduction

Metallation reactions are very often the method of choice for the activation of relatively unreactive carbon–hydrogen bonds. Especially interesting for this purpose is the application of transition metals as catalysts. The activation of olefinic,[2] acetylenic,[3] and even intramolecular aromatic[4] C–H bonds is a key step of palladium-catalyzed coupling reactions with vinyl and aryl halides. These well established reactions have been proven to be extremely useful for forming C–C bonds by dehydrohalogenation. Little information is available on the catalytic C–H activation at saturated alkyl and heteroalkyl groups, although such reactions could open up new and exciting synthetic pathways. Recently, we reported the first palladium catalyzed C–H activation at a methoxy group: 2-iodoanisole (1) reacts in a 3-fold homo-coupling process to give a 90% yield of the substituted dibenzopyran **5**.[5] This paper presents studies on scope and limitations of cross-coupling reactions based on palladium catalyzed C–H activation at methoxy groups.

Results and Discussion

As a result of our studies on palladium-catalyzed homo-coupling reactions of *o*-methoxyiodobenzenes under C–H activation we proposed heterocyclic Pd^{II} complexes like **8** (Scheme II) as key intermediates.[5] On the basis of this mechanistic consideration, suitable reaction partners for cross-coupling reactions should not enter the catalytic reaction cycle until the stage of these intermediates. Various reagents that have been tested as potential reaction partners failed to fulfill this requirement: Ordinary olefins like styrene and fumaric and maleic acid esters inhibit the C–H activation of the methoxy group by reacting with arylpalladium iodides at a preceding stage giving rise to normal Heck products.[2] Aryl iodides like 1-iodonaphthalene and 4-iodotoluene already react relatively fast with the active Pd^0 catalyst forming Ullmann homo-coupling products.[1] On the other hand 1-bromonaphthalene and 4-bromotoluene seem to react too sluggishly with the cyclic intermediate **8**. Even when 10 equiv of these aryl bromides are added to the reaction mixture the 3-fold homo-coupling process forming **5** is still the main reaction pathway.

Scheme I[a]



[a] 10 mol % $Pd(OAc)_2$, K_2CO_3, *n*-Bu_4NBr, DMF, N_2, 3 d, 100 °C; isolated yields are given.

Much more promising results were achieved by adding a 10-fold excess of bromo olefin **2** as the cross-coupling partner (Scheme I). Although formation of the dibenzopyran system **5** was not completely suppressed, the 4-substituted benzo[*b*]furans **3**, **4**, **6**, and **7** were isolated as cross-coupling products in 65% overall yield. A possible mechanism for the formation of the unusual benzofuran **3** with an exocyclic double bond includes oxidative addition of bromo olefin **2** to palladacycle **8** as a key step giving rise to a Pd(IV)[6] intermediate **9a** in analogy to the proposed

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(1) Transition Metal Catalyzed Annulation Reactions; Part 4. Part 3: Dyker, G. *J. Org. Chem.* **1993**, *58*, 234.

(2) Heck, R. F. *Org. React. (N.Y.)* **1982**, *27*, 345.

(3) Takahashi, S.; Kuroyama, Y.; Sonogashira, K.; Hagihara, N. *Synthesis* **1980**, 627.

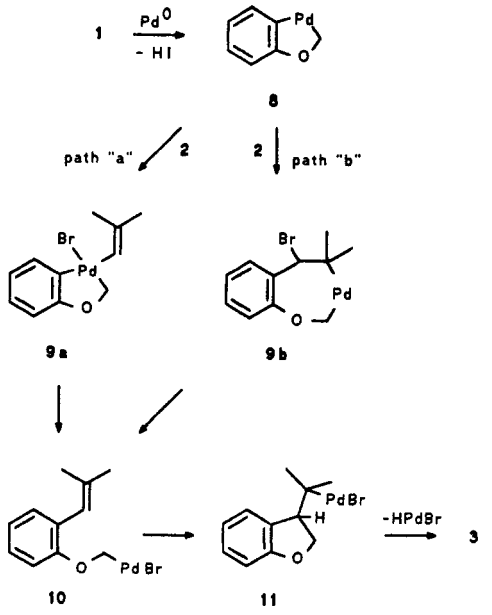
(4) Bringmann, G.; Walter, R.; Weirich, R. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 977.

(5) Dyker, G. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1023.

(6) Canty, A. J. *Acc. Chem. Res.* **1992**, *25*, 83.

0022-3263/93/1958-6426$04.00/0

Scheme II

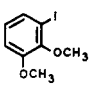
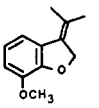
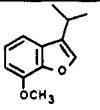
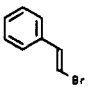
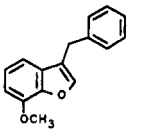
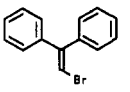
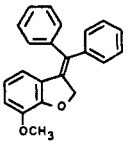
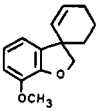
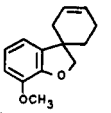
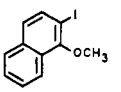
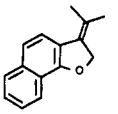
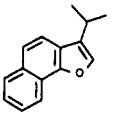


mechanism of the homo-coupling process[5] (Scheme II, path a; additional ligands on palladium have been omitted for clarity). Reductive elimination forming **10** and subsequent ring closure led to the condensation product **3**. Path b via seven-membered palladacycle **9b** formed by an olefin insertion reaction might be an alternative. Double bond isomerization to the aromatic product **4** should occur by readdition of hydridopalladium bromide when it is still coordinated to the double bond because **3** itself is stable under the reaction conditions. In an alternative approach to 3-substituted benzofurans, Larock and Stinn[7] described cyclizations of iodoaryl allyl ethers under similar reaction conditions; no products with exocyclic double bonds were reported. To prevent double bond isomerization during palladium catalysis the addition of silver salts has been recommended;[8] unfortunately in our case the coupling process is terminated by silver acetate and silver carbonate.[9]

The formation of the 1:2 product **6** and the 2:1 product **7** probably proceeds via cyclometalation of Pd(II) intermediates like **10** to the second ortho position. A blocking group in this position should successfully prevent formation of 1:2 and 2:1 products. Thus, with 1-iodo-2,3-dimethoxybenzene (**12**) as the aryl component a preparatively useful 82% overall yield of the 1:1 cross-coupling products **13** and **14** is obtained (Table I).

With bromostyrene (**15**), the 3-benzylbenzofuran **16** is isolated as the main product. In this case a large excess of bromo olefin clearly inhibits the reaction of the aryl iodide with the palladium catalyst. Probably the catalyst is consumed by homo-coupling processes of the bromo olefin (the subject of current investigation). The diphenyl-substituted bromo olefin **17** leads to benzofuran **18** with the especially stabilized exocyclic double bond.[10] In contrast, naphthalenofuran **23** is extremely sensitive under slightly acidic conditions. In chloroform solution **23** is rapidly transformed to its aromatic isomer **24** in quantitative yield.

Table I. Palladium-Catalyzed Cross-Coupling Reactions of *o*-Iodomethoxyarenes with Bromo Alkenes and Eno Triflates

entry	iodoarene	akene (equiv)	products (yield)[a]	
				
1	**12**	**2** (5 equiv)	**13** (32%)	**14** (29%)
2	**12**	**2** (10 equiv)	**13** (27%)	**14** (55%)
				
3	**12**	**15** (5 equiv)		**16** (35%)
4	**12**	**15** (5 equiv)		**16** (56%)[b]
5	**12**	**15** (10 equiv)		**16** (19%)
				
6	**12**	**17** (5 equiv)	**18** (42%)	
				
7	**12**	**19** (X = Br, 5 equiv)	**20** (1:3; 26%)	**21**
8	**12**	**19** (X = OSO_2CF_3, 5 equiv)	**20** (1:4; 18%)	**21**
				
9	**22**	**2** (10 equiv)	**23** (32%)	**24** (25%)

[a] Isolated yields are given; conditions: 10 mol % $Pd(OAc)_2$, K_2CO_3, *n*-Bu_4NBr, DMF, N_2, 3 d, 100 °C; isolated yields are given. [b] Six days overall reaction time with additional 10 mol % $Pd(OAc)_2$ added after three days.

The spirocyclic benzofurans **20** and **21** are formed by the cross-coupling reaction with bromocyclohexene (**19**).[11] The corresponding enol triflate gave similar results (entry 8).

The present study establishes the palladium-catalyzed C–H activation at methoxy groups as an initial step for cross-coupling reactions. With *o*-iodomethoxybenzenes and bromo olefins as coupling components, a new pathway for the synthesis of substituted benzofurans has been introduced.

Experimental Section

Melting point determinations are uncorrected. ^1H NMR spectra were recorded at 400.1 MHz using $CDCl_3$ as solvent and TMS as internal standard (except for **23**). ^{13}C NMR spectra were recorded at 100.6 MHz, using $CDCl_3$ as solvent and as

(7) Larock, R. C.; Stinn, D. E. *Tetrahedron Lett.* **1988**, *29*, 4687.
(8) (a) Karabelas, K.; Westerlund, C.; Hallberg, A. *J. Org. Chem.* **1985**, *50*, 3896. (b) Abelman, M. M.; Oh, T.; Overman, L. E. *J. Org. Chem.* **1987**, *52*, 4130.
(9) Under the reaction conditions the silver salts are efficiently reduced to elemental silver grains.
(10) The less-substituted 2,3-dihydro-4-methoxy-3-methylenebenzo-[c]furan has been reported to be unstable: Shankaran, K.; Sloan, C. P.; Snieckus, V. *Tetrahedron. Lett.* **1985**, *26*, 6001.
(11) Formation of spirocyclics by palladium catalysis: (a) Ashimori, A.; Overman, L. E. *J. Org. Chem.* **1992**, *57*, 4571. (b) Grigg, R.; Sridharan, V.; Stevenson, P.; Sukirthalingam, S. *Tetrahedron* **1989**, *45*, 3557.

internal standard (δ = 77.05 ppm). High- and low-resolution mass spectra were recorded at an ionizing voltage of 70 eV by electron impact. Unless otherwise stated, chemicals were purchased from commercial suppliers and used without further purification. 1-Bromo-2-diphenylethene (**17**),[12] 1-bromocyclohexene (**19**, X = Br),[13] and the enol triflate **19** (X = OSO_2CF_3)[14] were prepared by literature methods. 1-Iodo-2,3-dimethoxybenzene (**12**) and 2-iodo-1-methoxynaphthalene (**22**) were synthesized by iodolysis of the corresponding aryllithium compounds in analogy to published methods.[15]

Palladium-Catalyzed Cross-Coupling Reactions of *o*-Iodomethoxyarenes with Bromoalkenes (General Procedure). The procedure for the preparation of 2,3-dihydro-3-(1-methylethylidene)-7-methoxybenzo[*b*]furan (**13**) and 3-(2-methylethyl)-7-methoxybenzo[*b*]furan (**14**) is representative: A mixture of 1-iodo-2,3-dimethoxybenzene (**12**) (264 mg, 1.00 mmol), 1-bromo-2-methyl-1-propene (**2**) (1.35 g, 10.0 mmol), K_2CO_3 (1.1 g, 8.0 mmol), *n*-Bu_4NBr (645 mg, 2.00 mmol), $Pd(OAc)_2$ (22 mg, 0.10 mmol), and DMF (10 mL) in a sealed tube (for convenience) is stirred under N_2 at 100 °C for 3 d. After diluting with water (50 mL) the reaction mixture is extracted three times with ether (50 mL). The ether extract is filtered through silica and concentrated. The crude product was purified by flash chromatography (hexanes, silica gel) affording substituted benzofurans **14** (105 mg, 55%; less polar) and **13** (51 mg, 27%; for selected data see below and supplementary material).

All reactions were carried out on a 1-mmol scale in analogy to the foregoing procedure. The relative amounts of the reactants, the reaction time, and the isolated yields are given in the above schemes and tables. All new compounds were fully characterized by spectroscopic means (IR, MS, NMR, UV). Selected data of the isolated products:

2,3-Dihydro-3-(1-methylethylidene)benzo[*b*]furan (3): colorless solid; mp 39–40 °C (pentane); ^{1}H NMR δ 1.76 (s, br, 3 H), 2.06 (s, br, 3 H), 5.06 (m, 2 H), 6.82 (d, J = 8.0 Hz, 1 H), 6.88 (m_t,[16] 1 H), 7.11 (m_t, 1 H), 7.48 (d, J = 7.6 Hz, 1 H); ^{13}C NMR δ 20.9 (q), 23.3 (q), 74.7 (t), 109.9 (d), 120.4 (d), 123.5 (s), 123.7 (d), 126.7 (s), 128.1 (d), 128.9 (s), 164.0 (s).

3-(1-Methylethyl)benzo[*b*]furan (4): colorless oil;[7] ^{1}H NMR δ 1.36 (d, J = 6.9 Hz, 6 H), 3.10 (sept d, J = 6.9, 0.8 Hz, 1 H), 7.22 (m_t, 1 H), 7.27 (m_t, 1 H), 7.37 (d, J = 0.8 Hz, 1 H), 7.45 (d, J = 7.9 Hz, 1 H), 7.59 (d, J = 7.1 Hz, 1 H); ^{13}C NMR δ 22.5 (q), 24.7 (d), 111.5 (d), 120.1 (d), 122.1 (d), 124.0 (d), 127.6 (s), 127.7 (s), 139.7 (d), 155.7 (s).

3-(1-Methylethyl)-7-(2-methylpropen-1-yl)benzo[*b*]furan (6): colorless oil; ^{1}H NMR δ 1.36 (d, J = 6.9 Hz, 6 H), 1.87 (d, J = 1.4 Hz, 3 H), 1.99 (d, J = 1.3 Hz, 3 H), 3.09 (sept d, J = 6.9, 0.8 Hz, 1 H), 6.52 (s, br, 1 H), 7.15–7.22 (m, 2 H), 7.36 (d, J = 0.8 Hz, 1 H), 7.46 (m_d, 1 H); ^{13}C NMR δ 20.0 (q), 22.5 (q), 24.7 (d), 26.8 (q), 118.1 (d), 118.6 (d), 121.9 (d), 123.2 (s), 124.2 (d), 127.4 (s), 127.4 (s), 137.9 (s), 139.4 (d), 153.4 (s); HRMS m/z calcd for $C_{15}H_{18}O$ 214.1358, found 214.1357.

7-(2-Methoxyphenyl)-3-(1-methylethyl)benzo[*b*]furan (7): colorless crystals; mp 90–92 °C; ^{1}H NMR: δ 1.38 (d, J = 6.9 Hz, 6 H), 3.12 (sept d, J = 6.9, 0.8 Hz, 1 H), 3.80 (s, 3 H), 7.05 (d, J = 8.3 Hz, 1 H), 7.07 (m_t, 1 H), 7.28 (t, J = 7.5 Hz, 1 H), 7.35 (d, J = 0.8 Hz, 1 H), 7.36 (m_d, 1 H), 7.39 (m_t, 1 H), 7.46 (m_d, 1 H), 7.58 (m_d, 1 H); ^{13}C NMR: δ 22.5 (q), 24.8 (d), 55.7 (q), 111.4 (d), 119.3 (d), 120.6 (d), 122.0 (d), 122.9 (s), 125.6 (d), 125.8 (s), 127.3 (s), 127.8 (s), 129.2 (d), 131.6 (d), 139.7 (d), 153.3 (s), 157.0 (s). Anal. Calcd for $C_{18}H_{18}O_2$: C, 81.17; H, 6.81. Found: C, 80.93; H, 6.84.

2,3-Dihydro-7-methoxy-3-(1-methylethylidene)benzo[*b*]furan (13): colorless crystals; mp 105–106 °C (hexanes); ^{1}H NMR δ 1.75 (s, br, 3 H), 2.05 (t, J = 2.3 Hz, 3 H), 3.89 (s, 3 H), 5.13 (m, 2 H), 6.75 (d, J = 8.0 Hz, 1 H), 6.84 (t, J = 7.9 Hz, 1 H), 7.14 (d, J = 7.7 Hz, 1 H); ^{13}C NMR δ 20.7 (q), 23.2 (q), 56.0 (q), 75.4 (t), 111.1 (d), 116.2 (d), 120.8 (d), 123.3 (s), 127.8 (s), 129.3 (s), 144.9 (s), 152.6 (s). Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.74; H, 7.46.

7-Methoxy-3-(1-methylethyl)benzo[*b*]furan (14): colorless oil; ^{1}H NMR δ 1.35 (d, J = 6.9 Hz, 6 H), 3.07 (sept d, J = 6.9, 0.8 Hz, 1 H), 4.00 (s, 3 H), 6.79 (m_d, 1 H), 7.15 (t, J = 7.8 Hz, 1 H), 7.19 (m_d, 1 H), 7.37 (d, J = 0.8 Hz, 1 H); ^{13}C NMR δ 22.5 (q), 24.7 (d), 56.1 (q), 106.3 (d), 112.5 (d), 122.8 (d), 127.7 (s), 129.4 (s), 139.8 (d), 144.9 (s), 145.7 (s); HRMS m/z calcd for $C_{12}H_{14}O_2$ 190.0994, found 190.0993.

3-Benzyl-7-methoxybenzo[*b*]furan (16): colorless oil; ^{1}H NMR δ 4.00 (s, 3 H), 4.01 (s, br, 2 H), 6.79 (d, br, J = 7.8 Hz, 1 H), 7.00 (dd, J = 7.8, 0.8 Hz, 1 H), 7.10 (t, J = 7.8 Hz, 1 H), 7.19–7.32 (m, 5 H), 7.38 (s, br, 1 H); ^{13}C NMR δ 30.1 (t), 56.1 (q), 106.5 (d), 112.3 (d), 120.1 (s), 123.2 (d), 126.4 (d), 128.5 (d), 128.7 (d), 129.8 (s), 139.2 (s), 142.3 (d), 144.9 (s), 145.5 (s). Anal. Calcd for $C_{16}H_{14}O_2$: C, 80.65; H, 5.92. Found: C, 80.40; H, 5.90.

2,3-Dihydro-3-(diphenylmethylene)-7-methoxybenzo[*b*]furan (18): colorless crystals; mp 127 °C (pentane); ^{1}H NMR δ 3.87 (s, 3 H), 5.35 (s, 2 H), 5.95 (dd, J = 7.9, 0.9 Hz, 1 H), 6.53 (t, J = 7.9 Hz, 1 H), 6.71 (dd, J = 7.9, 0.9 Hz, 1 H), 7.18–7.43 (m, 10 H); ^{13}C NMR δ 56.0 (q), 76.2 (t), 112.2 (d), 116.8 (d), 120.6 (d), 127.0 (s), 127.3 (d), 127.6 (d), 128.1 (d), 128.6 (d), 128.9 (d), 129.6 (d), 132.8 (s), 134.3 (s), 141.2 (s), 142.0 (s), 145.1 (s), 153.1 (s). Anal. Calcd for $C_{22}H_{18}O_2$: C, 84.05 H, 5.77. Found: C, 84.26; H, 5.71.

7-Methoxyspiro[benzofuran-3(2*H*),1′-[2]cyclohexene] (20) and 7-Methoxyspiro[benzofuran-3(2*H*),1′-[3]cyclohexene] (21). By flash chromatography (hexanes, silica gel) a pure sample of the slightly less-polar **21** was obtained. The ^{1}H NMR data of **20** was determined by analyzing the NMR spectrum of a 1:3 mixture of **20** and **21**.

20: ^{1}H NMR δ 1.55–2.40 (m, 6 H), 3.88 (s, 3 H), 4.28 (d, J = 8.8 Hz, 1 H), 4.41 (d, J = 8.8 Hz, 1 H), 5.61 (m_d, J = 9.9 Hz, 1 H), 5.92 (dt, J = 9.9, 3.8 Hz, 1 H), 6.70–6.86 (m, 3 H).

21: colorless oil; ^{1}H NMR δ 1.70–1.80 (m, 1 H), 1.90–1.98 (m, 1 H), 2.10–2.34 (m, 4 H), 3.88 (s, 3 H), 4.32 (d, J = 8.7 Hz, 1 H), 4.36 (d, J = 8.7 Hz, 1 H), 5.70-5.82 (m, 2 H), 6.70–6.86 (m, 3 H); ^{13}C NMR δ 22.8 (t), 31.7 (t), 36.1 (t), 44.7 (s), 56.0 (q), 82.9 (t), 111.3 (d), 115.5 (d), 121.2 (d), 125.4 (d), 127.3 (d), 136.6 (s), 144.6 (s), 147.7 (s); HRMS m/z calcd for $C_{14}H_{16}O_2$ 216.1150, found 216.1150.

2,3-Dihydro-3-(1-methylethylidene)naphtho[1,2-*b*]furan (23): colorless crystals; mp 95 °C (pentane); ^{1}H NMR (acetone-d_6, TMS) δ 1.79 (m, 3 H), 2.11 (m, 3 H), 5.29 (m, 2 H), 7.43 (d, J = 8.6 Hz, 1 H), 7.44–7.47 (m, 2 H), 7.73 (d, J = 8.6 Hz, 1 H), 7.85 (m, 1 H), 7.96 (m, 1 H); ^{13}C NMR (acetone-d_6, TMS) δ 20.8 (q), 23.2 (q), 76.2 (t), 121.1 (d), 121.5 (s), 121.7 (s), 121.8 (s), 122.1 (d), 122.5 (d), 126.3 (d), 127.2 (d), 128.7 (d), 130.7 (s), 134.7 (s), 160.9 (s). Anal. Calcd for $C_{15}H_{14}O$: C, 85.68; H, 6.71. Found: C, 85.27; H, 6.69.

3-(1-Methylethyl)naphtho[1,2-*b*]furan (24): colorless oil; ^{1}H NMR δ 1.41 (d, J = 6.9 Hz, 6 H), 3.07 (sept d, J = 6.9, 1.1 Hz, 1 H), 7.48 (m_t, 1 H), 7.52 (d, J = 1.1 Hz, 1 H), 7.57 (m_t, 1 H), 7.64 (d, br, J = 8.5 Hz, 1 H), 7.68 (d, J = 8.5 Hz, 1 H), 7.92 (d, J = 8.3 Hz, 1 H), 8.29 (d, J = 8.5 Hz, 1 H); ^{13}C NMR: δ 22.7 (q), 24.8 (d), 118.8 (d), 120.1 (d), 121.7 (s), 122.8 (d), 123.0 (s), 125.0 (d), 126.2 (d), 128.3 (d), 128.6 (s), 131.3 (s), 139.0 (d), 151.2 (s). Anal. Calcd for $C_{15}H_{14}O$: C, 85.68; H, 6.71. Found: C, 85.72; H, 7.01.

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Supplementary Material Available: Photocopies of the ^{1}H NMR spectra and additional spectroscopic data (IR, UV, MS) of all new compounds and full assignment of the NMR data of compound **24** based on HH-COSY, CH-COSY and COLOC (14 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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