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Cyclopalladated complexes of Schiff bases of homoveratrylamine and tryptamine. Synthesis and CO insertion [1]

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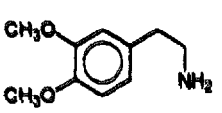
Abstract

$Pd(OAc)_2$ in CH_2Cl_2 with the Schiff bases of homoveratrylamine (**1a,b**) and tryptamine (**2a–c**), followed by treatment in situ with LiX (X = Cl, Br), gave the insoluble dimeric complexes (**3–7**) with chlorine or bromine bridges, having the dimethoxybenzene ring and the indole nucleus metallated at position 6 and 2, respectively. Complexes **4** and **6** gave the soluble, cyclometallated derivatives **8** and **9** by reaction with PPh_3 in methylene chloride. When compounds **3–6** were reacted with carbon monoxide at atmospheric pressure in methanol or ethanol and in the presence of NEt_3, the corresponding 6- and 2-carbalkoxy derivatives were isolated in high yields. Similarly, reactions of compounds **4** and **6** with CO in di-n-propylamine as solvent gave the corresponding 6- and 2-carboxamide derivatives.

Keywords: Palladium complexes; Cyclopalladate complexes; Schiff base complexes

1. Introduction

Cyclopalladation reactions permit selective activation of C–H bonds in heterosubstituted organic molecules [1]. Whereas heteroatom directed cyclometallation of benzenoid and heteroaromatic systems has been extensively investigated [1–3], only recently has this methodology been applied by us to indole derivatives [4a,b]. The carbonylation at atmospheric pressure in alcohols of the cyclopalladated complexes of gramine and 1-methyl gramine allowed the isolation of the corresponding 2-carbalkoxy indole derivatives in high yields [4c]. With the aim of obtaining useful intermediates for the synthesis of alkaloids [5a,b], we addressed the cyclopalladation reactions of Schiff bases derived from homoveratrylamine (**1**) and tryptamine (**2**) to C(6) and C(2) positions for **1a,b** and **2a-c**, respectively, using a strong electrophilic Pd(II) species in aprotic solvents (e.g. $Pd(OAc)_2/CH_2Cl_2$) [6]. Furthermore, any attempts to perform cyclopalladation with $Pd(OAc)_2$ in refluxing AcOH were frustrated by the overwhelming acid-catalysed cyclisation to get the benzylisoquinoline or β-carboline systems (Pictet–Spengler reaction) [7]. Reactions of the cyclopalladated products with carbon monoxide at atmospheric pressure in the presence of alcohols led to the isolation in high yields of the 6- and 2-carbethoxy derivatives **10**, **11** and **12**, **13**, respectively, and in the presence of di-n-propylamine gave the 6- and 2-carboxamide derivatives **14** and **15**.



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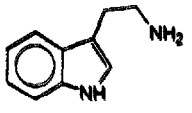

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2. Results and discussion

Li_2PdCl_4 in ethanol, with homoveratrylamine (**1**) and tryptamine (**2**), in the presence of NaOAc as a proton scavenger, gave a complex mixture of products. Among others, palladium metal and uncharacterisable compounds have been obtained. For this reason, the amino groups were protected by reacting homoveratrylamine (**1**) and tryptamine (**2**) with aromatic aldehydes to give the corresponding Schiff bases (Eqs. (1) and (2)) (see Section 4).

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[1] Dedicated to Professor Ivano Bertini, in recognition of his important contributions to bioinorganic chemistry.

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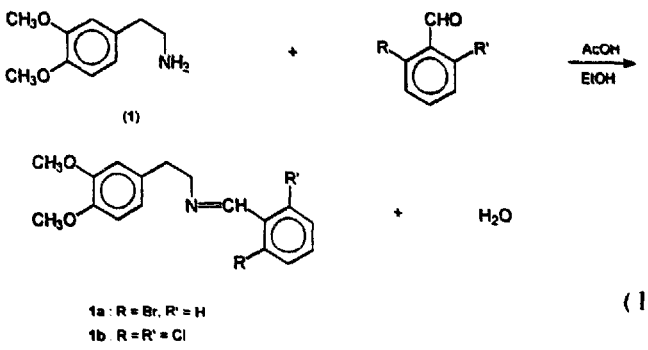

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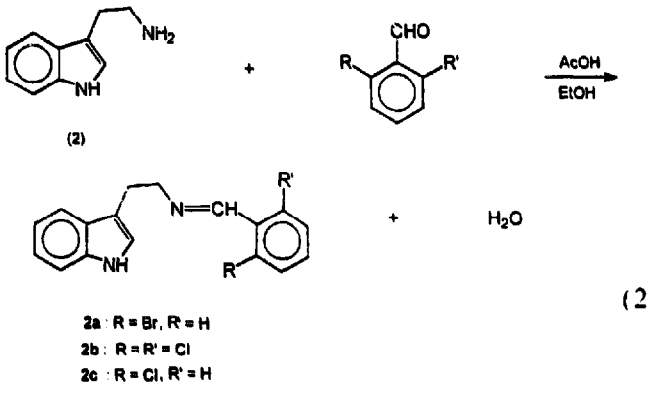

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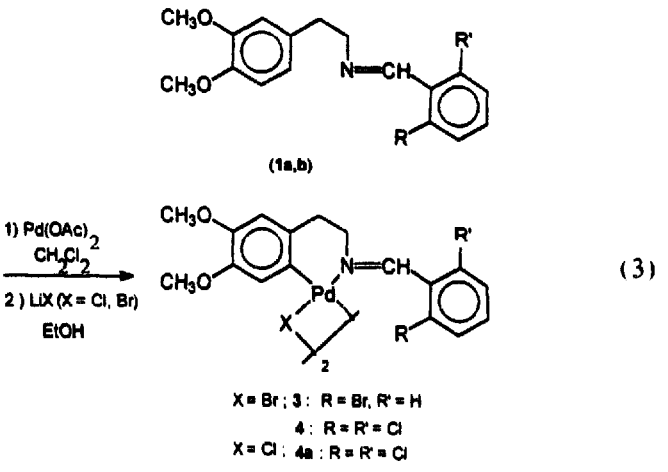
Once functionalised in the 6 and 2 position, compounds **1a,b** and **2a–c** can readily give back the free amino group by hydrolysis. At the beginning of our research, compounds **1b** and **2b**, having the *ortho* positions of the benzaldehyde residue blocked by the substituents, were investigated. The R and R' substituents in the 2' and 6' positions should in fact avoid the metallation at the phenyl ring, with formation of a five-membered metallacycle, which is thermodynamically favoured with respect to a six-membered metallacycle (metallation at the 2 position of the indole nucleus and at position 6 of the aromatic ring bearing the ethylimino substituent). However it was soon discovered that even when R' = H the metallation occurs at the desired 2 or 6 position. Responsible for the outcome of the reaction, is the fact that both the indole ring in 2 and the dimethoxy benzene ring in 6 are strongly activated towards electrophilic reagents, and palladium(II) can be considered a strong electrophile. The reactions of the Schiff bases with Li_2PdCl_4 in methanol did not give satisfactory results. The insoluble, yellow–orange materials obtained were mixtures of products. This has been confirmed by reaction with PPh_3, and NMR analyses of the soluble compounds thus obtained. The ^1H NMR spectra showed the presence of the desired cyclometallated product (see later for the discussion of the NMR spectra of the cyclometallated derivatives) together with complexes derived from the coordination to the metal of the Schiff bases only via the nitrogen atom of the imino group. It was in fact possible to detect the resonance of the proton in 2 in the case of the tryptamine derivative (**2a–c**) (δ = 6.82 ppm) and of the proton in 6 (part of an ABX system) of the aromatic ring in the case of the homoveratrylamine derivatives (**1a,b**) (δ = 7.11 and 7.08 ppm). We thus utilised a slightly different methodology, already employed for the synthesis of cyclometallated derivatives [4c,8]. The desired derivatives were obtained by reaction of $Pd(OAc)_2$ with the Schiff bases in CH_2Cl_2, followed by treatment in situ, after evaporation of the solvent, of the residue with an excess of LiCl or LiBr in ethanol, without isolating the intermediate dimeric acetate derivatives (Eqs. (3) and (4)) (Table 1).



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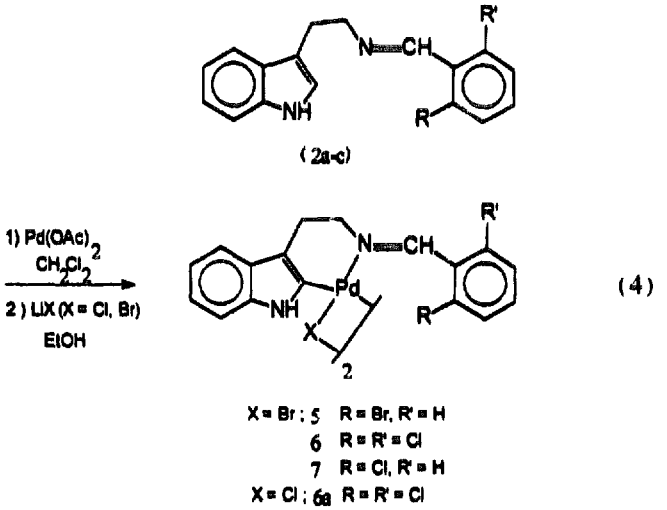

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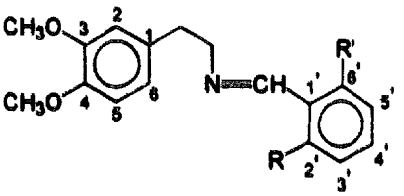
Compounds **3–7** gave satisfactory elemental analyses and showed the expected absorptions in the IR spectra (Table 1). These compounds are insoluble in the common organic solvents. In order to obtain derivatives suitable for a ^1H NMR spectroscopic characterisation, compounds **4** and **6** were treated with PPh_3 in dichloromethane. From these reactions, the monomeric, cyclopalladated complexes **8** and **9** were isolated (Eqs. (5) and (6)) (Tables 1–3).

Table 1
Analytical and IR data

Compound	Colour	Yield (%)	*Anal.* Calc. (Found) (%)			IR data (cm^{-1})	
			C	H	N	ν(C=N)	ν(Pd–Cl)
3	brown	87	38.27 (37.96)	3.13 (2.91)	2.63 (2.62)	1615	
4	green	83	39.00 (39.03)	3.10 (3.17)	2.70 (2.64)	1614	
4a	brown	86	45.67 (45.81)	3.61 (3.59)	3.13 (3.36)	1605	298
5	brown	88	39.92 (40.00)	2.56 (2.62)	5.48 (5.60)	1610	
6	red	95	40.72 (39.96)	2.39 (2.35)	5.58 (5.78)	1612	
6a	red	89	44.62 (44.95)	2.95 (3.01)	6.13 (5.93)	1610	298
7	brown	93	47.72 (47.87)	2.81 (2.92)	6.00 (5.94)	1605	
8	yellow	87	56.15 (55.96)	4.44 (4.16)	1.70 (1.86)	1644	
9	light green	91	55.19 (55.31)	3.63 (3.79)	3.60 (3.36)	1651	

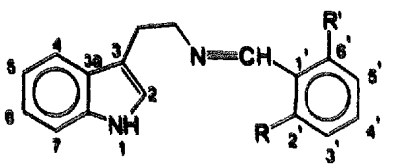
Table 2
^{1}H NMR spectra [a]



Compound	δ(=CH)	δ(CH aromatic)	δ(H-2)	δ(H5)	δ(H6)	δ(CH_2N)	δ(OMe)	δ(CH_2)
1a	8.53 (1H,s)	6.85–7.52 (4H, m)	6.86 (1H,d) $J_{H,H}$: 3.2	6.84 (1H,d) $J_{H,H}$: 8.5	7.12 (1H,dd) $J_{H,H}$ 8.5; 3.2	3.98 (2H,t)	3.88 (6H,s)	3.11 (2H, t)
1b	8.55 (1H,s)	6.82–7.65 (3H, m)	6.79 (1H, d) $J_{H,H}$: 3.1	6.81 (1H, d) $J_{H,H}$: 8.1	7.09 (1h, dd) $J_{H,H}$ 8.1; 3.1	3.97 (2H,t)	3.89 (6H,s)	3.09 (2H, t)
8	8.61 (1H,s)	6.79–7.56 (18H, m)	6.82 (1H, s)	6.93 (1H, s)		4.15 (2H,t)	3.93 (6H,s)	3.15 (2H, t)

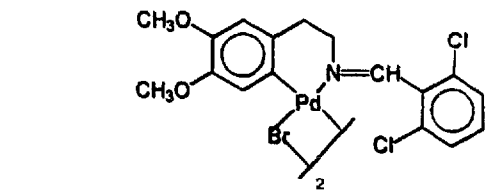
[a] Spectra measured at 200 MHz, $CDCl_3$; chemical shifts δ (ppm) with Me_4Si as internal standard; coupling constants J (Hz).

Table 3
^{1}H NMR spectra [a]



Compound	δ(H-1)	δ(=C-H)	δ(H-7)	δ(H4)	δ(C–H aromatic)	δ(CH_2N)	δ(CH_2)
2a	8.86 (1H, s)	8.55 (1H, s)	8.14 (1h, dd) $J_{H,H}$ 8.0; 3.1	7.82 (1h, dd) $J_{H,H}$ 8.1; 3.1	6.86–7.22 (7H, m)	4.08 (2H, t)	3.21 (2H, t)
2b	8.91 (1H, s)	8.49 (1H, s)	7.09 (1h, dd) $J_{H,H}$ 8.1; 3.1	7.66 (1h, dd) $J_{H,H}$ 8.2; 3.1	6.91–7.09 (6H, m) [b]	4.12 (2H, t)	3.23 (2H, t)
2c	8.9 (1H, s)	8.53 (1H, s)	8.12 (1h, dd) $J_{H,H}$ 8.2; 3.1	7.73 (1h, dd) $J_{H,H}$ 8.0; 3.2	6.88–7.11 (7H, m) [b]	4.13 (2H, t)	3.18 (2H, t)
9	9.22 (1H, s)	8.61 (1H, s)	7.87 (1h, dd) $J_{H,H}$ 8.1; 3.1		6.87–7.31 (21H, m) [c]	4.25 (2H, t)	3.29 (2H, t)

[a] Spectra measured at 200 MHz, $CDCl_3$; chemical shifts δ (ppm) with Me_4Si as internal standard; coupling constants J (Hz).
[b] The signal of H-2 of the indole nucleus is present in the multiplet.
[c] The signal of H-4 is present in the multiplet due to PPh_3 and the other aromatic hydrogens.



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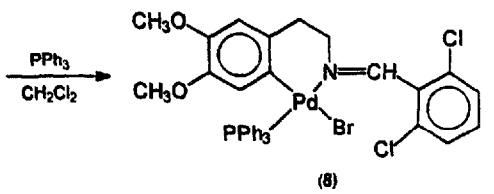

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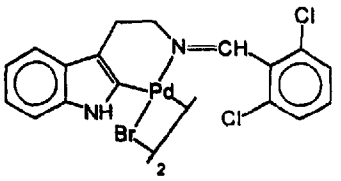

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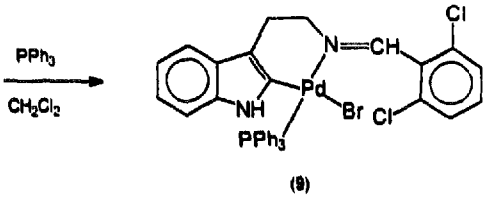
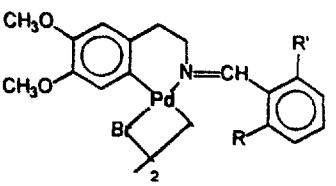


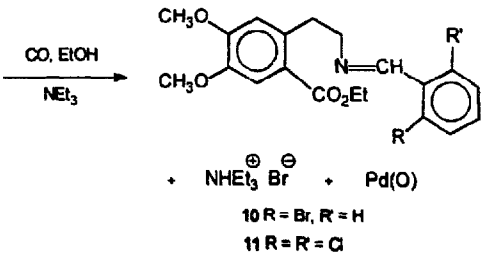
(9) (6)

Analogously to the corresponding derivatives of gramine [4c], compounds **8** and **9** probably have the halogen *trans* to the metallated carbon. In the ^{1}H NMR spectrum, compound **8** showed signals at δ 3.15 (2H, t, CH_2CH_2N), 3.93 (6H, s, OCH_3), 4.15 (2H, t, CH_2CH_2N), 6.82 (1H, s, H-2), 6.93 (1H, s, H-5), 7.36 (18H, m, PPh_3 and $C_6H_3Cl_2$) and 8.61 (1H, s, N=CH–). The signal of H-6 was absent confirming the proposed formulation. For compound **9** the corptions in the ^{1}H NMR spectrum were observed at δ 3.22 (2H, t, CH_2CH_2N), 4.23 (2H, t, CH_2CH_2N), 7.34 (21H, m, PPh_3 and $C_6H_3Cl_2$ and H4-6), 7.81 (1H, dd, H-7, $J_1 = 8$ Hz, $J_2 = 3$ Hz), 8.65 (1H, s, N=CH–) and 9.24 (1H, s, NH). The signal of H-2 was absent, again confirming the proposed structure. One of the main aims of our work was to synthesise cyclopalladated complexes, useful for functionalisation of the metallated rings. Compounds **3–6** proved to be useful starting materials for the synthesis of 6- and 2-carbalkoxy derivatives of compounds **1a,b** and **2a–c**.

Compounds **3** and **4**, suspended in alcohol, reacted with CO at atmospheric pressure and room temperature in the presence of Et_3N to give the desired organic compounds (Eq. (7)).



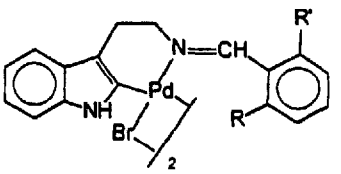
(3) and (4)



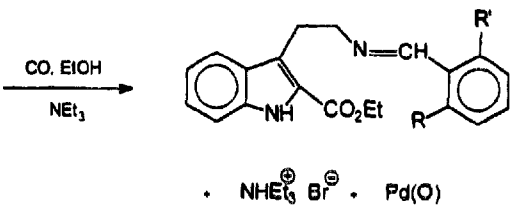
(7)

10 R = Br, R' = H
11 R = R' = Cl

A similar reaction was observed with compounds **5** and **6** (Eq. (8)).



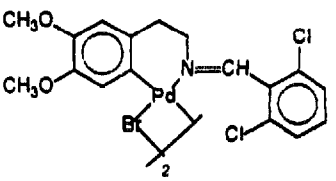
(5) and (6)



(8)

12 R = Br, R' = H
13 R = R' = Cl

Use of methanol instead of ethanol with compound **6** gave the corresponding carbomethoxy derivative. By using di-n-propylamine as the solvent of the reaction and compounds **4** and **6** as starting materials, the corresponding 6- (**14**) and 2- (**15**) carboxamide derivatives were also obtained (Eqs. (9) and (10)).



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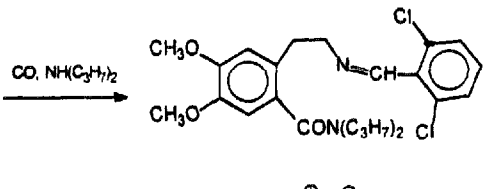

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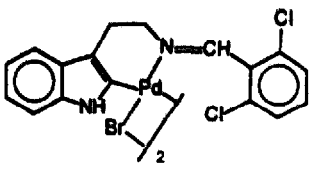
(14)



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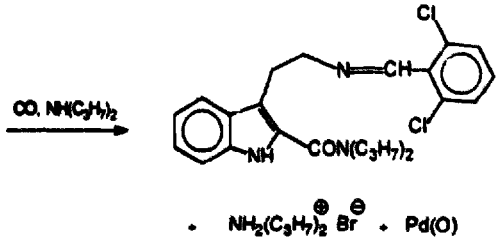

(15)

(10)

Analogous reactions attempted by using piperidine, NC_5H_{11}, as solvent, were unsuccessful.

3. Conclusions

The Schiff bases of homoveratrylamine (**1**) and of tryptamine (**2**) readily give cyclometallated complexes with palladium salts. The nitrogen atom of Schiff bases is capable of directing cyclometallation at the 6 and 2 positions of the aromatic (compounds **1a,b**) and indole nucleus (compounds **2a–c**), respectively, with formation of six-membered metallacycles **4–7**. The thermodynamically more favourable metallation at the 2′ position of the aromatic ring of the aldehyde residue, to give a five-membered metallacycle, is prevented by the fact that both the dimethoxy benzene ring and the indole nucleus are strongly activated towards electrophilic substitutions, and palladium(II) can be considered a good electrophile. The highly selective metallation reaction, and the easy reaction with carbon monoxide at atmospheric pressure in alcohol of the cyclopalladated complexes, allowed the synthesis of the 6- and 2-carbalkoxy derivatives of compounds **1a,b** and **2a–c** in excellent yields. A similar reaction to give the 6-carboxamide derivatives of compounds **1b** and **2b** was also observed. It is worth mentioning here that the classical organic synthesis of these organic compounds is not trivial. Reactions (7)–(10) probably proceed via bridge splitting by NEt_3 or $NH(C_3H_7)_2$ of compounds **3, 4, 5** and **6**, coordination and insertion of carbon monoxide into the Pd–C bond, and nucleophilic attack by alcohol or the secondary amine to the carbonyl function of the acyl palladium(II) intermediate to give the final products.

4. Experimental

IR spectra were recorded in nujol mull on Perkin-Elmer 1310 and Nicolet MX-1FT-IR spectrophotometers. Elemental analyses were carried out on a Perkin-Elmer 2400 CHN elemental analyser. ^{1}H NMR spectra were obtained using a Bruker AC-200 (200 MHz) spectrometer. Homoveratrylamine, tryptamine, 2,6-dichlorobenzaldehyde, 2-chloro- and 2-bromobenzaldehyde and palladium(II) acetate were purchased from Aldrich, and were used as received.

4.1. Preparation of Schiff base 1a,b

Homoveratrylamine (500 mg, 2.76 mmol) was dissolved in ethanol (5 ml). The substituted benzaldehyde (2.85 mmol) and 0.2 ml of AcOH were added and the solution heated under reflux conditions for 2 h. The solution was cooled with an ice bath and stored at −20°C overnight. The resulting crystalline product was filtered off, washed with cold ethanol–water (3×2 ml) and dried in vacuo. Yield: **1a**: 817 mg, 85%; **1b**: 787 mg, 82%. For the ^{1}H NMR data see Table 2.

4.2. Preparation of Schiff bases 2a–c

Tryptamine (3.12 mmol) was dissolved in ethanol (5 ml). The substituted benzaldehydes (3.12 mmol) and 0.2 ml of AcOH were added and the solution heated under reflux conditions for 2 h. The solution was cooled with an ice bath and stored at −20°C overnight. The resulting crystalline product was filtered off, washed with cold ethanol–water (3×2 ml) and dried in vacuo. Yield: **2a**: 805 mg, 79%; **2b**: 731 mg, 81%; **2c**: 686 mg, 78%. For the ^{1}H NMR data see Table 2.

4.3. Cyclopalladation of Schiff bases 1a,b and 2a–c

0.5 mmol of Schiff base was dissolved in 10 ml of degassed methylene chloride under N_2 and 0.5 mmol of $Pd(OAc)_2$ was added. The reaction was stirred at room temperature for 1 h. Evaporation of solvent in vacuo gave a yellow–orange product, which was dissolved, under N_2, in 10 ml of degassed methanol. 0.5 mmol of LiBr or LiCl dissolved in 5 ml of degassed EtOH was added and the solution was stirred for 1 h. Solid products (**3, 4, 4a, 5, 6, 6a, 7**) were filtered off and dried in vacuo. For yields and analytical data see Table 1.

4.4. Synthesis of triphenylphosphine complexes 8 and 9

A stirred suspension of the dimeric complexes **4** or **6** (0.4 mmol) in degassed dichloromethane (5 ml) was treated with PPh_3 (262 mg, 1 mmol) at room temperature for 1 h under a dinitrogen atmosphere. Addition of n-hexane (15 ml) to the solution resulted in the precipitation of the yellow solids. Recrystallisation of the crude products from dichloromethane/n-hexane gave the analytically pure yellow products. For yields and analytical data see Tables 1–3.

4.5. Preparation of carbethoxy derivatives 10, 11 and 12, 13

Carbonylation of the μ-dibromo complexes **3, 4** and **5, 6** (0.5 mmol) in ethanol (10 ml) at room temperature with CO

at atmospheric pressure was carried out in the presence of triethylamine (2 mmol) for 3 h. The precipitated palladium metal was separated by filtration and the solvent was evaporated to dryness. The residues were purified on a silica gel column eluting with dichloromethane–methanol (19:1) to give **10** (78%), **11** (81%), **12** (77%) and **13** (85%).

10 ($CDCl_3$, 200 MHz, δ): 1.14 (t, 3H, CH_3CH_2O), 3.22 (t, 2H, CH_2CH_2N), 3.89 (s, 6H, OMe), 3.91 (t, 2H, CH_2CH_2N), 4.26 (qt, 2H, CH_3CH_2O), 6.82–7.62 (m, 6H, aromatic), 8.52 (s, 1H, =CH). EI-MS (70 eV): *m/z* 421 (56%), 419 (54%), 376 (98%) 374 (100%), 348 (86%), 346 (85%), 196 (72%). IR (nujol mull): 1711 cm^{-1}.

11 ($CDCl_3$, 200 MHz, δ): 1.17 (t, 3H, CH_3CH_2O), 3.12 (t, 2H, CH_2CH_2N), 3.89 (s, 6H, OMe), 3.95 (t, 2H, CH_2CH_2N), 4.31 (qt, 2H, CH_3CH_2O), 6.82–7.62 (m, 5H, aromatic), 8.49 (s, 1H, =CH). EI-MS (70 eV): *m/z* 414 (66%), 412 (84%), 410 (32%), 369 (81%), 367 (100%), 363 (48%), 186 (72%). IR (nujol mull): 1704 cm^{-1}.

12 ($CDCl_3$, 200 MHz, δ): 1.15 (t, 3H, CH_3CH_2O), 3.22 (t, 2H, CH_2CH_2N), 4.02 (t, 2H, CH_2CH_2N), 4.31 (qt, 2H, CH_3CH_2O), 7.31–7.82 (m, 6H, aromatic), 7.91 (dd, 1H, H-4, $J=8.2$, $J=3.1$), 8.25 (dd, 1H, H-7, $J=8.3$, $J=3.2$), 8.49 (s, 1H, =CH), 8.82 (s, 1H, NH). EI-MS (70 eV): *m/z* 398 (66%), 396 (65%), 353 (33%), 351 (32%), 325 (97%), 323 (100%), 158 (32%). IR (nujol mull): 1718 cm^{-1}.

13 ($CDCl_3$, 200 MHz, δ): 1.16 (t, 3H, CH_3CH_2O), 3.24 (t, 2H, CH_2CH_2N), 4.04 (t, 2H, CH_2CH_2N), 4.35 (qt, 2H, CH_3CH_2O), 6.9–7.9 (m, 5H, aromatic), 7.78 (dd, 1H, H-4, $J=8.1$, $J=3.1$), 8.29 (dd, 1H, H-7, $J=8.2$, $J=3.2$), 8.51 (s, 1H, =CH), 8.84 (s, 1H, NH). EI-MS (70 eV): *m/z* 392 (66%), 390 (85%), 388 (35%), 347 (77%), 345 (100%), 343 (52%), 197 (32%), 115 (34%). IR (nujol mull): 1711 cm^{-1}.

4.6. *Preparation of carboxamide derivatives 14 and 15*

Carbonylation of the μ-dibromo complexes **4** and **6** (0.5 mmol) in di-n-propylamine (10 ml) at room temperature with CO at atmospheric pressure was carried out for 4 h. The precipitated palladium metal was separated by filtration and the solvent was evaporated to dryness. The residues were dissolved in methylene chloride, washed twice with water, dried over Na_2SO_4, evaporated in vacuo and then purified on a silica gel column eluting with dichloromethane–methanol (19:1) to give **14** (81%) and **15** (77%).

14 ($CDCl_3$, 200 MHz, δ): 0.95 (t, 6H, $N(CH_2CH_2CH_3)_2$), 1.51 (m, 4H, $N(CH_2CH_2CH_3)_2$), 2.17 (t, 4H, $N(CH_2CH_2CH_3)_2$), 3.22 (t, 2H, CH_2CH_2N), 3.85 (s, 6H, OMe), 4.04 (t, 2H, CH_2CH_2N), 6.83 (s, 2H, H-2 and H-5), 6.91–7.24 (m, 3H, aromatic), 8.32 (s, 1H, CH=N–). EI-MS (70 eV): *m/z* 368 (36%), 366 (59%), 363 (36%), 340 (73%), 338 (100%), 336 (54%), 186 (47%). IR (nujol mull): 1666 cm^{-1}.

15 ($CDCl_3$, 200 MHz, δ): 1.12 (t, 6H, $N(CH_2CH_2CH_3)_2$), 1.54 (m, 4H, $N(CH_2CH_2CH_3)_2$), 2.22 (t, 4H, $N(CH_2CH_2CH_3)_2$), 3.25 (t, 2H, CH_2CH_2N), 4.04 (t, 2H, CH_2CH_2N), 6.66–7.65 (m, 5H, aromatic), 7.79 (dd, 1H, H-4, $J=8.1$, $J=3.3$), 8.26 (dd, 1H, H-7, $J=8.3$, $J=3.2$), 8.42 (s, 1H, =CH), 8.86 (s, 1H, NH). EI-MS (70 eV): *m/z* 447 (33%), 445 (55%), 443 (13%), 355 (75%), 353 (100%), 351 (52%), 327 (47%), 325 (73%), 323 (25%), 130 (36%). IR (nujol mull): 1662 cm^{-1}.

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