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Improving regioselectivity in the rhodium catalyzed hydroformylation of protoporphyrin-IX and chlorophyll *a* derivatives

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Abstract

An efficient and selective catalytic process to promote the hydroformylation of protoporphyrin-IX dimethyl ester, the respective nickel(II) and zinc(II) complexes and also of methyl pheophorbide *a* allomer is described. The effect of the central metal ion, pressure, temperature and phosphine ligand structure on the regioselectivity of the reactions is discussed and molecular PM3 calculations are presented in order to rationalize these effects. The hydroformylation reaction of protoporphyrin-IX dimethyl ester using triphenylphosphine (PPh_3) as ligand, at 30 bar and 31 °C yielded 98% of branched aldehyde. However, using 9,9-dimethyl-4,6-bis(diphenylphosphino)xanthene (Xantphos), as ligand, at 20 bar and 80 °C, 74% of linear aldehyde was observed. The regioselectivity of the reaction is strongly dependent on the central metal ion. The zinc(II) complex of protoporphyrin-IX dimethyl ester favours the formation of the branched aldehyde (99%) independently of reaction conditions, while the regioselectivity with the nickel(II) complex showed a dependence both on pressure and temperature.

The hydroformylation of methyl pheophorbide *a* allomer yields 98% of the branched aldehyde even at 20 bar and 80 °C reaction conditions.

Keywords: Hydroformylation; Rhodium; Protoporphyrin-IX; Chlorophyll *a*; Phosphines; Regioselectivity

1. Introduction

The synthesis of pharmaceutical drugs and complex molecules for new materials is strongly dependent on the availability of reactive intermediates for further structural elaboration. The hydroformylation reaction catalyzed by rhodium modified phosphorous ligands is currently a very promising tool for organic chemistry involved in the production of a large variety of molecules [1–5].

The development of efficient regioselective synthetic methods for hydroformylation of β-vinylporphyrins is of great interest due to the multiple applications of tetrapyrrolic macrocyles in the development of new materials for molecular electronics purposes [6] new oxidation catalysts [7,8] and specially for medical applications [9,10].

For organic synthesis it is very important to develop efficient regio, chemo and enantioselective catalytic hydroformylation systems. There are several reviews on this field describing the effect of pressure, temperature and ligand structure on the regioselectivity of hydroformylation reactions, catalyzed by rhodium modified complexes [11–14].

Ojima et al. [15] and Tanaka and co-workers [16] showed that high pressure (30 bar) and low temperatures (40 °C) produced a 99:1 ratio of branched/linear aldehyde for the hydroformylation reaction of vinyl acetate and styrene catalyzed by rhodium modified catalysts, while with low pressure (1 bar) and high temperature (80 °C) a branched/linear aldehyde ratio of 1:3 was obtained. Clearly, the branched metal σ-alkyl is more stable than the linear species due to resonance stabilization [17]. Vinylporphyrins can be structurally similar regarded as styrene but with a larger aromatic ring, so the electronic stabilization of the branched σ-alkyl would be even more favourable.

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There is still some controversy relatively to the electronic and steric effects on the regioselectivity of hydroformylation reactions. [18,19] It is described that phosphines with large bite angle (120°) favour the terminal hydroformylation, so Xantphos and 2,2′-bis-[(diphenylphosphino)methyl]-1,1′-biphenyl (Bisbi) are now phosphines of choice to favour the formation of linear aldehydes [20].

For further chemical derivatizations of the new β-formyl porphyrins it is very important to obtain selectively the branched or the linear aldehyde. In a pioneer publication in this area [21] we presented the first direct introduction of formyl groups into β-vinylmetalloporphyrins. A significant effect of the central metal on the regioselectivity of the hydroformylation reaction of metal complexes of protoporphyrin-IX dimethyl ester, catalyzed by rhodium triphenylphosphine complexes, was observed for the first time.

In this publication we extend such studies to the free base protoporphyrin-IX dimethyl ester and to methyl pheophorbide *a* allomer obtained from the *Spirulina Maxima* alga. A systematic study of the influence of the central metal, phosphine structure, temperature and pressure on the regioselectivity of the reaction is discussed. To rationalize the effect of the central metal ion on the regioselectivity of these reactions, PM3 semi-empirical calculations are performed. Full discussion of the characterization of the new formylated derivatives is also presented.

2. Experimental

2.1. General procedure

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ solutions on Bruker Avance 300 and 500 spectrometers, operating at 300.13 and 500.13 for ^{1}H and 75.47 and 125.76 MHz for ^{13}C, respectively. ^{1}H assignments were made using 2D *g*COSY and NOESY (mixing time of 800 ms) experiments, while ^{13}C assignments were made using 2D *g*HSQC and *g*HMBC experiments (long range C/H coupling constants were optimized to 7 Hz).

The UV–vis spectra were recorded in a UV-2001 HITACHI using glass vessels with optical length of 1 cm.

MS-FAB$^+$ analysis was performed using a spectrometer VG AutoSpec Q, operating at 70 eV, using $CHCl_3$ as solvent and NBA (3-nitrobenzylic alcohol) as matrix.

Solvents were obtained from commercial sources (Aldrich) and distilled and dried before use, according to standard procedures [22].

$[Rh_2(\mu\text{-}OMe)_2(cod)_2]$ was synthesized by a slightly modified procedure with respect to those described in the literature [23].

All semi-empirical calculations carried out in this work used the GAMESS package [24] and were performed at the PM3 level. Prior assessment of the general structure of the molecule employed the TINKER [25] set of programs.

2.2. Metal complexes synthesis

2.2.1. Zinc(II) complex of protoporphyrin-IX dimethyl ester **2**

Zn(II) protoporphyrin-IX dimethyl ester **2**, was synthesized from protoporphyrin-IX dimethyl ester (100 mg, 0.17 mmol) by chloroform/methanol/$Zn(OAc)_2$ method [26,27] yielding 90% of Zn(II) protoporphyrin-IX dimethyl ester (100 mg). ^{1}H NMR (300 MHz, ppm) δ = 3.00–3.08 (2d, J = 8.3 Hz, 4H, CH_2-13^2 and -17^2), 3.35 (s, 3H, CH_3), 3.44 (s, 9H, 3 CH_3), 3.65 (2s, 6H, CH_{3ester}), 4.16 (2d, 4H, J = 8.3 Hz, CH_2-13^1 and -17^1) 6.07–6.29 (m, 4 H_{vinyl}), 7.92–8.15 (m, 2 H_{vinyl}), 9.14 (s, 1 H_{meso}), 9.15 (s, 1 H_{meso}), 9.31 (s, 1 H_{meso}), 9.43 (s, 1 H_{meso}).

2.2.2. Ni(II) complex protoporphyrin-IX dimethyl ester **3**

Ni(II) complex protoporphyrin-IX dimethyl ester **3**, was prepared from protoporphyrin-IX dimethyl ester (100 mg, 0.17 mmol) by dimethylformamide/$Ni(OAc)_2$ method [26,27] yielding 80% of isolated product (88.0 mg, 0.14 mmol). ^{1}H NMR (300 MHz, ppm): δ = 3.09 (t, J = 7.6 Hz, 4H, CH_2-13^2 and -17^2), 3.38 (s, 3H, CH_3), 3.39 (s, 3H, CH_3), 3.45 (s, 3H, CH_3), 3.46 (s, 3H, CH_3), 3.67 (s, 6H, 2 CH_{3ester}), 4.17 (t, J = 7.6 Hz, 4H, CH_2-13^1 and -17^1), 6.03–6.16 (m, 4 H_{vinyl}), 7.94–8.08 (m, 2 H_{vinyl}), 9.45 (s, 2 H_{meso}), 9.57 (s, 1 H_{meso}), 9.60 (s, 1 H_{meso}).

2.2.3. Methyl pheophorbide *a* allomer **9**

The extraction of methyl pheophorbide *a* allomer was done according to literature procedures [28,29]. *Spirulina Maxima* alga (500 g) was slurried in acetone (2 L) and then liquid nitrogen was added. The mixture was heated to reflux under nitrogen and stirring for 2 h. The supernatant was then filtered off and more acetone was added to the solid. The extraction and filtration was repeated two more times. The filtrate was then evaporated and purified by alumina (grade V) flash chromatography using in the beginning *n*-hexane as eluent to remove a yellow band and then dichloromethane to isolate the major band corresponding to pheophytin *a*. In order to obtain the methyl pheophorbide *a* allomer, the isolated band was treated with 5% of sulphuric acid in methanol and kept open to air during 24 h. After work-up and extraction with dichloromethane, the final product was isolated by alumina flash chromatography with dichloromethane as eluent and recrystallized with dichloromethane/methanol (150 mg).

MS (FAB) m/z: 622; ^{1}H NMR (300 MHz, ppm): δ = −1.79 (s, 2H, 2 NH), 1.63 (d, J = 7.3 Hz, 3H, CH_3-18), 1.74 (t, J = 7.8 Hz, 3H, CH_3-8^2), 2.29–2.98 (m, 4H, CH_2-17^1, -17^2) 3.28 (s, 3H, CH_3-3), 3.46 (s, 3H, CH_3-2), 3.59 (s, 3H, CH_3-7), 3.67 (s, 3H, OCH_3-13^2), 3.77 (s, 3H, OCH_3-17), 3.64–3.77 (m, 2H, CH_2-8^1) 4.17 (d, J = 9.3 Hz, H-17), 4.52 (q, J = 7.3 Hz, H-18), 5.54 (s, OH-13^2), 6.20–6.36 (m, 2 H_{vinyl}), 8.00–8.09 (dd, J = 6.2 and 11.5 Hz, 1H_{vinyl}), 8.67 (s, 1 H_{meso}), 9.50 (s, 1 H_{meso}) and 9.64 (s, 1 H_{meso}).

2.3. General hydroformylation procedure

The autoclave charged with porphyrinic substrates was purged by three cycles with vacuum and *syn*-gas. Being the reactor in vacuum, the phosphorus ligand (PPh_3 and Xantphos) and $[Rh_2(\mu\text{-}OMe)_2(cod)_2]$ dissolved in toluene were introduced, through the inlet cannula. The reactor was then pressurized with *syn-gas* pressure at the working temperature during 18 h. The conversions and regioselectivities were determined by ^{1}H NMR after evaporation of toluene from the reaction mixture.

2.3.1. 3^1,8^1-diformyl Zn(II) protoporphyrin-IX dimethyl ester **6**

This product was synthesized under catalytic hydroformylation reaction conditions using the general procedure described above. The autoclave was charged with substrate **2** (11 mg, 1.69×10^{-2} mmol) $[Rh_2(\mu\text{-}OMe)_2(cod)_2]$ (1.69×10^{-4} mmol) and triphenylphosphine (4.06×10^{-4} mmol) in toluene (6 mL). The autoclave was then pressurized with the *syn*-gas until the pressure reached to 20 bar (10 bar CO-10 bar H_2) and the temperature was raised to 80 °C. The mixture was analyzed by ^{1}H NMR showing 100% of conversion and chemoselectivity and 99% of regioselectivity for 3^1,8^1-diformyl Zn(II) protoporphyrinate-IX dimethyl ester **6**.

UV–vis: λ_{max} 414.0, 538.0 and 574 nm; MS (FAB) m/z: 714 (M^+); ^{1}H NMR (300 MHz, ppm) $\delta = 2.22$ (d, $J = 6.9$ Hz, 6 H, CH_3-3^2 and -8^2), 2.93 and 3.03 (2 t, $J = 7.7$ Hz, 4 H, CH_2-13^2 and -17^2), 3.51 (s, 3 H, CH_3), 3.58 (s, 9 H, 3 CH_3), 3.61 (s, 3 H, CH_3), 3.66 (s, 3 H, CH_3), 3.81 and 4.16 (2t, $J = 7.7$ Hz, 4 H, CH_2-13^1 and -17^1), 5.31–5.35 (m, 2 H, CH-3^1 and -8^1), 9.16 (s, 1 H_{meso}), 9.63 (s, 1 H_{meso}), 9.80 (s, 1 H_{meso}), 9.97 (s, 1 H_{meso}), 10.47 (d, $J = 2.4$ Hz, 2 H, CHO-$3^1$and -8^1).

2.3.2. 3^1,8^1-diformyl Ni(II) protoporphyrin-IX dimethyl ester **7**

The hydroformylation reaction was performed using the catalytic reaction conditions described above. After evaporation of the solvent the reaction mixture was analysed by 2D-NMR and FAB-MS, showing 99% of conversion with 75% of regioselectivity for 3^1,8^1-diformyl Ni(II) protoporphyrin-IX dimethyl ester, **7** and 25% of a mixture of branched-linear aldehyde.

MS (FAB) m/z: 708 (M^+); ^{1}H NMR (300 MHz, ppm): $\delta = 2.00$ (d, $J = 6.3$ Hz, 6H, CH_3-3^2), 3.09 (t, $J = 7.0$ Hz, 4H, CH_2-13^2 and -17^2), 3.39 and 3.42 (2s, 6H, CH_3), 3.60 and 3.61 (2s, 6H, CH_3), 4.16 (t, $J = 7.0$ Hz, 4H, CH_2-13^1 and -17^1), 5.22 (m, 2H, H-3^1 and -8^1), 9.54 (s, 1H_{meso}), 9.59 (s, 1H_{meso}), 9.70 (s, 1H_{meso}), 9.75 (s, 1H_{meso}), 9.99 (br s, CHO-3^2 or -8^2) 10.28 (br s, 2H, CHO-$3^1$and -8^1); $C_{38}H_{40}N_4NiO_6$: calcd C 64.52, H 5.70, N 7.92 found C 64.29, H 6.32, N 7.52.

2.3.3. 3^1,8^1-di(5,5′-dimethyl-1,3-dioxan-2-yl) Ni(II)-protoporphyrin-IX dimethyl ester **8**

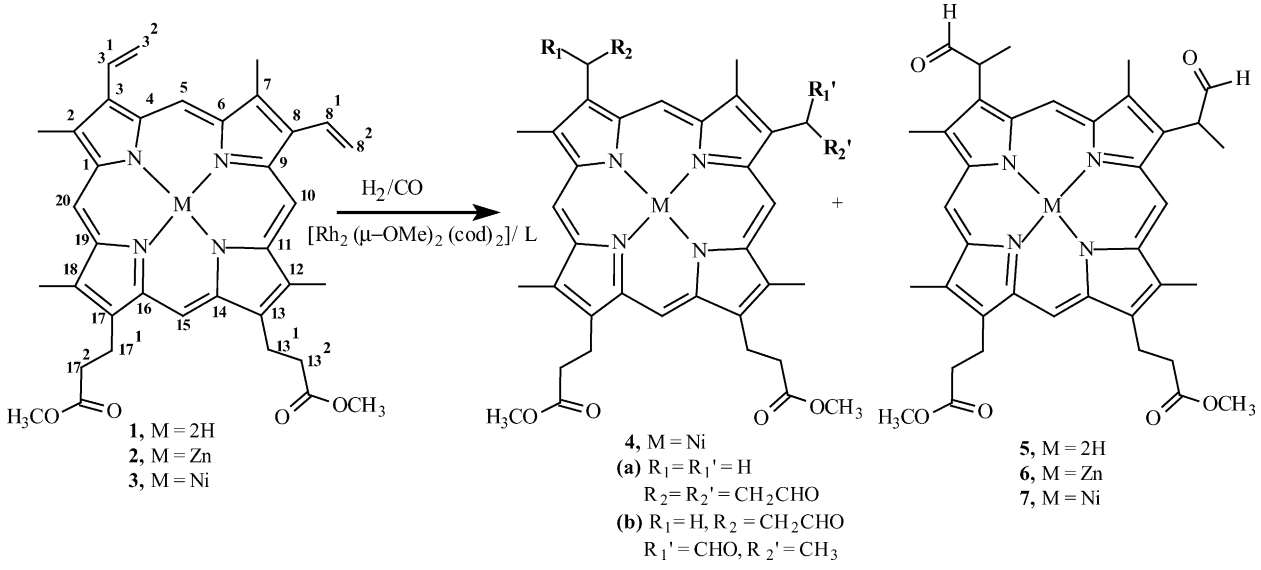
After evaporation of the solvent from the hydroformylation reaction mixture the residue (20 mg) was taken in toluene (60 mL) and neopentanediol (28 equiv., 0.79 mmol) and *p*-toluenesulfonic acid monohydrate (7.39×10^{-3} mmol) were added. This solution was refluxed during 10 h in a system equipped with Dean-Stark apparatus. After work-up the mixture was purified by silica–gel preparative thin-layer chromatography using dichloromethane as eluent. The major product corresponding to the first spot was isolated (11 mg) and it was fully characterised as the 3^1,8^1-di(5,5′-dimethyl-1,3-dioxan-2-yl) Ni(II)-protoporphyrin-IX dimethyl ester **8**.

UV–vis. λ_{max} (nm) (ε): 395.0 (8.70×10^4), 518.0 (2.67×10^3), 553.5 (7.52×10^3); MS (FAB) m/z: 879 (M^+); ^{1}H NMR (500 MHz, ppm) $\delta = 0.74$ and 0.75 (2 s, 6 H, $CH_{3acetal}$), 1.31 (s, 6 H, $CH_{3acetal}$), 2.02 (d, $J = 7.3$ Hz, 3 H, CH_3-H3^2 or H8^2), 2.02 (d, $J = 9.0$ Hz, 3 H, CH_3-H8^2 or H3^2), 3.16 and 3.18 (2t, $J = 7.7$ Hz, 4 H, CH_2-13^2 or 17^2), 3.47–3.50 (m, 2 H, $CH_{2acetal}$), 3.48 (s, 3 H, CH_3), 3.49 (s, 6 H, CH_3), 3.55 (s, 3 H, CH_3), 3.60–3.66 (m, 4 H, $CH_{2acetal}$), 3.68 and 3.69 (2 s, 2 × 3 H, 2 × OCH_3), 3.86 (dt, $J = 2.3$ and 11.1 Hz, 2 H, $CH_{2acetal}$), 4.25 (t, $J = 7.7$ Hz, 4 H, CH_2-13^1 and -17^1), 4.65–4.68 (m, 2 H, H3^1 and H8^1), 5.34–5.36 (m, 2 H, H3^3 and H8^3), 9.72 (s, 1 H_{meso}), 9.77 (s, 1 H_{meso}), 10.01 (s, 1 H_{meso}) and 10.02 or 10.03 (s, 1 H_{meso}); ^{13}C NMR: $\delta = 11.6$, 11.7 and 12.7 (2,7,12,18-CH_3), 17.0 (C-3^2 and C-8^2), 21.8 and 23.2 (4 × $CH_{3acetal}$), 36.8 (C-13^2 and C-17^2), 38.5 (C-3^1 and C-8^1), 77.48, 77.51, 77.56 and 77.62 (4 × $CH_{2acetal}$), 96.2, 97.0, 98.30, 98.34 and 98.4 (C-5, C-10, C-15 and C-20) 104.9 (C-3^3 and C-8^3); 137.3, 137.43, 137.45, 137.65, 137.9, 139.0, 139.1, 140.26, 140.31, 140.9, 141.1, 141.2, 141.3, 141.48, 141.54 and 141.6.

2.3.4. 3^1-Formyl methyl pheophorbide a allomer **10**

Methyl pheophorbide *a* allomer **9**, was submitted to the catalytic hydroformylation reaction conditions using the general procedure described above. The autoclave was charged with substrate **9** (20 mg, 1.60×10^{-2} mmol) $[Rh_2(\mu\text{-}OMe)_2(cod)_2]$ (3.20×10^{-4} mmol) and triphenylphosphine (3.84×10^{-4} mmol) in toluene (8 mL). The autoclave, was then pressurized with the *syn*-gas until the pressure reached 20 bar (10 bar CO-10 bar H_2) and the temperature raise to 80 °C. After toluene evaporation total conversion, 100% of chemo and 98% of regioselectivity for 3^1-formyl methyl pheophorbide *a* allomer **10**, was observed by ^{1}H NMR. After purification by column chromatography using dichloromethane as eluent the 3^1-formyl methyl pheophorbide *a* allomer, **10** (15.3 mg) was isolated and fully characterized by 2D NMR and FAB-MS.

UV–vis. λ_{max}, nm (ε): 409.0 (2.0×10^5), 501.0 (5.15×10^3), 531.0 (5.55×10^3), 606.0 (5.19×10^3) 663.5 (4.11×10^4); MS (FAB) m/z: 652; ^{1}H NMR (300 MHz, ppm): $\delta = -1.88$ (s, 2H, NH), 1.63 (d, $J = 7.3$ Hz, 3H, CH_3-18), 1.74 (t, $J = 7.8$ Hz, 3 H, CH_3-8^2), 2.08 (d, $J = 6.9$ Hz, 3 H, CH_3-3^1) 2.29–2.98 (m, 4 H, 2 CH_2-17^1 and 17^2) 3.27 (s, CH_3-3), 3.36 (s, CH_3-1), 3.56 (s, CH_3-7), 3.62 (s, OCH_3-13^2), 3.74 (s, CH_3-12), 3.62–3.76 (m, CH_2-8^1), 4.17 (d, $J = 9.3$ Hz, H-17), 4.50 (q, $J = 7.3$ Hz, H-18), 5.11 (m, 1H, H-3^1), 5.52 (s, O*H*-13^2), 8.67 (s, 1 H_{meso}), 9.24 (s, 1 H_{meso}) and 9.67 (s, 1



Scheme 1. Hydroformylation reaction of substrates **1–3** with the catalytic systems $[Rh_2(\mu\text{-}OMe)_2(cod)_2]/PPh_3$ and $[Rh_2(\mu\text{-}OMe)_2(cod)_2]$/Xantphos.

H_{meso}), 10.33 (br s, 1H, C*H*O); $C_{37}H_{40}N_4O_7.2H_2O$: calcd C 64.52, H 6.44, N 8.13 found C 64.29, H 6.77, N 8.51.

3. Results and discussion

3.1. Hydroformylation of protoporphyrin-IX dimethyl ester and the respective metal complexes

In a typical experiment, protoporphyrin-IX dimethyl ester **1**, is introduced in an autoclave and degassed. The rhodium phosphine catalyst was generated in situ by mixing the appropriate amounts of $[Rh_2(\mu\text{-}OMe)_2(cod)_2]$ and phosphine ligand (triphenylphosphine or Xantphos) under 20 bar of CO and H_2 pressure and 80 °C of temperature, using toluene as solvent (Scheme 1).

The effect of ligand structure, pressure and temperature on the regioselectivity of the hydroformylation reaction was studied and the results are collected in Table 1.

Under standard conditions, the hydroformylation of β-vinylporphyrin **1**, at 20 bar and 80 °C, provide 99% of conversion, 100% of chemoselectivity and 72% of regioselectivity for branched aldehyde (Table 1, entry 2). Optimization of the catalytic system was carried out in order to improve the regioselectivity of the reaction. Thus, when the pressure was decreased to 3 bar while keeping the temperature at 80 °C, the regioselectivity for branched aldehyde decreased to 59% (Table 1, entry 1). However, raising the pressure to 30 bar and decreasing the temperature to 40 °C increased the regioselectivity for the branched aldehyde to 90% (Table 1, entry 3). Optimized reaction conditions were obtained from a simple 2^2 factorial design. A point on the profile relating pressure and temperature for 100% predicted regioselectivity, chosen from moderate operational conditions (P = 30 bar and 31 °C) has yielded experimentally >98% of branched aldehyde (Table 1, entry 4). These results are in good agreement with the mechanistic studies proposed for hydroformylation of styrene, in similar reaction conditions [17].

In order to preferentially obtain the linear aldehyde, we enlarge the hydroformylation catalytic studies of 1, using the diphosphine Xantphos (Table 1, entry 5). Even at

Table 1
Hydroformylation studies of free base protoporphyrin-IX dimetyl ester **1**, under different reaction conditions

Entry	Catalytic system[a]	P (bar)	T (°C)	Conversion[b] (%)	Linear aldehydes(%)[c]	Branched aldehydes(%)[c]
1	Rh/PPh_3	3	80	78	41	59
2	Rh/PPh_3	20	80	>99	28	72
3	Rh/PPh_3	30	40	95	7	90
4	Rh/PPh_3	30	31	97	0	>98
5	Rh/Xantphos	20	80	>95	74	26
6	Rh/Xantphos	3	80	0	0	0
7	Rh/Xantphos	10	80	0	0	0

[a] Reaction conditions: 1.69×10^{-2} mmol of protoporphyrin-IX dimethyl ester **1**, dissolved in 6 mL of toluene; $[Rh_2(\mu\text{-}OMe)_2(cod)_2]$ (1.69×10^{-4} mmol); PPh_3/Rh = 1.2 and Xantphos/Rh = 1; time: 18 h.

[b] 100% of chemoselectivity was obtained.

[c] Analysis of the total formation of linear or branched aldehydes was obtained by the relative integrations of the respective peaks at δ = 10.09 (br s) and 10.45 (d) in the reaction mixture ^{1}H NMR spectrum.

Table 2
Hydroformylation studies of metalloprotoporphyrin-IX **2** and **3**, under different reaction conditions

Entry	Porphyrin[a]	*P* (bar)	*T* (°C)	Conversion[b] (%)	Linear aldehyde(%)[c]	Branched aldehyde (%)[c]
1	**2**	3	80	58	2	98
2	**2**	20	80	>99	1	99
3	**2**	30	40	65	3	97
4	**3**	3	80	>95	29	71
5	**3**	20	80	>95	25	75
6	**3**	30	40	76	10	90

[a] Reaction conditions: 1.69×10^{-2} mmol of substrates **2** and **3**, dissolved in 6 mL of toluene; $[Rh_2(\mu\text{-}OMe)_2(cod)_2]$ (1.69×10^{-4} mmol); $PPh_3/Rh = 1.2$; time: 18 h.
[b] 100% of chemoselectivity was obtained.
[c] Analysis of the total formation of linear or branched aldehydes was obtained by the relative integrations of the respective aldehydic peaks in the reaction mixture ^1H NMR spectrum.

unfavourable reaction conditions (20 bar and 80 °C) 74% of linear aldehyde was obtained (Table 1, entry 5). At lower pressures, 3 and 10 bar (Table 1, entry 6 and 7) no reaction was observed.

These results are in accordance with the styrene hydroformylation using Xantphos as phosphine ligand, where the linear aldehyde was also formed preferentially [30].

It is remarkable the influence of the phosphine structure on the regioselectivity, yielding 72:28 of total branched/total linear (b/l) aldehydes with triphenylphosphine and 26:74 (b/l) with Xantphos.

The important influence of the central metal ion in the hydroformylation regioselectivity of protoporphyrin-IX dimethyl ester [21] prompted us to extend those studies to other reaction conditions. The desired Zn(II) and Ni(II) complexes, **2** and **3**, respectively, were synthesized according to literature procedures [26,27], and the effects of pressure, temperature and central metal on hydroformylation reaction were studied using $[Rh_2(\mu\text{-}OMe)_2(cod)_2]/PPh_3$ as catalyst. The results obtained are collected in Table 2.

Clearly Zn(II) as central metal favours the formation of the branched aldehyde (>97%) (Table 2, entries 1–3), comparatively to Ni(II) (71–90%) (Table 2, entries 4–6). The effect of pressure and temperature on hydroformylation reactions of porphyrin **1**, and metalloporphyrins **2** and **3**, are compared in Fig. 1.

On the right side (Fig. 2), using Zn(II) complex **2**, the effect of the central metal ion is always predominant relatively to the pressure and temperature effects, so the regioselectivity is independent of pressure and temperature, always yielding the branched aldehydes as main product (up to 98%).

Contrarily to this observation, the introduction of Ni(II) as central metal did not affect significantly the regioselectivity of the hydroformylation reaction and similar results have been

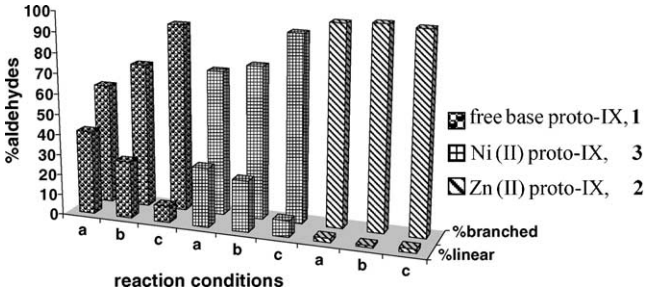


Fig. 1. Yield of linear or branched aldehydes formation from porphyrins **1**, **2** e **3**, at different hydroformylation catalytic reaction conditions a) *P* = 3 bar *T* = 80 °C; b) *P* = 20 bar *T* = 80 °C; c) *P* = 30 bar *T* = 40 °C.

obtained for free base porphyrin **1**, and the Ni(II) complex **3** (Fig. 1). An increase on the formation of branched aldehyde was observed with both substrates, when the pressure was raised from 3 to 20 and the temperature maintained at 80 °C (Fig. 1a and b). A remarkable increase on the branched aldehyde was observed for both systems decreasing the temperature to 40 °C and increasing the pressure to 30 bar (Fig. 1c). These results are in good agreement with previously reported hydroformylation reactions of styrene systems [11].

To rationalize the effect of the central metal on the regioselectivity of the hydroformylation reaction we have performed molecular orbital calculations of the porphyrin and metalloporphyrin using simple semi-empirical PM3 calculations. Even though they are inexpensive in computational terms, semi-empirical PM3 calculations are known to produce accurate geometries, with average absolute errors 0.050 Å for bond lengths and 3.9° for bond angles. [31] The optimized structures and selected charges from electron density of free base porphyrin **1**, and of the Zn(II) metal complex **2**, were obtained and are presented in Fig. 2a and b, respectively.

Table 3
Selected dihedral angles of protoporphyrin-IX dimethyl ester **1**, and of Zn(II) complex **2**, obtained by PM3 semi-empirical calculations

Porphyrin	Diedral angle (°)			
	C5—C4—C3—$C3^1$	C10—C9—C8—$C8^1$	C4—C3—$C3^1$—$C3^2$	C9—C8—$C8^1$—$C8^2$
1	3.3	−0.5	21.1	−8.9
2	0.0	−1.0	23.2	−16.5

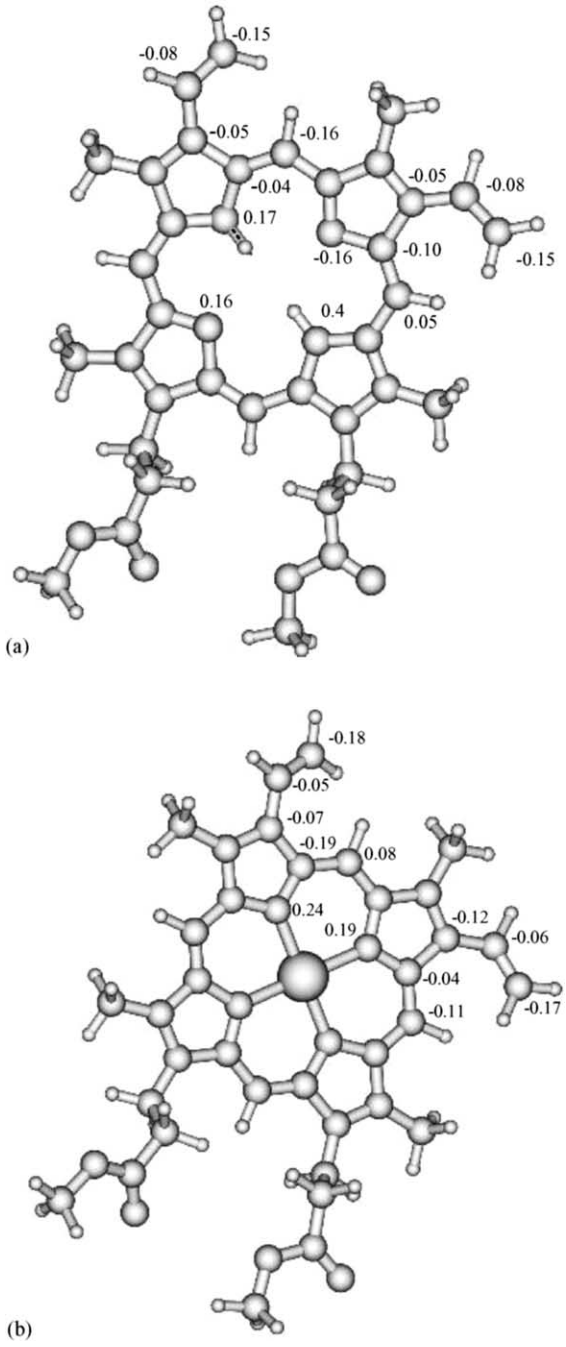


Fig. 2. Optimized structure and selected density charges, obtained by PM3 calculation of: (a) protoporphyrin-IX dimethyl ester **1**; (b) Zn(II) complex of protoporphyrin-IX dimethyl ester **2**.

The structure of the Ni(II) metal complex **3**, was not determined due to absence of parameters for these semi-empirical calculations. The dihedral angles formed between carbons C4–C3–C3^1–C3^2, C9–C8–C8^1–C8^2, C5–C4–C3–C3^1 and C10–C9–C8–C8^1 for protoporphyrin-IX dimethyl ester **1** and the corresponding Zn(II) complex **2**, are presented in Table 3.

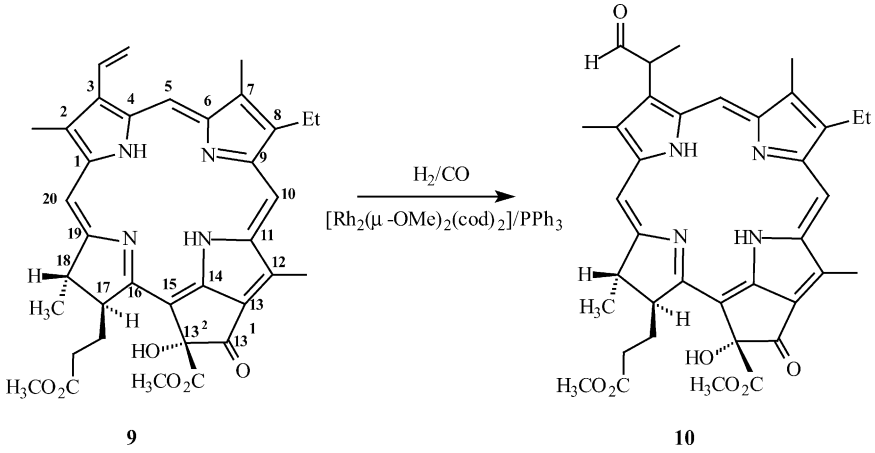
The complexation of protoporphyrin-IX dimethyl ester **1**, with zinc(II) affects the overall peripheral structure and also electron density distribution. One of the main consequences is a modification of the conformation of the double bond relative to the central ring plane. This is seen by the observed differences in dihedral angles C5–C4–C3–C3^1 and C10–C9–C8–C8^1 (Table 3). It is possible to conclude that C3^1 and C8^1 are, in both compounds **1** and **2**, almost coplanar with the surface ring (Table 3). However, from the dihedral angles obtained between C4–C3–C3^1–C3^2 and C9–C8–C8^1–C8^2 it is evident that in the structure of the Zn(II) complex, C3^2 and C8^2 are significantly out of the plane, which can be contrasted with the corresponding C8^{2}carbon atom in the free base porphyrin **1**.

For both substrates, **1** and **2**, the high α-regioselectivity observed for the branched aldehyde isomer during the hydroformylation reaction results essentially from the preferential formation of the branched alkyl-metal intermediate, electronically stabilized, as also observed in styrene hydroformylation studies [32,33].

However, in the hydroformylation reaction of free base porphyrin **1**, a dependence on the regioselectivity from pressure and temperature was observed, while with the Zn(II) complex **2**, up to 98% of branched aldehydes derivative was obtained, irrespective of the reaction conditions (Fig. 1). This behaviour can be rationalized by differences of dihedral angles involving external double bonds and electronic density of the substrates (Table 3 and Fig. 2). The uniform positive charge localized in all nitrogen atoms in Zn(II) complex, as well as the higher differences in out planarity of C3^2 and C8^2 can contribute to the stabilization of C3^1 and C8^1 σ-alkyl complexes due to π cloud delocalization on the surface of the aromatic ring, favouring the preferential formation of branched aldehydes.

The studies on the effects of central metal and reaction conditions over the regioselectivity of hydroformylation reactions were followed by ^{1}H NMR characterization of the final branched derivative **6**, using the previously described reaction conditions (Table 2, entry 2). After toluene evaporation the ^{1}H NMR spectrum reveals total conversion with 100% of chemoselectivity and 99% of regioselectivity for 3^1, 8^1-diformyl Zn(II) protoporphyrin-IX dimethyl ester **6**. This is inferred from the proton resonances of CHO at $\delta = 10.47$ (doublet) and the four meso protons (singlets) at $\delta = 9.17$, 9.63, 9.80 and 9.97.

As previously described [21] in all attempts of aldehyde purification by preparative thin-layer silica–gel chromatography, partial degradation of the product with partial decomplexation has been observed. To overcome these problems, the Ni(II) complex **3**, was also submitted to the same hydroformylation reaction conditions (Table 2, entry 5). After evaporation of toluene, 75% of the branched aldehyde was obtained concomitantly with 25% of a mixture of compounds with linear aldehydes (4a) and (4b) which have been identified by 2D NMR spectroscopy. [21] The reaction was repeated several times and is fully reproducible. To avoid the problems of aldehydes purification by thin layer chromatography, the derivatization of the reaction mixture to



Scheme 2. Hydroformylation reaction of methyl pheophorbide *a* allomer **9**, using the catalytic system $[Rh_2(\mu\text{-}OMe)_2(cod)_2]/PPh_3$.

the corresponding acetals was carried out using neopentanediol. The corresponding product was isolated by preparative thin layer silica–gel chromatography using dichloromethane as eluent and characterized as 3^1,8^1-di(5,5′-dimethyl-1,3-dioxan-2-yl) Ni(II)-protoporphyrin-IX dimethyl ester **8**. The compound gives a FAB mass spectrum with a molecular ion at m/z 879 and it was also fully characterized using ^{1}H, ^{13}C, COSY, HMBC, HSQC NMR techniques [21].

3.2. Hydroformylation of methyl pheophorbide a allomer

To enlarge the potential of the hydroformylation reaction it was decided to promote the direct formylation of another natural tetrapyrrolic macrocycle derivative. The typical reaction conditions described above [Table 2, entry 2; 20 bar 80 °C and $[Rh_2(\mu\text{-}OMe)_2(cod)_2]/PPh_3$)] were applied to methyl pheophorbide *a* allomer **9**, obtained from the natural alga *Spirulina maxima*, according to the literature procedure [28,29].

Interestingly, the hydroformylation reaction of **9**, even at non-favourable reaction conditions (P = 20 bar and T = 80 °C) afforded 98% of branched aldehydes **10**, Scheme 2. This reveals that there is again an important σ-alkyl stabilization of the branched isomer that is strongly dependent upon the whole macrocycle structure. Optimized structure and density charges obtained by PM3 calculations are presented in Fig. 3. The dihedral angles between the carbons C5–C4–C3–$C3^1$ and C4–C3–$C3^1$–$C3^2$ are 2.5 and 36.8, respectively. These are similar to the ones obtained for the zinc(II) dimethyl ester of protoporphyrin-IX structure, supporting the formation of the branched σ-alkyl metal intermediate.

Later than 18 h the autoclave was depressurized and toluene was evaporated. After work-up the reaction mixture was purified by column chromatography using dichloromethane as eluent yielding 73% of 3^1-formyl methyl pheophorbide *a* allomer **10**. The compound presents a FAB mass spectrum with a molecular ion at m/z 652 and was fully characterized by ^{1}H, ^{13}C, COSY, HMBC, HSQC and NOESY NMR techniques.

The ^{1}H NMR of **10** showed the resonance of the aldehydic proton as a doublet (J = 1.5 Hz) at δ 10.33 ppm, and those of the *meso* positions as singlets at δ 9.68, 9.25 and 8.67 ppm. From 2D NMR spectra it was possible to confirm the presence of 1-methyl-2-formylethyl chain: (a) in the COSY spectrum it was detected a correlation of CHO with H-3^1 (δ 5.09–5.15 ppm, m) and of this proton with the 3^1-methyl group (δ 2.08 ppm, d, J = 6.9 Hz); (b) in the NOESY spectrum, a close proximity of H-3^1 with CHO, CH_3-3^1, H-

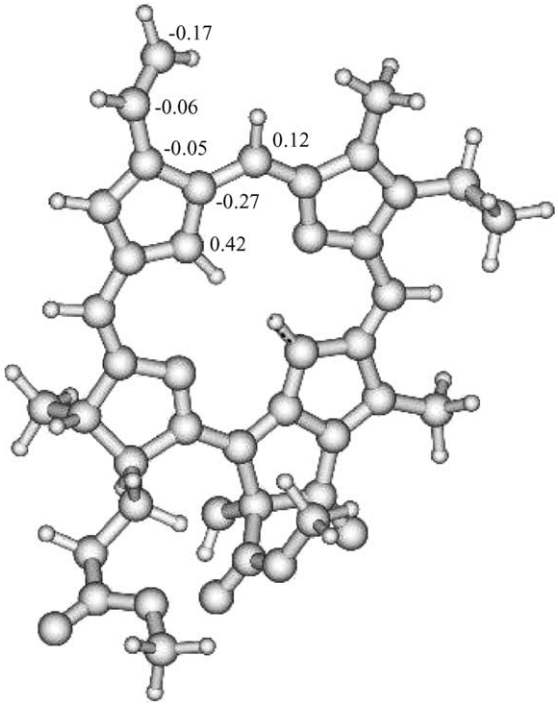


Fig. 3. Optimized structure and selected density charges, obtained by PM3 calculation of methyl pheophorbide *a* allomer **9**.

5 (δ 9.25 ppm, s) and CH_3-2 have also been observed; (c) from HSQC and HMBC spectra we could assign the carbon resonances of CHO, C-3^1 and CH_3-3^1 at δ 200.7, 46.2 and 15.7 ppm, respectively. Furthermore, from the HSQC spectrum the signal at δ 5.57 does not present any correlation with carbon atoms showing that an OH at position 13^2 is present, which is typical of the methyl pheophorbide *a* allomer. This feature was also present in the substrate HSQC spectrum. From the NOESY spectrum it was also possible to confirm the stereochemistry at C-13^2. NOE cross peaks between the proton resonances of OH-13^2 and H-17 suggest a close proximity between these atoms.

4. Conclusion

A new versatile method has been developed to hydroformylate protoporphyrin-IX dimethyl ester, their metal complexes and methyl pheophorbide *a* allomer. The modulation of linear or branched aldehyde was achieved with protoporphyrin-IX dimethyl ester and the respective nickel(II) complex, by varying the phosphine structure and reaction conditions, pressure and temperature. Using triphenylphosphine as ligand, at 30 bar and 40 °C, 90% of branched aldehydes were obtained with both porphyrins. However, using Xantphos as ligand, at $T = 80\,^{\circ}C$ and $P = 20$ bar, a significantly enhancement (74%) on the formation of protoporphyrin-IX dimethyl ester linear aldehydes was observed.

When zinc(II) is used as central metal ion, the exclusive formation of branched aldehyde derivatives was observed independently of the reaction conditions (99%). This behaviour was rationalized by PM3 calculations.

Differences in the dihedral angles of vinyl double bond atoms can contribute to the stabilization of branched σ-alkyl complexes favouring the preferential formation of branched aldehydes.

The hydroformylation of pheophorbide *a* allomer, with just one external double bond, gave mainly the branched aldehyde (98%) with 98% of conversion even at non-favourable reaction conditions.

Furthermore, in all the catalytic systems studied, the chemoselectivity for aldehydes was up to 99%.

These studies provide an important contribution to the one-step regioselective synthesis of formyl-tetrapyrrolic macrocycles which are important derivatives for fine-chemical production.

This catalytic system is currently being extended to other vinylporphyrins using chiral ligands in order to develop the synthesis of new chiral porphyrins and chlorins.

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References

[1] M. Beller, C. Bolm (Eds.), Transition Metals for Organic Synthesis, Building Blocks and Fine Chemistry, 1, Wiley-VCH, Weinheim, 1998, p. 25.
[2] P. Eilbracht, L. Bärfacker, C. Buss, C. Hollmann, B. Kitsos-Rzychon, C. Kranemann, T. Rische, R. Roggenbuck, A. Schmidt, Chem. Rev. 99 (1999) 3329.
[3] F. Ungváry, Coord. Chem. Rev. 228 (2002) 61.
[4] B. Breit, Acc. Chem. Res. 36 (2003) 264.
[5] F. Ungváry, Coord. Chem. Rev. 241 (2003) 295.
[6] Q. Li, G. Mathur, S. Gowda, S. Surthi, Q. Zhao, L. Yu, J.S. Lindsey, D.F. Bocian, V. Misra, Adv. Mater. 16 (2004) 133.
[7] T. Zhiwei, S. Tetsuya, T. Katsuhiko, Mater. Lett. 57 (2003) 2258.
[8] S.L.H. Rebelo, M.M.Q. Simões, M.G.P.M.S. Neves, A.M.S. Silva, J.A.S. Cavaleiro, A.F. Peixoto, M.M. Pereira, Eur. J. Org. Chem. (2004) 4778.
[9] R.K. Pandey, G. Zheng, in: K.M. Kadish, K.M. Smith, R. Guilard (Eds.), The Porphyrins Handbook Applications: Past, Present and Future, Academic Press, New York, 2000, p. 157.
[10] I. Scalise, E.N. Durantini, J. Photochem. Photobiol. A: Chem. 162 (2004) 105.
[11] P.W.N.M. van Leeuwen, C. Claver, Rhodium Catalyzed Hydroformylation, Kluwer Academic Publishers, Dordrecht, 2000, pp. 140.
[12] B. Breit, W. Seiche, Synthesis (2001) 1.
[13] P.W.N.M. van, Leeuwen (Eds.), Homogeneous Catalysis Understanding the Art, Kluwer Academic Publishers, Dordrecht, 2004 (Chapter 8).
[14] B. Cornils, W.A. Herrmann, J. Catal. 216 (2003) 23.
[15] I. Ojima, K. Kato, M. Okabe, T. Fuchikami, J. Am. Chem. Soc. 109 (1987) 7714.
[16] H. Yamashita, B.L. Roan, T. Sakakura, M. Tanaka, J. Mol. Catal. 81 (1993) 255.
[17] P.W.N.M. van Leeuwen, C. Claver (Eds.), Rhodium Catalyzed Hydroformylation, Kluwer Academic Publishers, Dordrecht, 2000 (Chapter 2).
[18] L.A. van der Veen, M.D.K. Boele, F.R. Bregman, P.C. Kamer, P.W.N.M. van Leeuwen, K. Goubitz, J. Fraanje, H. Schenk, C. Bo, J. Am. Chem. Soc. 120 (1998) 11616.
[19] M. Diéguez, M.M. Pereira, A.M. Masdeu-Bultó, C. Claver, J.C. Bayón, J. Mol. Catal. A: Chem. 143 (1999) 111.
[20] P. Dierkes, P.W.N.M. van Leeuwen, J. Chem. Soc., Dalton Trans. (1999) 1519.
[21] A. Peixoto, M.M. Pereira, M.G.P.M.S. Neves, A.M.S. Silva, J.A.S. Cavaleiro, Tetrahedron Lett. 44 (2003) 5593.
[22] H. Burrows, M.M. Pereira (Eds.), Síntese e Estrutura, Escolar Editora, Lisboa, 2005 (Chapter 1).
[23] R. Usón, L.A. Oro, J. Cabeza, J. Inorg. Synth. 23 (1985) 126.
[24] M.W. Schmidt, K.K. Baldridge, J.A. Boatz, S.T. Elbert, M. Gordon, J.H. Jensen, S. Koseki, N. Matsunaga, K.A. Nguyen, S.J. Su, T.L. Windus, M. Dupuis, J.A. Montegomery, J. Comput. Chem. 14 (1993) 1347.
[25] R.V. Pappu, R.K. Hart, J.W. Ponder, J. Phys. Chem. B 102 (1998) 9725.
[26] SmithF K.M. (Ed.), Porphyrins and Metalloporphyrins, Elsevier, Amsterdam, 1975, p. 207.
[27] A.D. Adler, F.R. Longo, F. Kampas, J. Inorg. Nucl. Chem. 32 (1970) 2443.
[28] K.M. Smith, D.A. Goff, D.J. Simpson, J. Am. Chem. Soc. 107 (1985) 4946.

[29] P.S. Woolley, A.J. Moir, R.E. Hester, B.J. Keely, J. Chem. Soc., Perkin Trans. 2 (1998) 1833.
[30] L.A. van der Veen, P.H. Keeven, G.C. Schoemaker, J.N.H. Reek, P.C.J. Kamer, P.W.N.M. van Leeuwen, M. Lutz, A.L. Spek, Organometallics 19 (2000) 872.
[31] J.J.P. Stewart, J. Comput. Chem. 10 (1989) 221.
[32] R. Lazzaroni, A. Raffaelli, R. Settambolo, S. Bertozzi, G. Vitulli, J. Mol. Catal. 50 (1989) 1.
[33] A. Caiazzo, R. Settambolo, L. Pontorno, R. Lazzaroni, J. Organomet. Chem. 599 (2000) 298.