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An Easy and Practical Synthetic Route to Electron Rich Water Soluble Ligands: α-Aminomethylation of Trishydroxymethylphosphine

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Abstract—Hydrophilic aminomethylphosphines **6a**–**e** were prepared in excellent yield by the condensation of $P(CH_2OH)_3$ (THP) with a variety of easily accessible water soluble secondary amines, such as sarcosine (**5a**), *N*-methyltaurine (**5b**), *N*-methylethanolamine (**5c**), diethanolamine (**5d**) and 3-(*N*-butylamino)propanesulfonic acid sodium salt (**5e**). All products **6** are highly water soluble and are stable in air as well as under a wide pH range. The basic character of **6a**–**e** has been proven by titration and by infrared analysis of the ν(CO) A_1 frequencies of their corresponding nickel complexes **7a**–**e** of the type $Ni(CO)_3L$.

Introduction

In homogeneous catalysis, phosphines are still the most important class of ligands for late-transition metal catalyzed processes.[1] Unfortunately, often the ligand and the metal catalyst are not easily recyclable after the reaction, which is a prerequisite for practical applications. This is a general problem in homogeneous catalysis and has been smoothly solved by applying biphasic solvent mixtures (two phase catalysis).[2] In order to recycle the catalyst efficiently in a biphasic medium—usually water and an organic solvent—it is necessary to have an appropriate hydrophilic ligand, which makes the catalyst water soluble, while the starting materials and products are soluble in the organic phase. In recent years numerous new water-soluble ligands have been reported.[2b] Surprisingly, only a few hydrophilic alkylphosphines have been prepared. Some examples are depicted in Fig. 1. In terms of the basicity of the phosphorous atom, most of the water soluble phosphine ligands that were prepared are triarylphosphines comparable to TPPTS (trisodium salt of meta trisulfonated triphenylphosphine).

In general these hydrophilic triarylphosphines are extremely useful for numerous catalytic reactions. However, for some hydrogenations, activation of C–Cl bonds[7] and cobalt-catalyzed hydroformylations[8] basic ligands are more suitable. Despite the significant utility offered by highly water soluble basic phosphines, synthetic strategies for such ligands are still in their infancy. Here, we report a general synthesis, isolation and full characterization of highly hydrophilic aminomethylphosphines, which show a comparable basicity to trialkylphosphines.

Results and Discussion

The synthesis of tris(dialkylaminomethyl)phosphines from dialkylamines and tetrakis(hydroxymethyl)phosphonium chloride (TETRAKIS) was described for the first time in 1960 in a patent by Coates and Hoye.[9] Since that time only a few examples of the α-aminomethylation of the PH_3 equivalent tris(hydroxymethyl)phosphine $P(CH_2OH)_3$ (THP) with simple alkylamines have been described.[10] Most notably the first reaction of THP with an amino acid (glycine) for the development of new bioconjugates was reported parallel to this work[11] by Katti and co-workers.[12]

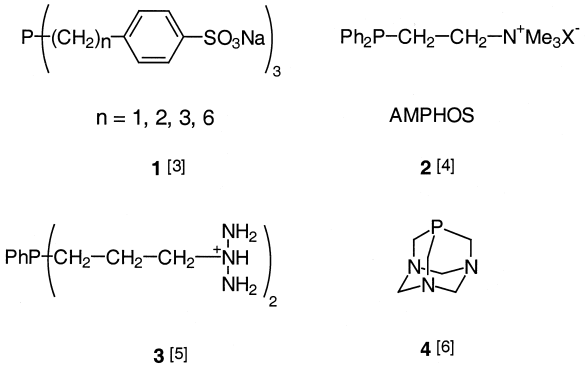

Figure 1. Selected examples of water soluble alkylphosphines.[4,5,6]

Keywords: P,N-ligands; aminomethylphosphines; amino acids; trishydroxymethylphosphine.

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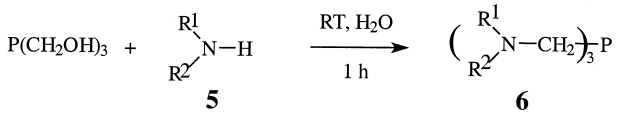
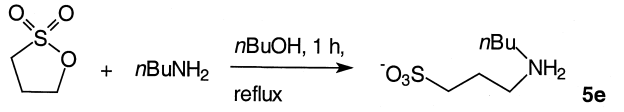


Scheme 1. Synthesis of aminomethylphosphines **6a**–**e** (**5a**, **6a**: R1=CH_3, R2=CH_2CO_2Na. **5b**, **6b**: R1=CH_3, R2=$CH_2CO_2SO_3Na$. **5c**, **6c**: R1=CH_3, R2=CH_2CH_2OH. **5d**, **6d**: R1=R2=CH_2CH_2OH. **5e**, **6e**: R1=*n*Bu, R2=$CH_2CH_2CH_2SO_3Na$.

In order to study the reaction of $P(CH_2OH)_3$ (THP) and water soluble amines **5** we prepared THP from commercially available $[P(CH_2OH)_4]^+Cl^-$.[13] Initially the reaction of sarcosine (**5a**) and THP was studied as a model reaction under various conditions. After considerable optimization it was shown that the reaction proceeds cleanly by slowly adding an aqueous solution of 3 equiv. of the amine to a solution of THP under fairly concentrated (1–3 M) conditions at 1–10°C. After removal of the water the remaining white precipitate (99% yield) was found to be analytically pure. Other commercially available hydrophilic amines such as *N*-methyltaurine (**5b**), *N*-methylethanolamine (**5c**), and diethanolamine (**5d**) also work well in this reaction (Scheme 1). During addition of the amine a slight increase in temperature of 5–10°C is observed. Yields of **6a**–**d** range between 95–99%. The crude product obtained from the reaction is typically >95% pure as determined by ^1H and ^{31}P NMR spectroscopy.



Scheme 2. Synthesis of **5e**.

Table 1. Water solubility of **6a**–**e**

Entry	Compound	Water solubility	
		(mol/l)	(g/l)
1	**6a**	2.5	1130
2	**6b**	5.8	3550
3	**6c**	2.5	760
4	**6d**	6.0	2320
5	**6e**	1.4	1020
6	TPPTS	2.4	1400

Further purification can be achieved by recrystallization from mixtures of methanol and acetone. In principle the reaction can be carried out with $[P(CH_2OH)_4]^+Cl^-$ instead of $P(CH_2OH)_3$ but since both chloride and ammonium salts must be removed, the purification is much more complicated.

In order to make this synthetic route more general we looked for an easy method to generate water soluble secondary amines from primary amines. As an example, we prepared 3-(*N*-butylamino)propanesulfonic acid sodium salt (**5e**) from propanesultone and *n*-butylamine in *n*-butanol in 70% yield (Scheme 2).[14] The aminomethylation of THP with **5e** yields **6e** in 85%. It is obvious that this simple two step procedure will allow the preparation of other new aminomethylphosphines depending only on the availability of primary amines.

Regarding the limitations of this method, water soluble primary amines and secondary aryl amines do not yield products of type **6** in a selective manner. In agreement with the literature,[15] the reaction of THP with primary amines instead of secondary amines does not lead to monomeric compounds but instead to polymers which were of interest as flame retardants. The ^{31}P NMR spectra of the reaction of 3-(*N*-phenylamino)propanesulfonic acid sodium salt with THP shows three phosphorous resonances in the region $\delta=-30$ to -70 ppm, which we attribute to the corresponding $R_2NCH_2P(CH_2OH)_2$, $(R_2NCH_2)_2PCH_2OH$, and $(R_2NCH_2)_3P$ species. However, even after a longer reaction time or at higher reaction temperatures no selective formation of $(R_2NCH_2)_3P$ is observed.

Next, the water solubility of the ligands **6a**–**e** was determined. As shown in Table 1, all new ligands have excellent water solubility which is a prerequisite for later use in biphasic catalysis. For comparison the water solubility of TPPTS is also listed. Surprisingly **6d**, which is a non-ionic amine with six hydroxy groups has the best solubility, 6.0 mol L^{-1} (about 2.4 times that of TPPTS!). In comparison to substituted aryl phosphines the sulfonic acid residues make **6b** much more soluble than the corresponding carboxylic acid derivative **6a**. Except for **6e**, all new aminomethylphosphines have a comparable or better solubility in water with regard to TPPTS.

Some physical properties of the new ligands are listed in Table 2. For comparison, the corresponding data for TPPTS

Table 2. Selected physical properties of the ligands **6a**–**e**

Entry	Compound	δ (^{31}P NMR)	$Ni(CO)_3L$	A_1 ν(CO)	Titration[c]	
					1.tp	2.tp
1	**6a**	−63.1	**7a**	2060.3[a]	–	3.3
2	**6b**	−57.8	**7b**	2063.1[a]	11.5	3.6
3	**6c**	−61.8	**7c**	2063.0[a]	10.3	4.4
4	**6d**	−62.5	**7d**	2061.4[a]	11.5	4.0
5	**6e**	−69.1	**7e**	2059.1[a]	12.0	4.7
6	$(Et_2NCH_2)_3P$	−64.9	**7f**	2060.6[a] 2061.2[b]	–	–
7	$(Me_2NCH_2)_3P$	−53.9	**7g**	2062.7[a] 2063.8[b]	–	–
8	THP **1**	−30.7[3]	L=**1** (n=3)	2060.8[a3]	9.9[3]	n.d.
9	TPPTS	−5.9	L=TPPTS	2070.3[a]	7.0[3]	–

[a] Measured in THF/H_2O 5:1.
[b] Measured in CH_2Cl_2.
[c] Turning point.

and the related ligands (tris(diethylaminomethyl)phosphine and tris(dimethylaminomethyl)phosphine) are also shown. The chemical shifts of the ligands **6a**–**e** in the ^{31}P NMR spectra are typical for strong basic phosphorous compounds. All aminomethylphosphines show a single resonance downfield from THP between −57 and −69 ppm ($\Delta\delta$= 27−39).

It is known that the ν(CO) A_1 stretching frequencies in $R_3PNi(CO)_3$ complexes correlate with the electronic character of the phosphorous ligand.[16] Due to the solubility behavior we measured the data in aqueous THF (THF/water 5:1).

The nickel complexes **7a**–**e** were prepared in situ from $Ni(CO)_4$ and **6a**–**e** using a slight excess of ligand and were characterized by their infrared spectra. The results are summarized in Table 2. As revealed by the data the aminomethylphosphines are significantly more electron rich compared to TPPTS. In fact **7a**–**e** show comparable IR stretching frequencies to the *n*-Bu_3P Ni-complex. Titration of **6a**–**e** were also performed and the turning points of these titrations are shown in Table 2. All titration curves show a buffering plateau between pH 12–14, which is assigned to the neutralization of the corresponding phosphonium salts. Since all curves show only two turning points it must be assumed that the titration curves of the two basic centers (nitrogen and phosphorous) coincide. The strong basicity of **6e** (BUPHOS) corresponds to the highest pH for the first turning point.

In conclusion, we have demonstrated that hydrophilic secondary amines react cleanly with tris(hydroxymethyl)-phosphine to give tris(aminomethyl)phosphines **6** in excellent yield. The resulting products show similar physical properties compared to electron rich trialkylphosphines. Clearly, an advantage of the ligand synthesis presented here stems from the fact that traditional syntheses of phosphines utilize sensitive starting materials, e.g. alkali metal phosphides and require careful manipulation at low temperature and anaerobic conditions. In contrast hydrophilic aminomethylphosphines **6** can be synthesized in a one pot procedure without extensive purification. Several catalytic reactions have been described in the literature that are positively influenced by the use of related P,N-ligands either in terms of selectivity or rate. As an example Amer et al. described the use of P,N bidentate ligands in the rhodium-catalyzed hydroformylation of olefins[17] and Joó and Darensbourg investigated the rhodium-catalyzed hydrogenation of unsaturated aldehydes.[18] Apart from the potential of these ligands in biphasic catalysis, the reactions presented here are also of general interest for the actual topic of conjugation of amino acid derivatives and peptides[12] with hydroxymethylphosphines.

Experimental

All reactions were carried out under an atmosphere of argon using standard Schlenk technique. Water was distilled and degassed. Tetrakis(hydroxymethyl)phosphonium chloride (Fluka), *N*-methylaminoethanol (Aldrich), *N*-methyltaurine (Hoechst AG), sarcosine (Fluka), *n*-butylamine (Aldrich), propansultone (Aldrich), diethylamine (Fluka), dimethylamine (40% in water) (Fluka) were used as received. Diethanolamine (Fluka) was distilled prior to use. NMR spectra were recorded on a JEOL 270 MHz spectrometer. The ^1H and ^{13}C chemical shifts are reported relative to TMS. ^{31}P NMR chemical shifts are reported relative to an external standard of 85% H_3PO_4. Infrared spectra were recorded on a Perkin–Elmer 1600 series FT-IR using either 0.1 mm CaF_2 cells (THF/water 5:1) or 0.1 mm KBr cells (CH_2Cl_2). The titrations were done on a Metrohm Titroprocessor 686. Elemental analyses were done by the microanalytical laboratory of TU München. 3-(*n*-Butylamino)propanesulfonic acid sodium salt[14] (**5e**) and the phosphines $(Et_2NCH_2)_3P$[9] and $(Me_2NCH_2)_3P$[9] were prepared according to the literature.

General procedure for 6a–e

3.10 g (25 mmol) $P(CH_2OH)_3$[13] were dissolved in 3 mL water and a solution of **5a**–**e** (75 mmol) in 20 mL water was added at 0–5°C. The reaction was stirred at room temperature for 1 h. Then the water was evaporated under reduced pressure. The remaining white residue was analyzed and re-precipitated from methanol/acetone if necessary.

Tris(*N*-methyl-*N*-sodiumcarboxylatomethylaminomethyl)-phosphine trihydrate (6a·3H$_2$O). Yield 11.4 g (99%), white solid. IR (KBr): ν=2969 cm^{-1} (CH), 2936 (CH), 2836 (CH_2N), 2780 (CH_2N), 1591 (COO), 1409 (COO), 1328 (COO) 1032 (COO). ^1H NMR (270 MHz, D_2O): δ=2.38 (s, 3 H), 2.88 (s, 2 H), 3.15 (s, 2 H). $^{13}C-\{^1H\}$ NMR (68 MHz, D_2O): δ=43.3 (d, $^1J_{CP}$=8.3 Hz), 57.1 (s), 61.9 (d, $^3J_{CP}$=9.3 Hz), 178.2 (s). $^{31}P-\{^1H\}$ NMR (109 MHz, D_2O): δ=−63.1. $C_{12}H_{21}N_3Na_3O_6P\cdot 3H_2O$ (403.25·3H_2O): calcd C 31.52 H 5.95 N 9.19; found C 31.97 H 5.86 N 9.49.

Tris(*N*-methyl-*N*-2-sodiumsulfonatoethylaminomethyl)-phosphine trihydrate (6b·3H$_2$O). Yield 15.2 g (99%), white solid. IR (KBr): ν=2942 cm^{-1} (CH), 2847 (CH_2N), 2790 (CH_2N), 1652 (s), 1464 (m), 1192 (SO_3) 1043 (SO_3). ^1H NMR (270 MHz, D_2O): δ=2.50 (s, 3 H), 2.94 (s, 2 H), 3.07 (s br, 2 H), 3.22 (s br, 2 H). $^{13}C-\{^1H\}$ NMR (68 MHz, D_2O): δ=42.7 (d, $^1J_{CP}$=8.8 Hz), 47.7 (s), 52.9 (d, $^3J_{CP}$=7.8 Hz), 56.4 (s). $^{31}P-\{^1H\}$ NMR (109 MHz, D_2O): δ=−57.8. $C_{12}H_{27}N_3Na_3S_3O_9P\cdot 3H_2O$ (553.48·3H_2O): calcd C 23.72 H 5.47 N 6.92; found C 23.92 H 5.20 N 6.84.

Tris(*N*-2-hydroxyethyl-*N*-methylaminomethyl)phosphine (6c·3H$_2$O). Yield 7.4 g (99%), colorless oil. IR (neat): ν=3364 cm^{-1} (OH), 2941 (CH), 2831 (CH_2N), 2783 (CH_2N), 1033 (OH). ^1H NMR (270 MHz, D_2O): δ=2.32 (s, 3 H), 2.64 (t, $^3J_{HH}$=6.2 Hz, 2 H), 2.79 (s, 2 H), 3.66 (t, $^3J_{HH}$=6.2 Hz, 2 H). $^{13}C-\{^1H\}$ NMR (68 MHz, D_2O): δ=43.3 (d,), 57.5 (s), 58.7 (s), 56.4 (s), 59.1 (d, $^3J_{CP}$=7.8 Hz). $^{31}P-\{^1H\}$ NMR (109 MHz, D_2O): δ=−61.8. $C_{12}H_{30}N_3O_3P\cdot 3H_2O$ (295.36): calcd C 23.72 H 5.47 N 6.92; found C 23.92 H 5.20 N 6.84.

Tris[bis(*N*-2-hydroxyethyl)aminomethyl]phosphine (6d·3H$_2$O). Yield 8.0 g (95%), colorless oil. IR (neat): ν=3356 cm^{-1} (OH), 2943 (CH), 2875 (CH_2N), 2810

(CH_2N), 1032 (OH). ^1H NMR (270 MHz, D_2O): δ=2.92 (s br, 2 H), 3.71 (s br, 2 H), 2.83 (s br, 2 H). $^{13}C-\{^1H\}$ NMR (68 MHz, D_2O): δ=55.1 (s), 56.6 (d, $^1J_{CP}$=7.3 Hz), 58.9 (s). $^{31}P-\{^1H\}$ NMR (109 MHz, D_2O): δ=−62.5. $C_{15}H_{36}N_3O_6P\cdot 3H_2O$ (337.44): calcd C 23.72 H 5.47 N 6.92; found C 23.92 H 5.20 N 6.84.

Tris(*N*-*n*-butyl-*N*-3-sodiumsulfonatopropylaminomethyl)-phosphine trihydrate (6e·3H₂O). Yield 16.5 g (85%), white solid. IR (KBr): ν=2958 cm^{-1} (CH), 2919 (CH), 2861 (CH_2N), 2792 (CH_2N), 1184 (SO_3), 1055 (SO_3). ^1H NMR (270 MHz, D_2O): δ=1.08 (s, 3 H), 1.48 (s, 2 H), 1.62 (s, 2 H), 2.05 (s, 2 H), 2.75 (s br, 3 H), 2.99 (s br, 5 H). $^{13}C-\{^1H\}$ NMR (68 MHz, D_2O): δ=14.1 (s), 20.8 (s), 22.2 (s), 28.6 (s), 49.6 (s), 54.2 (d, $^1J_{CP}$=7.3 Hz), 54.5 (s), 54.7 (s). $^{31}P-\{^1H\}$ NMR (109 MHz, D_2O): δ=−69.1. $C_{24}H_{51}N_3Na_3S_3O_9P\cdot 3H_2O$ (721.8·3H_2O): calcd C 37.15 H 7.41 N 5.42; found C 37.44 H 7.65 N 5.43.

Syntheses of 7a–e

0.14 mmol **6a–e**, $(Et_2NCH_2)_3P$, or $(Me_2NCH_2)_3P$ was added to 0.5 mL of a 0.56 M solution of $Ni(CO)_4$ in aqueous THF (THF/water 5:1) and stirred at room temperature for 15 min and then analyzed by infrared spectroscopy.

Tricarbonyl[tris(*N*-methyl-sodiumcarboxylatomethyl-aminomethyl)phosphine]nickel (7a). IR (THF/H_2O 5:1): ν=2060.3 cm^{-1} (CO), 1981.0 (CO).

Tricarbonyl[tris(*N*-methyl-2-sodiumsulfonatoethylamino-methyl)phosphine]nickel (7b). IR (THF/H_2O 5:1): ν=2063.1 cm^{-1} (CO), 1990.9 (CO).

Tricarbonyl[tris(2-hydroxyethyl-methylaminomethyl)-phosphine]nickel (7c). IR (THF/H_2O 5:1): ν=2063.0 cm^{-1} (CO), 1989.8 (CO).

Tricarbonyl[tris(bis-2-hydroxyethylaminomethyl)phos-phine]nickel (7d). IR (THF/H_2O 5:1): ν=2061.4 cm^{-1} (CO), 1986.0 (CO).

Tricarbonyl[tris(*n*-butyl-3-sodiumsulfonatopropylamino-methyl)phosphine]nickel (7e). IR (THF/H_2O 5:1): ν=2059.1 cm^{-1} (CO), 1985.6 (CO).

Tricarbonyl[tris(diethylaminomethyl)phosphine]nickel (7f). IR (THF/H_2O 5:1): ν=2060.6 cm^{-1} (CO), 1987.2 (CO); IR (CH_2Cl_2): ν=2061.2 cm^{-1} (CO), 1985.9 (CO).

Tricarbonyl[tris(dimethylaminomethyl)phosphine]nickel (7g). IR (THF/H_2O 5:1): ν=2062.7 cm^{-1} (CO), 1989.8 (CO); IR (CH_2Cl_2): ν=2063.8 cm^{-1} (CO), 1987.9 (CO).

Titration of 6a–e

0.3 mmol of each ligand was dissolved in 15 mL water under an argon atmosphere. Each solution was then alkalized with NaOH (0.1N) to pH 13.8 and then titrated with 0.1N HCl. The titration curves were recorded automatically.

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References

1. (a) Cornils, B.; Herrmann, W. A. *Applied Homogeneous Catalysis with Organometallic Compounds;* VCH: Weinheim, 1996. (b) Beller, M.; Bolm, C. *Transition Metals for Organic Synthesis;* Wiley-VCH: Weinheim, 1998.
2. (a) Herrmann, W. A.; Kohlpaintner, C. W. *Angew. Chem.* **1993**, *105*, 1588; *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1524. (b) Cornils, B.; Herrmann, W. A. *Aqueous-phase Organometallic Catalysis;* Wiley-VCH: Weinheim, 1998.
3. Bartik, T.; Bartik, B.; Hanson, B. E.; Guo, I.; Tóth, I. *Organometallics* **1993**, *12*, 164.
4. Markiewicz, M. K.; Baird, M. C. *Inorg. Chim. Acta* **1986**, *113*, 95.
5. (a) Dibowski, H.; Schmidtchen, F. P. *Tetrahedron* **1995**, *51*, 2325. (b) Heßler, A.; Stelzer, O.; Dibowski, H.; Worm, K.; Schmidtchen, F. P. *J. Org. Chem.* **1997**, *62*, 2362.
6. (a) Daigle, D. J.; Pepperman, A. B.; Vail, S. C. *J. Heterocycl. Chem.* **1974**, *11*, 407. (b) Daigle, D. J.; Pepperman, A. B. *J. Heterocycl. Chem.* **1975**, *12*, 579.
7. (a) Grushin, V. V.; Alper, H. *Chem. Rev.* **1994**, *94*, 1047. (b) Riermeier, T. H.; Zapf, A.; Beller, M. *Top. Catal.* **1997**, *4*, 301.
8. Bartik, T.; Bartik, B.; Guo, I.; Hanson, B. E. *J. Organomet. Chem.* **1994**, *480*, 15.
9. Coates, H.; Hoye, P.A.T. (Albright & Wilson) GB 842593, 1960.
10. (a) Diagle, D. J.; Reeves, W. A.; Donaldson, D. J. *Text. Res. J.* **1970**, *40*, 580. (b) Kellner, K.; Tzschach, A. *Z. Chem.* **1984**, *10*, 365.
11. Krauter, J.G.E. Ph.D. Thesis, TU München, 1998.
12. Berning, D. E.; Katti, K. V.; Barnes, C. L.; Volkert, W. A. *J. Am. Chem. Soc.* **1999**, *121*, 1658.
13. Ellis, J. W.; Harrison, K. N.; Hoye, P. A. T.; Orpen, A. G.; Pringle, P. G.; Smith, M. B. *Inorg. Chem.* **1992**, *31*, 3026.
14. (a) Zeid, I.; Ismail, I.; Helferich, B. *Liebigs Ann. Chem.* **1972**, *761*, 118. (b) Fischer, R. F. *Ing Eng. Chem.* **1964**, *56*, 41.
15. (a) Daigle, D. J.; Frank, A. W. *Text. Res. J.* **1982**, *52*, 751. (b) Frank, A. W.; Drake, G. L. *J. Org. Chem.* **1972**, *37*, 2752.
16. Tolman, C. A. *Chem. Rev.* **1977**, *77*, 313.
17. (a) Abu-Gnim, C.; Amer, I. *J. Mol. Catal.* **1993**, *85*, L275. (b) Abu-Gnim, C.; Amer, I. *J. Chem. Soc., Chem. Commun.* **1994**, 115.
18. (a) Joó, F.; Nádasdi, L.; Bényei, A. Cs.; Darensbourg, D. J. *J. Organomet. Chem.* **1996**, *512*, 45. (b) Darensbourg, D. J.; White Stafford, N.; Joó, F.; Reibenspies, J. H. *J. Organomet. Chem.* **1995**, *488*, 99.