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Graphical abstract

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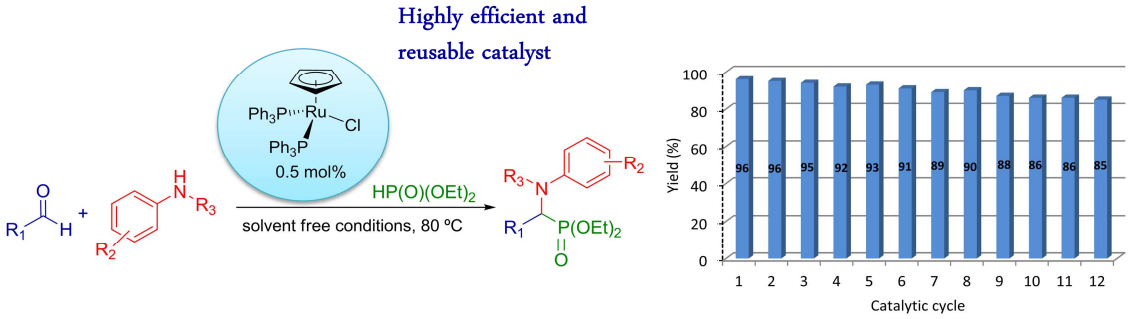

Direct Aminophosphonylation of Aldehydes Catalyzed by Cyclopentadienyl Ruthenium(II) Complexes

Ivânia R. Cabrita, Sara C. A. Sousa, Pedro R. Florindo and Ana C. Fernandes*

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Abstract: This work reports a novel method for the direct aminophosphonylation of aldehydes catalyzed by cyclopentadienyl ruthenium(II) complexes. The system $HP(O)(OEt)_2$/$[CpRu(PPh_3)_2Cl]$ was very efficient for the aminophosphonylation of aldehydes with primary and secondary amines, producing the corresponding α-aminophosphonates in good to excellent yields. This novel method has several advantages including the use of a small amount of catalyst (0.5 mol%), high chemoselectivity, solvent-free conditions and application of the catalyst $[CpRu(PPh_3)_2Cl]$ for at least 12 cycles with excellent activity.

Keywords: aminophosphonylation, aldehydes, α-aminophosphonates, ruthenium complexes

1.Introduction

α-Aminophosphonates and α-aminophosphonic acids[1] are structurally analogous to α-amino acids and constitute an important class of compounds with diverse biological activities and potential to be employed as enzyme inhibitors,[2,3] antibiotics,[4] and antitumor agents.[5,6] They also have a wide range of antiviral[7] and antifungal properties and are extensively used as insecticides and herbicides.[8] Thus, a number of methods have been developed for the synthesis of α-aminophosphonates both in racemic and in optically active forms.[9-15] Among the available synthetic methods for α-aminophosphonates, the three-component reaction of aldehyde, amine, and phosphite, also known as Kabachnik–Fields reaction, has gained much attention due to its one-pot manner and convenience of synthesis of these compounds.[16,17] Different catalysts have been employed for the synthesis of α-aminophosphonates including $SnCl_2.2H_2O$,[18]

$ZnBr_2$,[19] $HfCl_4$,[20] lanthanide triflate,[21] $Yb(PFO)_3$,[22] SmI_2,[23] $TaCl_5$,[24] $Cd(ClO_4)_2{\cdot}xH_2O$,[25] $BiCl_3$,[26] $LiClO_4$,[27] $FeCl_3$[28] or MoO_2Cl_2.[29] In the last years, several methods for the synthesis of α-aminophosphonates have also been developed using microwaves radiations.[30-34] However, the use of ruthenium complexes as catalysts for the synthesis of α-aminophosphonates has never been studied. In this work we reported the first method for the synthesis of *α*-aminophosphonates with high yields catalyzed by cyclopentadienyl ruthenium(II) complexes.

2.Results and discussion

The catalytic activity of several cyclopentadienyl ruthenium(II) complexes was evaluated in the aminophosphonylation of 4-(methylthio)benzaldehyde with aniline and $HP(O)(OEt)_2$ under solvent-free conditions in air atmosphere (Table 1). All the catalysts were very efficient, producing the α-aminophosphonate in excellent yields. The best result (95%) was obtained in the presence of 0.5 mol% of $[CpRu(PPh_3)_2Cl]$ after 15 min (Table 1, entry 1). Using 0.25 mol% of this catalyst the reaction required 1h and the α-aminophosphonate was isolated in only 51% yield (Table 1, entry 2). The reaction carried out at room temperature afforded the product in only 42% yield after 24 h (Table 1, entry 3). The catalysts $[CpRu(PPh_3)(2,2'\text{-bipy})][PF_6]$ **2**, [CpRu(dppe)Cl] **3** and $[CpRu(PPh_3)(phen)][PF_6]$ **4** were also very efficient, giving excellent yields of α-aminophosphonate (Table 1, entries 4-6). The reactions carried out with the complexes containing a carbohydrate moiety derived from xylose and fructose also produced excellent yields of the product (Table 1, entries 7 and 8). Finally, in the absence of catalyst only 19% of product was obtained after 1 h (Table 1, entry 9).

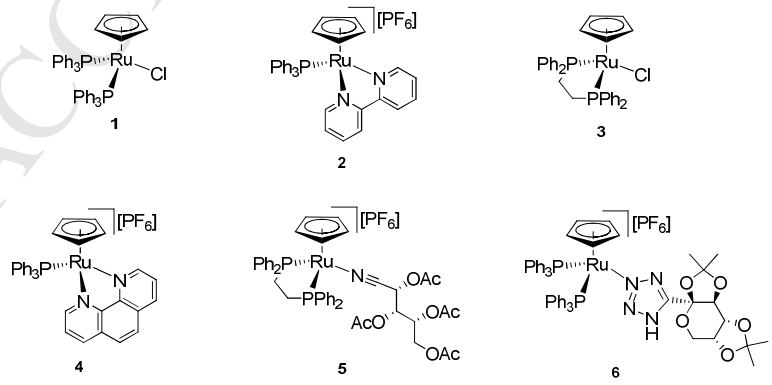
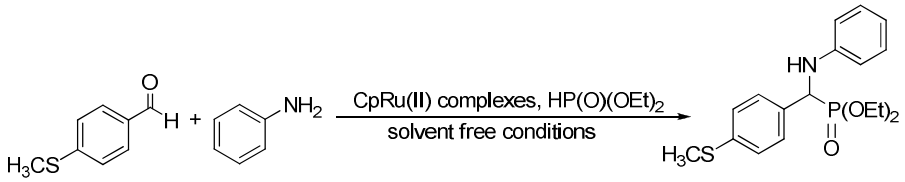


Fig. 1. Structure of catalysts **1**-**6**.

Table 1

Direct aminophosphonylation of aldehydes catalyzed by CpRu(II) complexes[a]



Entry	Catalyst	Catalyst (mol%)	Temp. (ºC)	Time	Yield (%)[b]
1	[CpRu(PPh_3)$_2$Cl] **1**	0.5	80	15 min	95
2	[CpRu(PPh_3)$_2$Cl] **1**	0.25	80	1 h	51
3	[CpRu(PPh_3)$_2$Cl] **1**	0.5	r.t.	24 h	42
4	[CpRu(PPh_3)(2,2′-bipy)][PF_6] **2**	0.5	80	30 min	94
5	[CpRu(dppe)Cl] **3**	0.5	80	40 min	93
6	[CpRu(PPh_3)(phen)][PF_6] **4**	0.5	80	50 min	91
7	[CpRu(PPh_3)$_2$(NCXylAc)][PF_6] **5**	0.5	80	40 min	95
8	[CpRu(PPh_3)$_2$(Fru)][PF_6] **6**	0.5	80	20 min	92
9	Without catalyst	–	80	1 h	19

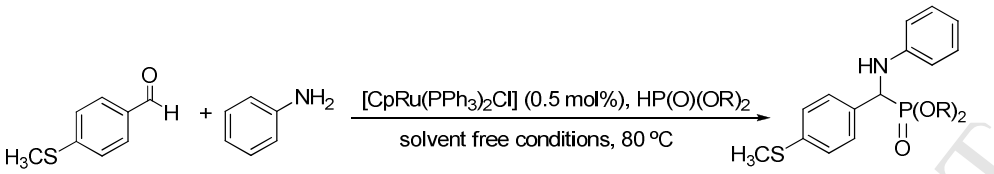
[a] All reactions were carried out with 2.0 mmol of 4-(methylthio)benzaldehyde, 2.0 mmol of aniline and 2.0 mmol of $HP(O)(OEt)_2$.

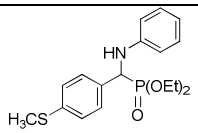
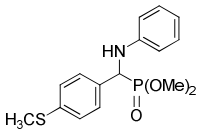
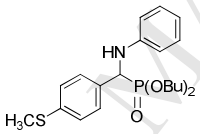
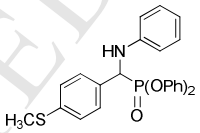
[b] Isolated yields

Aminophosphonylation of 4-(methylthio)benzaldehyde with aniline catalyzed by [CpRu(PPh_3)$_2$Cl] (0.5 mol%) was investigated with the H-phosphonates $HP(O)(OEt)_2$, $HP(O)(OMe)_2$, $HP(O)(OBu)_2$ and $HP(O)(OPh)_2$ under solvent-free conditions at 80 ºC in air atmosphere (Table 2). Although all H-phosphonates afforded the α-aminophosphates in excellent yields, the reaction with $HP(O)(OEt)_2$ was much faster, requiring only 15 minutes (Table 2, entry 1). In contrast, the reaction performed with $HP(O)(OPh)_2$ needed 24 h to be completed (Table 2, entry 4).

Table 2

Direct aminophosphonylation of 4-(methylthio)benzaldehyde with aniline catalyzed by $[CpRu(PPh_3)_2Cl]$ using different $HP(O)(OR)_2$[a]



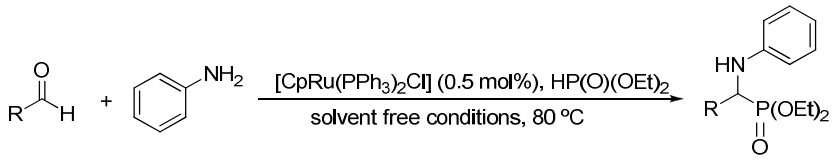
Entry	$HP(O)(OR)_2$	Product	Time	Yield (%)[b]
1	$HP(O)(OEt)_2$		15 min	95
2	$HP(O)(OMe)_2$		25 min	94
3	$HP(O)(OBu)_2$		1 h	94
4	$HP(O)(OPh)_2$		24 h	94

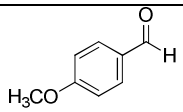
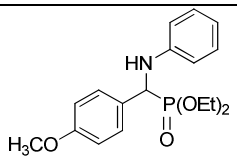
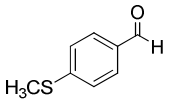
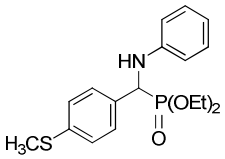
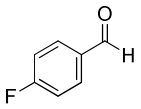
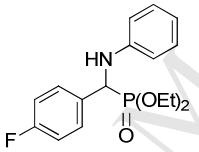
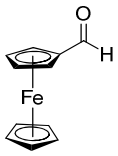
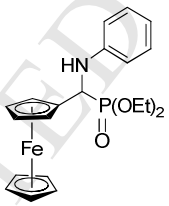
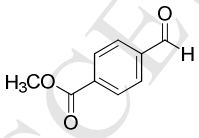
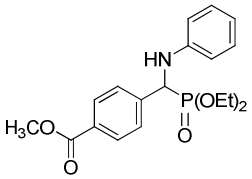
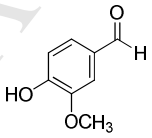
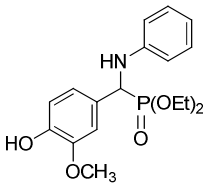
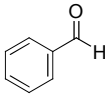
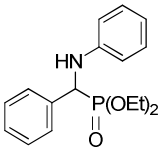
[a] The reactions were carried out with 2.0 mmol of 4-(methylthio)benzaldehyde, 2.0 mmol aniline and 2.0 mmol of $HP(O)(OR)_2$.
[b] Isolated yields.

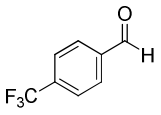
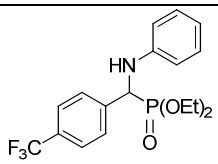
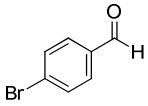
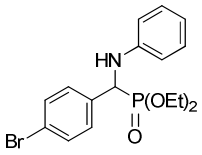
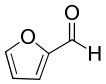
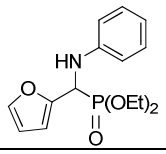
To evaluate the efficiency of the system $HP(O)(OEt)_2/[CpRu(PPh_3)_2Cl]$ (0.5 mol%), it was tested in the direct aminophosphonylation of a large variety of aldehydes with aniline under solvent-free conditions at 80 ºC in air atmosphere (Table 3). In general, the reactions were very fast, affording the corresponding α-aminophosphonates in good to excellent yields, with high chemoselectivity, tolerating several functional groups such as $-OCH_3$, $-SCH_3$, -F, -Br, $-CF_3$, -OH, $-CO_2R$, and heterocyclic or Cp rings.

Table 3

Direct aminophosphonylation of aldehydes with the system $HP(O)(OEt)_2/[CpRu(PPh_3)_2Cl]$[a]



Entry	Aldehyde	Product	Time	Yield (%)[b]
1			20 min	97
2			15 min	95
3			35 min	95
4			30 min	95
5			30 min	94
6			20 min	92
7			20 min	91

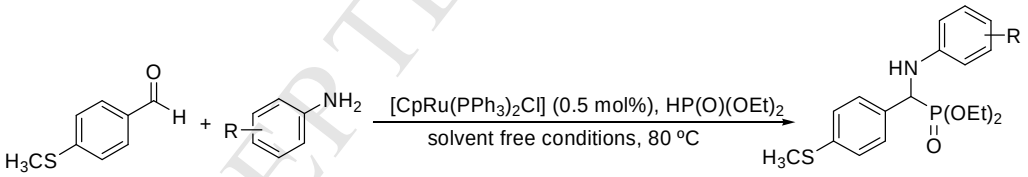
8			40 min	80
9			2 h	75
10			1.5 h	98

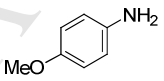
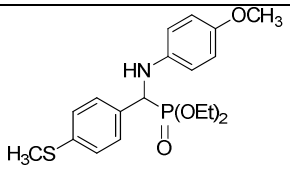
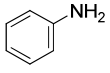
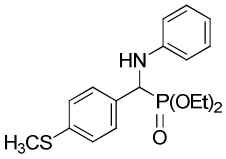
[a] The reactions were carried out with 2.0 mmol of aldehyde, 2.0 mmol aniline and 2.0 mmol of $HP(O)(OEt)_2$.
[b] Isolated yields.

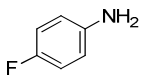
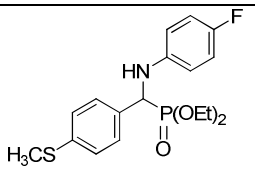
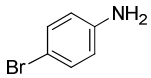
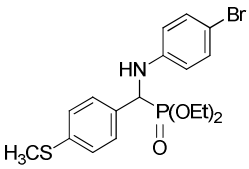
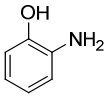
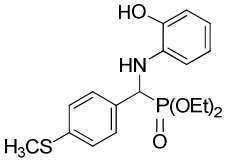
Direct aminophosphonylation of 4-(methylthio)benzaldehyde was also explored using different anilines containing electron-donating and electron-withdrawing groups with the system $HP(O)(OEt)_2$/$[CpRu(PPh_3)_2Cl]$ (0.5 mol%) producing the corresponding α-aminophosphonates in excellent yields (Table 4).

Table 4

Direct aminophosphonylation of 4-(methylthio)benzaldehyde with different anilines using the system $HP(O)(OEt)_2$/$[CpRu(PPh_3)_2Cl]$[a]



Entry	Aniline	Product	Time	Yield (%)[b]
1			10 min	99
2			15 min	95

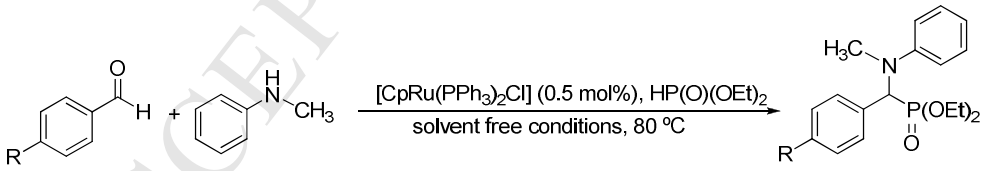
3			15 min	95
4			30 min	75
5			1h 30 min	85

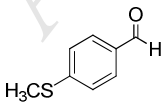
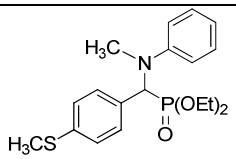
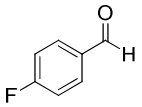
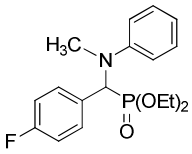
[a] The reactions were carried out with 2.0 mmol of 4-(methylthio)benzaldehyde, 2.0 mmol aniline and 2.0 mmol of $HP(O)(OEt)_2$.
[b] Isolated yields.

Finally, the direct aminophosphonylation of different aldehydes using methyl-*N*-aniline with the system $HP(O)(OEt)_2$/$[CpRu(PPh_3)_2Cl]$ (0.5 mol%) was studied, obtaining the corresponding tertiary α-aminophosphonates in good to excellent yields.

Table 5

Direct aminophosphonylation of aldehydes with methyl-*N*-aniline using the system $HP(O)(OEt)_2$/$[CpRu(PPh_3)_2Cl]$[a]



Entry	Aldehyde	Product	Time (h)	Yield (%)[b]
1			2	94
2			2	79

3	2.5	70
4	3	73
5	3	70

[a] The reactions were carried out with 2.0 mmol of aldehyde, 2.0 mmol methyl-*N*-aniline and 2.0 mmol of $HP(O)(OEt)_2$.
[b] Isolated yields.

To study the possible use of the complex $[CpRu(PPh_3)_2Cl]$ (0.5 mol%) as catalyst in multiple cycles, successive reactions were carried out by sequential addition of fresh substrate 4-(methylthio)benzaldehyde, aniline and $HP(O)(OEt)_2$ to the reaction mixture. The results showed that $[CpRu(PPh_3)_2Cl]$ can be used for at least 12 catalytic cycles with excellent yields (Figure 2).

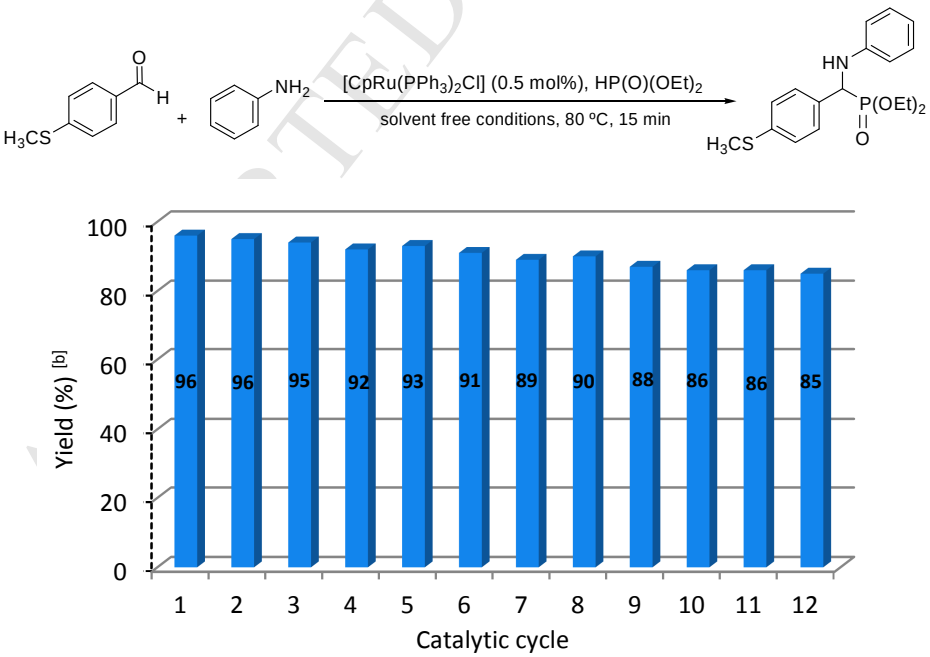


Fig 2. Use of the complex $[CpRu(PPh_3)_2Cl]$ as catalyst in multiple cycles. The reactions were carried out by successive addition of 4-(methylthio)benzaldehyde (1 mmol), aniline (1 mmol) and $HP(O)(OEt)_2$ (2 mmol). Yields were determined by ^1H NMR spectroscopy, using mesitylene as an internal standard.

Aminophosphonylation of aldehydes catalyzed by cyclopentadienyl ruthenium complexes should start with the formation of the imine by reaction between the aldehyde and aniline. Then, the activation of the H-phosphonate by the catalyst $[CpRu(PPh_3)_2Cl]$ should occur, producing the species $[CpRu(PPh_3)Cl(PO)(OEt)_2]^-$, detected by mass spectrometry. Finally, the reaction between this species and the imine lead to the formation of α-aminophosphonate.

3.Conclusions

In this work it has been demonstrated that the system $HP(O)(OEt)_2$/$[CpRu(PPh_3)_2Cl]$ (0.5 mol%) is very efficient for the aminophosphonylation of a large variety of aldehydes with different anilines under solvent-free conditions. This is the first example of aminophosphonylation of aldehydes catalyzed by a ruthenium complex. This method is highly chemoselective, tolerating a large range of functional groups including $-SCH_3$, $-OCH_3$, -F, -Br, $-CF_3$, -OH, CO_2CH_3, and heterocyclic or Cp rings.

The reactions were performed with a small amount of catalyst (0.5 mol%), with high yields and short reaction times, and the complex $[CpRu(PPh_3)_2Cl]$ can be used for at least 12 cycles with excellent activity. This work extends the use of CpRu(II) complexes as efficient catalysts for C-P bond forming reactions.

4 . Experimental Section

4.1 General information

Aldehydes, anilines and H-phosphonates were obtained from commercial suppliers and were used without further purification. The catalysts $[CpRu(PPh_3)_2Cl]$,[35] $[CpRu(PPh_3)(2,2'\text{-bipy})][PF_6]$,[36] [CpRu(dppe)Cl],[35] $[CpRu(PPh_3)(phen)][PF_6]$[37] $[CpRu(PPh_3)_2(NCXylAc)][PF_6]$,[38] and $[CpRu(PPh_3)_2(Fru)][PF_6]$[39] were prepared according to literature procedures. Flash chromatography was performed on MN Kieselgel 60M 230-400 mesh. ^1H NMR, ^{13}C NMR and ^{31}P NMR spectra were measured on a Bruker Avance II^+ 400 MHz and 300 MHz spectrometers. Chemical shifts are reported in parts per million (ppm) downfield from an internal standard. Microanalyses were performed at Laboratório de Análises do Instituto Superior Técnico, using a Fisons Instruments EA1108 system and data acquisition, integration and handling were performed using the software package Eager-200 (Carlo Erba Instruments).

4.2. General Procedure for Direct Aminophosphonylation of Aldehydes with $HP(O)(OEt)_2$/$[CpRu(PPh_3)_2Cl]$

The mixture of aldehyde (2 mmol), aniline (2 mmol) and $[CpRu(PPh_3)_2Cl]$ (0.5 mol%, 0.073 g) was stirred during 5 minutes at room temperature. To this mixture was added $HP(O)(OEt)_2$ (2.0 mmol, 0.26 mL) and the reaction mixture was stirred at 80 °C under air atmosphere (the reaction times are indicated in Tables 3-5). The progress of the reaction was monitored by TLC and ^1H NMR spectroscopy. When the reaction is complete, water (3.0 mL) was added and the mixture was stirred at 80 °C. After 1 hour, the reaction mixture was cooled to ambient temperature and extracted with ethyl acetate (2×10.0 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent removed under reduced pressure. The residue was purified by flash chromatography with *n*-hexane:ethyl acetate (3:1) to afford the α-aminophosphonates, which are known compounds.[20,22,27]

4.3. NMR characterization of products

Table 2, entry 1: Beige solid. ^1H NMR ($CDCl_3$, 400 MHz) δ 7.38 (d, *J* = 8.0 Hz, 2H, H-arom), 7.20 (d, *J* = 8.0 Hz, 2H, H-arom), 7.09 (t, *J* = 8.0 Hz, 2H, H-arom), 6.68 (t, *J* = 8.0 Hz, 1H, H-arom), 6.58 (d, *J* = 8.0 Hz, 2H, H-arom), 4.98 (s, 1H, NH), 4.75 (d, *J* = 24.0 Hz, 1H, CH), 4.17-4.06 (m, 2H, $OC\underline{H}_2CH_3$), 3.99-3.93 (m, 1H, $OC\underline{H}_2CH_3$), 3.77-3.71 (m, 1H, $OC\underline{H}_2CH_3$), 2.43 (s, 3H, $SC\underline{H}_3$), 1.27 (t, *J* = 4.0, 8.0 Hz, 3H, $OCH_2C\underline{H}_3$), 1.14 (t, *J* = 8.0 Hz, 3H, $OCH_2C\underline{H}_3$) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.29 (d, *J* = 15.15 Hz, Cq), 138.26 (d, *J* = 4.04 Hz, Cq), 132.65 (d, *J* = 3.03 Hz, Cq), 129.21 (s, CH-arom), 128.34 (d, *J* = 6.06 Hz, CH-arom), 126.61 (d, *J* = 3.03 Hz, CH-arom), 118.52 (s, CH-arom), 113.94 (s, CH-arom), 63.43 (t, *J* = 6.06, 7.07 Hz, $O\underline{C}H_2CH_3$), 55.66 (d, *J* = 152.51 Hz, CH), 16.47 (d, *J* = 6.06 Hz, $OCH_2\underline{C}H_3$), 16.28 (d, *J* = 6.06 Hz, $OCH_2\underline{C}H_3$), 15.67 (s, $S\underline{C}H_3$) ppm. ^{31}P NMR (162 MHz, $CDCl_3$) δ 22.77 ppm. Anal. Calcd. for $C_{18}H_{24}NO_3PS$: C, 59.16; H, 6.62; N, 3.83. Found: C, 59.07; H, 6.50; N, 3.69.

Table 2, entry 2: Beige solid. ^1H NMR ($CDCl_3$, 400 MHz) δ 7.41 (d, *J* = 8.0 Hz, 2H, H-arom), 7.24 (d, *J* = 8.0 Hz, 2H, H-arom), 7.14 (t, *J* = 8.0 Hz, 2H, H-arom), 6.74 (t, *J* = 4.0, 8.0 Hz, 1H, H-arom), 6.61 (d, *J* = 8.0 Hz, 2H, H-arom), 4.79 (d, *J* = 20.0 Hz, 2H, NH, CH), 3.80 (d, *J* = 12.0 Hz, 3H, $OC\underline{H}_3$), 3.55 (d, *J* = 8.0 Hz, 3H, $OC\underline{H}_3$), 2.48 (s, 3H, $SC\underline{H}_3$) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.9 (d, *J* = 15.15 Hz, Cq), 138.55 (d, *J* = 4.04 Hz, Cq), 132.39 (d, *J* = 3.03 Hz, Cq), 129.32 (s, CH-arom), 128.32 (d, *J* = 5.05

Hz, CH-arom), 126,72 (d, *J* = 2.02 Hz, CH-arom), 118.77 (s, CH-arom), 114.01 (s, CH-arom), 55.36 (d, *J* = 152.51 Hz, CH), 53.99 (d, *J* = 4.04 Hz, OCH_3), 53.92 (d, *J* = 4.04 Hz, OCH_3), 15.67 (s, SCH_3) ppm. ^{31}P NMR (162 MHz, $CDCl_3$) δ 25.22 ppm. Anal. Calcd. for $C_{16}H_{20}NO_3PS$: C, 56.96; H, 5.98; N, 4.15. Found: C, 56.79; H, 5.83; N, 4.01.

Table 2, entry 3: Beige solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.38 (d, *J* = 8.0 Hz, 2H, H-arom), 7.20 (d, *J* = 8.0 Hz, 2H, H-arom), 7.10 (t, *J* = 8.0 Hz, 2H, H-arom), 6.69 (t, *J* = 8.0 Hz, 1H, H-arom), 6.57 (d, *J* = 8.0 Hz, 2H, H-arom), 4.78-4.67 (m, 2H, CH+NH), 4.10-3.98 (m, 2H, $OCH_2CH_2CH_2CH_3$), 3.94-3.87 (m, 1H, $OCH_2CH_2CH_2CH_3$), 3.71-3.63 (m, 1H, $OCH_2CH_2CH_2CH_3$), 2.44 (s, 3H, SCH_3), 1.62-1.58 (m, 2H, $OCH_2CH_2CH_2CH_3$), 1.48-1.44 (m, 2H, $OCH_2CH_2CH_2CH_3$), 1.38-1.32 (m, 2H, $OCH_2CH_2CH_2CH_3$), 1.27-1.21 (m, 2H, $OCH_2CH_2CH_2CH_3$), 0.89 (t, *J* = 8.0 Hz, 3H, $OCH_2CH_2CH_2CH_3$), 0.84 (t, *J* = 8.0 Hz, 3H, $OCH_2CH_2CH_2CH_3$) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.35 (d, *J* = 15.15 Hz, Cq), 138.21 (d, *J* = 4.04 Hz, Cq), 132.89 (d, *J* = 3.03 Hz, Cq), 129.27 (s, CH-arom), 128.37 (d, *J* = 5.05 Hz, CH-arom), 126.70 (d, *J* = 3.03 Hz, CH-arom), 118.54 (s, CH-arom), 113.94 (s, CH-arom), 67.09 (d, *J* = 7.07 Hz, $OCH_2CH_2CH_2CH_3$), 66.08 (d, *J* = 8.08 Hz, $OCH_2CH_2CH_2CH_3$), 55.70 (d, *J* = 151.50 Hz, CH), 32.64 (d, *J* = 5.05 Hz, $OCH_2CH_2CH_2CH_3$), 32.47 (d, *J* = 5.05 Hz, $OCH_2CH_2CH_2CH_3$), 18.71 (d, *J* = 10.10 Hz, $OCH_2CH_2CH_2CH_3$), 15.80 (s, SCH_3), 13.66 (d, *J* = 5.05 Hz, $OCH_2CH_2CH_2CH_3$) ppm. ^{31}P NMR (162 MHz, $CDCl_3$) δ 22.76 ppm. Anal. Calcd. for $C_{22}H_{32}NO_3PS$: C, 62.68; H, 7.65; N, 3.32. Found: C, 62.55; H, 7.57; N, 43.29.

Table 2, entry 4: Beige solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.45 (dd, *J* = 4.0, 8.0 Hz, 2H, H-arom), 7.26-7.19 (m, 6H, H-arom), 7.17-7.07 (m, 6H, H-arom), 6.90 (d, *J* = 8.0 Hz, 2H, H-arom), 6.74 (t, *J* = 4.0, 8.0 Hz, 1H, H-arom), 6.62 (d, *J* = 8.0 Hz, 2H, H-arom), 5.10 (dd, *J* = 8.0, 16.0 Hz, 1H, CH), 4.92 (t, *J* = 8.0 Hz, 1H, NH), 2.43 (s, 3H, SCH_3) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.47 (d, *J* = 10.10 Hz, Cq), 150.29 (d, *J* = 10.10 Hz, Cq), 145.88 (d, *J* = 5.05 Hz, Cq), 138.99 (d, *J* = 3.03 Hz, Cq), 129.83 (d, *J* = 8.08 Hz, Cq), 129.40 (s, CH-arom), 128.67 (s, CH-arom), 126.87 (d, *J* = 3.03 Hz, CH-arom), 120.77 (d, *J* = 4.04 Hz, CH-arom), 120.43 (s, CH-arom), 114.18 (s, CH-arom), 55.87 (d, *J* = 144.54 Hz, CH), 15.76 (s, SCH_3) ppm. ^{31}P NMR (162 MHz, $CDCl_3$) δ 15.43 ppm. Anal. Calcd. for $C_{26}H_{24}NO_3PS$: C, 67.66; H, 5.24; N, 3.03. Found: C, 67.50; H, 5.19; N, 2.93.

Table 3, entry 1[22]: Beige solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.38 (d, *J* = 8.0 Hz, 2H, H-arom), 7.09 (t, *J* = 8.0 Hz, 2H, H-arom), 6.85 (d, *J* = 8.0 Hz, 2H, H-arom), 6.67 (t, *J* = 4.0, 8.0 Hz, 1H, H-arom), 6.59 (d, *J* = 8.0 Hz, 2H, H-arom), 4.81 (brs, 1H, NH), 4.70 (d, *J* = 24.0 Hz, 1H, CH), 4.15-4.07 (m, 2H, OCH_2CH_3), 3.99-3.89 (m, 1H, OCH_2CH_3), 3.75-3.66 (m, 4H, OCH_2CH_3+OCH_3), 1.27 (t, *J* = 4.0, 8.0 Hz, 3H, OCH_2CH_3), 1.13 (t, *J* = 4.0, 8.0 Hz, 3H, OCH_2CH_3) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.39 (d, *J* = 3.03 Hz, Cq), 146,46 (d, *J* = 15.15 Hz, Cq), 129.22 (s, CH-arom), 129.04 (d, *J* = 6.06 Hz, CH-arom), 127.78 (d, *J* = 3.03 Hz, Cq), 118.42 (s, CH-arom), 114.14 (d, *J* = 3.03 Hz, CH-arom),113.97 (s, CH-arom), 63.32 (d, *J* = 4.04 Hz, OCH_2CH_3), 63.25 (d, *J* = 4.04 Hz, OCH_2CH_3), 55.45 (d, *J* = 153.52 Hz, CH), 55.30 (s, OCH_3), 16.53 (d, *J* = 6.06 Hz, OCH_2CH_3), 16.35 (d, *J* = 6.06 Hz, OCH_2CH_3) ppm. ^{31}P NMR (162 MHz, $CDCl_3$) δ 23.29 ppm. Anal. Calcd. for $C_{18}H_{24}NO_4P$: C, 61.88; H, 6.92; N, 4.01. Found: C, 61.02; H, 6.89; N, 3.94.

Table 3, entry 3[21]: Beige solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.45 (dd, *J* = 4.0 Hz, *J* = 8.0 Hz, 2H, H-arom), 7.11 (t, *J* = 8.0 Hz, 2H, H-arom), 7.02 (t, *J* = 8.0 Hz, 2H, H-arom), 6.70 (d, *J* = 4.0, 8.0 Hz, 1H, H-arom), 6.57 (d, *J* = 8.0 Hz, 2H, H-arom), 4.74 (d, *J* = 24.0 Hz, 1H, CH), 4.47 (brs, 1H, NH), 4.14-4.08 (m, 4H, OCH_2CH_3), 3.98-3.94 (m, 1H, OCH_2CH_3), 3.78-3.72 (m, 1H, OCH_2CH_3), 1.28 (t, *J* = 8.0 Hz, 3H, OCH_2CH_3), 1.14 (t, *J* = 4.0, 8.0 Hz, 3H, OCH_2CH_3) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.74 (d, *J* = 4.04 Hz, Cq), 161.32 (t, *J* = 8.08, 4.04 Hz, Cq), 146.20 (d, *J* = 15.15 Hz, Cq), 131.75 (t, *J* = 3.03 Hz, Cq), 129.53 (t, *J* = 3.03, 6.06 Hz, CH-arom), 129.37 (d, *J* = 15.15 Hz, CH-arom), 118.67 (s, CH-arom), 115.77 (d, *J* = 3.03 Hz, CH-arom), 115.55 (d, *J* = 2.02 Hz, CH-arom), 113.93 (s, CH-arom), 63.46 (d, *J* = 7.07 Hz, OCH_2CH_3), 63.34 (s, OCH_2CH_3), 55.46 (d, *J* = 152.51 Hz, CH), 16.52 (d, *J* = 5.05 Hz, OCH_2CH_3), 16.32 (d, *J* = 6.06 Hz, OCH_2CH_3) ppm. ^{31}P NMR (162 MHz, $CDCl_3$) δ 22.93 ppm. Anal. Calcd. for $C_{17}H_{21}FNO_3P$: C, 60.53; H, 6.27; N, 4.15. Found: C, 59.98; H, 6.11; N, 4.03.

Table 3, entry 4: Beige solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.24 (t, *J* = 8.0 Hz, 2H, H-arom), 6.83-6.78 (m, 3H, H-arom), 4.50 (d, *J* = 16.0 Hz, 1H, CH), 4.30 (s, 2H, Cp), 4.30-3.90 (m, 11H, Cp, OCH_2CH_3) 1.21-1.14 (m, 6H, OCH_2CH_3) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.23 (d, *J* = 6.06 Hz, Cq), 129.30 (s, CH-arom), 118.30 (s, CH-arom), 113.55 (s, CH-arom), 85.33 (d, *J* = 7.07 Hz, Cq), 68.69 (s, CH, Cp), 68.03 (s, CH, Cp), 67.67 (s, CH, Cp), 65.93 (d, *J* = 2.02 Hz, CH, Cp), 63.13 (d, *J* = 7.07 Hz, OCH_2CH_3), 62.55 (d, *J* = 7.07 Hz, OCH_2CH_3), 51.77 (d, *J* = 162.61 Hz, CH), 16.45 (d,

J = 5.05 Hz, $OCH_2\underline{C}H_3$), 16.35 (d, *J* = 5.05 Hz, $OCH_2\underline{C}H_3$) ppm. ^{31}P NMR (162 MHz, $CDCl_3$) δ 21.91 ppm. Anal. Calcd. for $C_{23}H_{32}FeNO_3P$: C, 60.40; H, 7.05; N, 3.06. Found: C, 59.99; H, 6.90; N, 2.94.

Table 3, entry 5: Beige solid. ^1H NMR ($CDCl_3$, 400 MHz) δ 8.01 (d, *J* = 8.0 Hz, 2H, H-arom), 7.56 (d, *J* = 8.0 Hz, 2H, H-arom), 7.09 (t, *J* = 8.0, 4.0 Hz, 2H, H-arom), 6.70 (t, *J* = 8.0 Hz, 1H, H-arom), 6.57 (d, *J* = 8.0 Hz, 2H, H-arom), 5.35 (brs, 1H, N<u>H</u>), 4.82 (d, *J* = 24.0 Hz, 1H, C<u>H</u>), 4.17-4.07 (m, 2H, $OC\underline{H}_2CH_3$), 4.00-3.94 (m, 1H, $OC\underline{H}_2CH_3$), 3.89 (s, 3H, $OC\underline{H}_3$), 3.78-3.70 (m, 1H, $OC\underline{H}_2CH_3$), 1.28 (t, *J* = 8.0, 4.0 Hz, 3H, $OCH_2C\underline{H}_3$), 1.14 (t, *J* = 4.0, 8.0 Hz, 3H, $OCH_2C\underline{H}_3$) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.87 (s, <u>C</u>=O), 146.10 (d, *J* = 15.15 Hz, <u>C</u>q), 141.57 (d, *J* = 3.03 Hz, <u>C</u>q), 129.95 (d, *J* = 3.03 Hz, <u>C</u>H-arom), 129.86 (d, *J* = 3.03 Hz, <u>C</u>H-arom), 129.33 (s, <u>C</u>H-arom), 127.97 (d, *J* = 5.05 Hz, <u>C</u>q), 118.79 (s, <u>C</u>H-arom), 113.92 (s, <u>C</u>H-arom), 63.64 (d, *J* = 7.07 Hz, $O\underline{C}H_2CH_3$), 63.54 (d, *J* = 7.07 Hz, $O\underline{C}H_2CH_3$), 56.20 (d, *J* = 149.48 Hz, <u>C</u>H), 52.23 (s, $O\underline{C}H_3$), 16.51 (d, *J* = 8.08 Hz, $OCH_2\underline{C}H_3$), 16.32 (d, *J* = 8.08 Hz, $OCH_2\underline{C}H_3$) ppm. ^{31}P NMR (162 MHz, $CDCl_3$) δ 21.69 ppm.Anal. Calcd. for $C_{19}H_{24}NO_5P$: C, 60.47; H, 6.41; N, 3.71. Found: C, 59.23; H, 6.02; N, 3.59.

Table 3, entry 6[40]: Beige solid. ^1H NMR ($CDCl_3$, 400 MHz) δ 7.07 (t, *J* = 8.0, 4.0 Hz, 2H, H-arom), 7.00 (s, 1H, H-arom), 6.91 (d, *J* = 8.0 Hz, 1H, H-arom), 6.84 (d, *J* = 8.0 Hz, 1H, H-arom), 6.66 (t, *J* = 8.0, 4.0 Hz, 1H, H-arom), 6.61 (d, *J* = 8.0 Hz, 2H, H-arom), 4.89 (brs, 1H, N<u>H</u>), 4.70 (d, *J* = 24.0 Hz, 1H, C<u>H</u>), 4.16-4.05 (m, 2H, $OC\underline{H}_2CH_3$), 3.97-3.91 (m, 1H, $OC\underline{H}_2CH_3$), 3.74-3.66 (m, 4H, $OC\underline{H}_2CH_3$+$OC\underline{H}_3$), 1.25 (t, *J* = 4.0, 8.0 Hz, 3H, $OCH_2C\underline{H}_3$), 1.11 (t, *J* = 4.0, 8.0 Hz, 3H, $OCH_2C\underline{H}_3$) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) 147.19 (d, *J* = 3.03 Hz, <u>C</u>q), 146.29 (d, *J* = 4.04 Hz, <u>C</u>q), 145.75 (d, *J* = 3.03 Hz, <u>C</u>q), 128.96 (s, <u>C</u>H-arom), 127.00 (d, *J* = 2.02 Hz, <u>C</u>q), 120.78 (d, *J* = 8.08 Hz, <u>C</u>H-arom), 118.21 (s, <u>C</u>H-arom), 114.72 (d, *J* = 2.02 Hz, <u>C</u>H-arom), 113.77 (s, <u>C</u>H-arom), 110.53 (d, *J* = 5.05 Hz, <u>C</u>H-arom), 63.21 (t, *J* = 7.07 Hz, $O\underline{C}H_2CH_3$), 55.62 (d, *J* = 153.52 Hz, <u>C</u>H), 55,71 (s, $O\underline{C}H_3$), 16.25 (d, *J* = 5.05 Hz, $OCH_2\underline{C}H_3$), 16.09 (d, *J* = 5.05 Hz, $OCH_2\underline{C}H_3$) ppm. ^{31}P NMR (162 MHz, $CDCl_3$) δ 22.86 ppm. Anal. Calcd. for $C_{18}H_{24}NO_5P$: C, 59.17; H, 6.62; N, 3.83. Found: C, 58.24; H, 5.97; N, 3.69.

Table 3, entry 7[22]: Beige solid. ^1H NMR ($CDCl_3$, 400 MHz) δ 7.47 (d, *J* = 8.0 Hz, 2H, H-arom), 7.32 (t, *J* = 8.0 Hz, 2H, H-arom), 7.25 (t, *J* = 8.0 Hz, 1H, H-arom), 7.09 (t, *J* = 8.0 Hz, 2H, H-arom), 6.68 (t, *J* = 4.0, 8.0 Hz, 1H, H-arom), 6.60 (d, *J* = 12.0 Hz, 2H, H-arom), 4.88 (brs, 1H, N<u>H</u>), 4.76 (d, *J* = 24.0 Hz, 1H, C<u>H</u>), 4.14-4.08 (m, 2H,

$OC\underline{H}_2CH_3$), 3.94-3.90 (m, 1H, $OC\underline{H}_2CH_3$), 3.70-3.64 (m, 1H, $OC\underline{H}_2CH_3$), 1.28 (t, *J* = 4.0, 3H, 8.0 Hz, $OCH_2C\underline{H}_3$), 1.10 (t, *J* = 4.0, 3H, 8.0 Hz, $OCH_2C\underline{H}_3$) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.43 (d, *J* = 15.15 Hz, Cq), 136.01 (s, Cq), 128.67 (d, *J* = 2.02 Hz, CH-arom), 128.00 (d, *J* = 2.02 Hz, CH-arom), 127.92 (s, CH-arom), 118.47 (s, CH-arom), 113.95 (s, CH-arom), 63.41 (d, *J* = 1.01 Hz, $O\underline{C}H_2CH_3$), 63.34 (d, *J* = 2.02 Hz, $O\underline{C}H_2CH_3$), 56.16 (d, *J* = 151.5 Hz, CH), 16.51 (d, *J* = 6.06 Hz, $OCH_2\underline{C}H_3$), 16.27 (d, *J* = 6.06 Hz, $OCH_2\underline{C}H_3$) ppm. ^{31}P NMR (162 MHz, $CDCl_3$) δ 23.02 ppm. Anal. Calcd. for $C_{17}H_{22}NO_3P$: C, 63.94; H, 6.94; N, 4.39. Found: C, 63.80; H, 6.77; N, 4.28.

Table 3, entry 8: Beige solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.60 (s, 4H, H-arom), 7.12 (t, *J* = 8.0 Hz, 2H, H-arom), 6.73 (t, *J* = 4.0, 8.0 Hz, 1H, H-arom), 6.56 (d, *J* = 8.0 Hz, 2H, H-arom), 4.83 (d, *J* = 20.0 Hz, 2H, N<u>H</u>+C<u>H</u>), 4.16-4.10 (m, 2H, $OC\underline{H}_2CH_3$), 4.04-3.98 (m, 1H, $OC\underline{H}_2CH_3$), 3.85-3.79 (m, 1H, $OC\underline{H}_2CH_3$), 1.29 (t, *J* = 4.0, 8.0 Hz, 3H, $OCH_2C\underline{H}_3$), 1.16 (t, *J* = 8.0 Hz, 3H, $OCH_2C\underline{H}_3$) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.02 (d, *J* = 15.15 Hz, Cq), 140.51 (s, Cq), 130.09 (s, Cq), 129.42 (s, CH-arom), 128,26 (d, J = 5.05 Hz, CH-arom), 125.65 (s, CH-arom), 118.95 (s, CH-arom), 113.92 (s, CH-arom), 63.69 (d, *J* = 7.07 Hz, $O\underline{C}H_2CH_3$), 64.00 (d, *J* = 7.07 Hz, $O\underline{C}H_2CH_3$), 56.04 (d, *J* = 150.49 Hz, CH), 16.53 (d, *J* = 6.06 Hz, $OCH_2\underline{C}H_3$), 16.31 (d, *J* = 6.06 Hz, $OCH_2\underline{C}H_3$) ppm. ^{31}P NMR (162 MHz, $CDCl_3$) δ 21.91 ppm. Anal. Calcd. for $C_{18}H_{21}F_3NO_3P$: C, 55.82; H, 5.46; N, 3.62. Found: C, 55.70; H, 5.31; N, 3.53.

Table 3, entry 9[27]: Beige solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.46 (d, *J* = 8.0 Hz, 2H, H-arom), 7.36 (t, *J* = 4.0, 8.0 Hz, 2H, H-arom), 7.11 (t, *J* =8.0, 12.0 Hz, 2H, H-arom), 6.71 (t, *J* = 12.0, 8.0 Hz, 1H, H-arom), 6.56 (d, *J* = 12.0 Hz, 2H, H-arom), 4.76-4.66 (m, 2H, N<u>H</u>, C<u>H</u>), 4.18-3.92 (m, 3H, $OC\underline{H}_2CH_3$), 3.85-3.72 (m, 1H, $OC\underline{H}_2CH_3$), 1.29 (t, *J* = 8.0, 12.0 Hz, 3H, $OCH_2C\underline{H}_3$), 1.14 (t, *J* = 8.0, 12.0 Hz, 3H, $OCH_2C\underline{H}_3$) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.15 (d, *J* = 19.19 Hz, Cq), 135.32 (d, *J* = 4.04 Hz, Cq), 131.86 (d, *J* = 4.04 Hz, CH-arom), 129.63 (d, *J* = 7.07 Hz, CH-arom), 129.37 (s, CH-arom), 121.98 (d, *J* = 6.06 Hz, Cq), 118.82 (s, CH-arom), 113.98 (s, CH-arom), 63.55 (d, *J* = 9.09 Hz, $O\underline{C}H_2CH_3$), 63.42 (s, $O\underline{C}H_2CH_3$), 55.77 (d, *J* = 200.99 Hz, CH), 16.57 (d, *J* = 8.08 Hz, $OCH_2\underline{C}H_3$), 16.39 (d, *J* = 8.08 Hz, $OCH_2\underline{C}H_3$) ppm. ^{31}P NMR (162 MHz, $CDCl_3$) δ 22.10 ppm. Anal. Calcd. for $C_{17}H_{21}BrNO_3P$: C, 51.27; H, 5.32; N, 3.52. Found: C, 51.04; H, 5.19; N, 3.38.

Table 3, entry 10[20]: Brown solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.40 (s, 1H, H-arom), 7.17 (t, *J* = 8.0 Hz, 2H, H-arom), 6.76 (t, *J* = 8.0, 4.0 Hz, 1H, H-arom), 6.69 (d,

J = 8.0 Hz, 2H, H-arom), 6.41 (t, *J* = 4.0 Hz, 1H, H-arom), 6.34 (s, 1H, H-arom), 4.93 (d, *J* = 24.0 Hz, 1H, CH), 4.44 (brs, 1H, NH), 4.25-4.15 (m, 2H, OCH_2CH_3), 4.13-4.04 (m, 1H, OCH_2CH_3), 3.95-3.85 (m, 1H, OCH_2CH_3), 1.32 (t, *J* = 4.0, 8.0 Hz, 3H, OCH_2CH_3), 1.22 (t, *J* = 8.0, 4.0 Hz, 3H, OCH_2CH_3) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.13 (s, Cq), 145.96 (d, *J* = 45.45 Hz, Cq), 142.50 (s, CH-arom), 129.20 (s, CH-arom), 118.20 (s, CH-arom), 113.95 (s, CH-arom), 110.79 (s, CH-arom), 108.80 (d, *J* = 7.07 Hz, CH-arom), 63.36 (s, OCH_2CH_3), 50.23 (d, *J* = 160.59 Hz, CH), 16.45 (d, *J* = 6.06 Hz, OCH_2CH_3), 16.30 (d, *J* = 6.06 Hz, OCH_2CH_3) ppm. ^{31}P NMR (162 MHz, $CDCl_3$) δ 20.61 ppm. Anal. Calcd. for $C_{15}H_{20}NO_4P$: C, 58.25; H, 6.52; N, 4.53. Found: C, 57.96; H, 6.41; N, 4.38.

Table 4, entry 1: Beige solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.37 (d, *J* = 8.0 Hz, 2H, H-arom), 7.20 (d, *J* = 8.0 Hz, 2H, H-arom), 6.69 (d, *J* = 8.0 Hz, 2H, H-arom), 6.56 (d, *J* = 12.0 Hz, 2H, H-arom), 5.42 (brs, 1H, NH), 4.66 (d, *J* = 24.0 Hz, 1H, CH), 4.18-4.07 (m, 2H, OCH_2CH_3), 4.00-3.94 (m, 1H, OCH_2CH_3), 3.79-3.71 (m, 1H, OCH_2CH_3), 3.68 (s, 3H, OCH_3), 2.48 (s, 3H, SCH_3), 1.29 (t, *J* = 8.0 Hz, 3H, OCH_2CH_3), 1.15 (t, *J* = 8.0 Hz, 3H, OCH_2CH_3) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.92 (s, Cq), 140.11 (d, *J* = 16.16 Hz, Cq), 138.29 (d, *J* = 4.04 Hz, Cq), 132.65 (d, *J* = 3.03 Hz, Cq), 128.46 (d, *J* = 6.06 Hz, CH-arom), 126.60 (d, *J* = 3.03 Hz, CH-arom), 115.55 (s, CH-arom), 114.83 (s, CH-arom), 63.58 (d, *J* = 7.07 Hz, OCH_2CH_3), 63.46 (d, *J* = 7.07 Hz, OCH_2CH_3), 56.70 (d, *J* = 152.51 Hz, CH), 55.74 (s, OCH_3), 16.54 (d, *J* = 6.06 Hz, OCH_2CH_3), 16.35 (d, *J* = 6.06 Hz, OCH_2CH_3), 15.71 (s, SCH_3) ppm. ^{31}P NMR (162 MHz, $CDCl_3$) δ 22.75 ppm. Anal. Calcd. for $C_{19}H_{26}NO_4PS$: C, 57.71; H, 6.63; N, 3.54. Found: C, 57.62; H, 6.54; N, 3.40.

Table 4, entry 3: Beige solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.36 (d, *J* = 4.0 Hz, 2H, H-arom), 7.21 (d, *J* = 8.0 Hz, 2H, H-arom), 6.81 (t. *J* = 8.0 Hz, 2H, H-arom), 6.52-6.49 (m, 2H, H-arom), 6.64 (d, *J* = 24,0 Hz, 1H, CH), 4.14-4.09 (m, 2H, OCH_2CH_3), 3.99-3.93 (m, 1H, OCH_2CH_3), 3.77-3.71 (m, 1H, OCH_2CH_3), 2.81 (brs, 1H, NH), 2.46 (s, 3H, SCH_3), 1.30 (t, *J* = 4.0, 8.0 Hz, 3H, OCH_2CH_3), 1.15 (t, *J* = 8.0 Hz, 3H, OCH_2CH_3) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.52 (s, Cq), 155.18 (s, Cq), 142.66 (d, *J* = 2.02 Hz, Cq), 138.46 (d, *J* = 3.03 Hz, Cq), 132.37 (d, *J* = 3.03 Hz, Cq), 128.35 (d, *J* = 5.05 Hz, CH-arom), 126.59 (d, *J* = 3.03 Hz, CH-arom), 115.58 (s, CH-arom), 114.96 (d, *J* = 7.07 Hz, CH-arom), 63.49 (d, *J* = 7.07 Hz, OCH_2CH_3), 56.32 (d, *J* = 152.51 Hz, CH), 16.47 (d, *J* = 5.05 Hz, OCH_2CH_3), 16.28 (d, *J* = 6.06 Hz, OCH_2CH_3), 15.62 (s,

S<u>C</u>H$_3$) ppm. ^{31}P NMR (162 MHz, CDCl$_3$) δ 22.62 ppm. Anal. Calcd. for $C_{18}H_{23}FNO_3PS$: C, 56.39; H, 6.05; N, 3.65. Found: C, 56.22; H, 5.93; N, 3.55.

Table 4, entry 4: Beige solid. ^{1}H NMR (CDCl$_3$, 400 MHz) δ 7.35 (t, *J* = 4.0 Hz, 2H, H-arom), 7.22-7.16 (m, 4H, H-arom), 6.45 (d, *J* = 8.0 Hz, 2H, H-arom), 4.84 (brs, 1H, N<u>H</u>), 4.66 (d, *J* = 24.0 Hz, 1H, C<u>H</u>), 4.19-4.08 (m, 2H, OC<u>H$_2$</u>CH$_3$), 3.97-3.92 (m, 1H, OC<u>H$_2$</u>CH$_3$), 3.76-3.72 (m, 1H, OC<u>H$_2$</u>CH$_3$), 2.45 (s, 3H, SC<u>H$_3$</u>), 1.29 (t, *J* = 8.0 Hz, 3H, OCH$_2$C<u>H$_3$</u>), 1.14 (t, *J* = 4.0, 8.0 Hz, 3H, OCH$_2$C<u>H$_3$</u>) ppm. ^{13}C NMR (CDCl$_3$, 101 MHz) δ 145.39 (d, *J* = 15.2 Hz, <u>C</u>q), 138.64 (s, <u>C</u>q), 132.21 (s, <u>C</u>q), 132.03 (s, <u>C</u>H-arom), 128.32 (d, *J* = 5.05 Hz, <u>C</u>H-arom), 126.70 (d, *J* = 3.03 Hz, <u>C</u>H-arom), 115.61 (s, <u>C</u>H-arom), 110.39 (s, <u>C</u>q), 63.56 (d, *J* = 7.07 Hz, O<u>C</u>H$_2$CH$_3$), 63.47 (d, *J* = 7.07 Hz, O<u>C</u>H$_2$CH$_3$), 55.78 (d, *J* = 152.51 Hz, <u>C</u>H), 16.55 (d, *J* = 6.06 Hz, OCH$_2$<u>C</u>H$_3$), 16.37 (d, *J* = 5.05 Hz, OCH$_2$<u>C</u>H$_3$), 15.72 (s, S<u>C</u>H$_3$) ppm. ^{31}P NMR (162 MHz, CDCl$_3$) δ 22.38 ppm. Anal. Calcd. for $C_{18}H_{23}BrNO_3PS$: C, 48.66; H, 5.22; N, 3.15. Found: C, 48.51; H, 5.08; N, 3.03.

Table 4, entry 5: Beige solid. ^{1}H NMR (CDCl$_3$, 400 MHz) δ: 7.32 (d, *J* = 8.0 Hz, 2H, H-arom), 6.97 (d, *J* = 8.0 Hz, 2H, H-arom), 6.77 (d, *J* = 4.0 Hz, 1H, H-arom), 6.62 (d, *J* = 8.0 Hz, 1H, H-arom), 6.54 (d, *J* = 8.0 Hz, 1H, H-arom), 6.48 (d, *J* = 8. 0 Hz, 1H, H-arom), 4.86 (d, *J* = 24.0 Hz, 1H, C<u>H</u>), 4.29-4.21 (m, 2H, OC<u>H$_2$</u>CH$_3$), 4.00-3.90 (m, 1H, OC<u>H$_2$</u>CH$_3$), 3.74-3.65 (m, 1H, OC<u>H$_2$</u>CH$_3$), 2.32 (s, 3H, SC<u>H$_3$</u>), 1.29 (t, *J* = 8.0 Hz, 3H, OCH$_2$C<u>H$_3$</u>), 1.13 (t, *J* = 8.0 Hz, 3H, OCH$_2$C<u>H$_3$</u>) ppm. ^{13}C NMR (101 MHz, CDCl$_3$) δ 145.25 (s, <u>C</u>q), 138.17 (d, *J* = 3.03 Hz, <u>C</u>q), 134.84 (d, *J* = 17.2 Hz, <u>C</u>q), 132.30 (d, *J* = 1.01 Hz, <u>C</u>q), 128.55 (d, *J* = 6.06 Hz, <u>C</u>H-arom), 126.35 (d, *J* = 2.02 Hz, <u>C</u>H-arom), 119.93 (s, <u>C</u>H-arom), 118.44 (s, <u>C</u>H-arom), 114.56 (s, <u>C</u>H-arom), 112.07 (s, <u>C</u>H-arom), 64.32 (d, *J* = 7.07 Hz, O<u>C</u>H$_2$CH$_3$), 63.77 (d, *J* = 8.08 Hz, O<u>C</u>H$_2$CH$_3$), 55.52 (d, *J* = 155.54 Hz, <u>C</u>H), 16.47 (d, *J* = 5.05 Hz, OCH$_2$<u>C</u>H$_3$), 16.22 (d, *J* = 6.06 Hz, OCH$_2$<u>C</u>H$_3$), 15.47 (s, S<u>C</u>H$_3$) ppm. ^{31}P NMR (162 MHz, CDCl$_3$) δ: 24.08 ppm. Anal. Calcd. for $C_{18}H_{24}NO_4PS$: C, 56.68; H, 6.34; N, 3.67. Found: C, 56.60; H, 6.27; N, 3.59.

Table 5, entry 1: Beige solid. ^{1}H NMR (CDCl$_3$, 400 MHz) δ 7.41 (d, *J* = 8.0 Hz, 2H, H-arom), 7.19 (t, *J* = 8.0 Hz, 2H, H-arom), 7.14 (d, *J* = 8.0 Hz, 2H, H-arom), 6.85 (d, *J* = 12.0 Hz, 2H, H-arom), 6.74 (t, *J* = 4.0, 12.0 Hz, 1H, H-arom), 5.28 (d, *J* = 24.0 Hz, 1H, C<u>H</u>), 4.18-3.95 (m, 4H, OC<u>H$_2$</u>CH$_3$), 2.91 (s, 3H, C<u>H$_3$</u>), 2.34 (s, 3H, SC<u>H$_3$</u>), 1.19-1.14 (m, 6H, OCH$_2$C<u>H$_3$</u>) ppm. ^{13}C NMR (101 MHz, CDCl$_3$) δ 149.62 (d, *J* = 7.07 Hz, <u>C</u>q), 138.00 (s, <u>C</u>q), 130.44 (d, *J* = 8.08 Hz, <u>C</u>q), 128.91 (s, <u>C</u>H-arom), 128.76 (d, *J* = 9.09 Hz, <u>C</u>H-arom), 125.68 (s, <u>C</u>H-arom), 117.67 (s, <u>C</u>H-arom), 113.47 (s,

CH-arom), 62.57 (d, *J* = 7.07 Hz, O$\underline{C}H_2CH_3$), 61,62 (d, *J* = 7.07 Hz, O$\underline{C}H_2CH_3$), 60.82 (d, *J* = 154.53 Hz, $\underline{C}$H), 34.12 (s, $\underline{C}H_3$), 16.02 (d, *J* = 5.05 Hz, OCH$_2\underline{C}H_3$), 15.85 (d, *J* = 5.05 Hz, OCH$_2\underline{C}H_3$), 14.81 (s, S$\underline{C}H_3$) ppm. ^{31}P NMR (162 MHz, $CDCl_3$) δ 22.13 ppm. Anal. Calcd. for $C_{19}H_{26}NO_3PS$: C, 60.14; H, 6.91; N, 3.69. Found: C, 59.97; H, 6.85; N, 3.54.

Table 5, entry 2: Beige solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.49 (dd, *J* = 4.0, 8.0 Hz, 2H, H-arom), 7.23 (t, *J* = 8.0 Hz, 2H, H-arom), 6.98 (t, *J* = 8.0 Hz, 2H, H-arom), 6.87 (d, *J* = 8.0 Hz, 2H, H-arom), 6.78 (t, *J* = 4.0, 8.0 Hz, 1H, H-arom), 5.30 (d, *J* = 24.0 Hz, 1H, C$\underline{H}$), 4.21-4.00 (m, 4H, 2OC$\underline{H}_2CH_3$), 2.93 (s, 3H, C$\underline{H}_3$), 1.22-1.17 (m, 6H, 2OCH$_2$C$\underline{H}_3$) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.45 (s, $\underline{C}$q), 160.99 (s, $\underline{C}$q), 149.91 (d, *J* = 8.08 Hz, $\underline{C}$q), 130.58 (s, $\underline{C}$H-arom), 129.08 (s, $\underline{C}$H-arom), 118.16 (s, $\underline{C}$H-arom), 115.32 (s, $\underline{C}$H-arom), 113.85 (s, $\underline{C}$H-arom), 63.04 (d, *J* = 7.07 Hz, O$\underline{C}H_2CH_3$), 62.03 (d, *J* = 7.07 Hz, O$\underline{C}H_2CH_3$), 61.01 (d, *J* = 161.60 Hz, $\underline{C}$H), 34.39 (s, $\underline{C}H_3$), 16.30 (d, *J* = 5.05 Hz, OCH$_2\underline{C}H_3$), 16.11 (d, *J* = 6.06 Hz, OCH$_2\underline{C}H_3$) ppm. ^{31}P NMR (162 MHz, $CDCl_3$) δ 22.05 ppm. Anal. Calcd. for $C_{18}H_{23}FNO_3P$: C, 61.53; H, 6.60; N, 3.99. Found: C, 60.38; H, 6.49; N, 3.84.

Table 5, entry 3: Beige solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.41 (q, *J* = 8.0 Hz, 4H, H-arom), 7.23 (t, *J* = 8.0 Hz, 2H, H-arom), 6.85 (d, *J* = 8.0 Hz, 2H, H-arom), 6.78 (t, *J* = 8.0 Hz, 1H, H-arom), 5.26 (d, *J* = 24.0 Hz, 1H, C$\underline{H}$), 4.20-4.00 (m, 4H, OC$\underline{H}_2CH_3$), 2.92 (s, 3H, C$\underline{H}_3$), 1.22-1.18 (m, 6H, OCH$_2$C$\underline{H}_3$) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.87 (d, *J* = 7.07 Hz, $\underline{C}$q), 133.46 (d, *J* = 7.07 Hz, $\underline{C}$q), 131.51 (s, $\underline{C}$H-arom), 130.40 (d, *J* = 9.09 Hz, $\underline{C}$H-arom), 129.14 (s, $\underline{C}$H-arom), 121.93 (s, $\underline{C}$q), 118.27 (s, $\underline{C}$H-arom), 113.88 (s, $\underline{C}$H-arom), 63.12 (d, *J* = 7.07 Hz, O$\underline{C}H_2CH_3$), 62.11 (d, *J* = 7.07 Hz, O$\underline{C}H_2CH_3$), 61.22 (d, *J* = 160.59 Hz, $\underline{C}$H), 34.57 (s, $\underline{C}H_3$), 16.39 (d, *J* = 6.1 Hz, OCH$_2\underline{C}H_3$), 16.22 (d, *J* = 5.1 Hz, OCH$_2\underline{C}H_3$) ppm. ^{31}P NMR (162 MHz, $CDCl_3$) δ 21.66 ppm. Anal. Calcd. for $C_{18}H_{23}BrNO_3P$: C, 52.44; H, 5.62; N, 3.40. Found: C, 52.33; H, 5.47; N, 3.29.

Table 5, entry 4: Beige solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.30 (d, *J* = 8.0 Hz, 2H, H-arom), 7.06 (s, 1H, H-arom), 6.92 (d, *J* = 2.0 Hz, 2H, H-arom), 6.80 (d, *J* = 8.0 Hz, 1H, H-arom), 6.53 (d, *J* = 8.0 Hz, 2H, H-arom), 4.25 (d, *J* = 24.0 Hz, 1H, C$\underline{H}$), 3.99-3.94 (m, 2H, OC$\underline{H}_2CH_3$), 3.84-3.80 (m, 5H, OC$\underline{H}_2CH_3$+OC$\underline{H}_3$), 2.75 (s, 3H, C$\underline{H}_3$), 1.14-1.11 (t, *J* = 4.0, 8.0 Hz, 6H, OCH$_2$C$\underline{H}_3$) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.38 (s, $\underline{C}$q), 146.77 (s, $\underline{C}$q), 144.95 ($\underline{C}$q), 130.04 (d, *J* = 8.08 Hz, $\underline{C}$H-arom), 128.93 (s, CH-arom), 125.19 (d, *J* = 5.05 Hz, $\underline{C}$q), 122.14 (d, *J* = 9.09 Hz, $\underline{C}$H-arom), 114.64 (s,

CH-arom), 112.47 (s, CH-arom) 112.27 (d, *J* = 7.07 Hz, CH-arom), 62.68 (d, *J* = 7.07 Hz, OCH_2CH_3), 62.54 (d, *J* = 7.07 Hz, OCH_2CH_3), 55.83 (s, OCH_3), 49.72 (d, *J* = 139.38 Hz, CH), 30.64 (s, CH_3), 16.31 (s, OCH_2CH_3), 16.25 (s, OCH_2CH_3) ppm. ^{31}P NMR (162 MHz, $CDCl_3$) δ 26.36 ppm. Anal. Calcd. for $C_{19}H_{26}NO_5P$: C, 60.15; H, 6.91; N, 3.69. Found: C, 59.01; H, 6.79; N, 3.53.

Table 5, entry 5: Beige solid. ^1H NMR ($CDCl_3$, 400 MHz) δ 8.00 (d, *J* = 8.0 Hz, 2H, H-arom), 7.60 (d, *J* = 8.0 Hz, 2H, H-arom), 7.25 (t, *J* = 8.0 Hz, 2H, H-arom), 6.87 (d, *J* = 8.0 Hz, 2H, H-arom), 6.80 (t, *J* = 8.0 Hz, 1H, H-arom), 5.37 (d, *J* = 24.0 Hz, 1H, CH), 4.20-4.03 (m, 4H, OCH_2CH_3), 3.89 (s, 3H, OCH_3), 2.98 (s, 3H, CH_3), 1.24-1.19 (m, 6H, OCH_2CH_3) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.70 (s, C=O), 149.95 (s, Cq), 139.92 (s, Cq), 129.71 (s, CH-arom), 129.23 (s, CH-arom), 128.70 (s, Cq), 118.15 (s, CH-arom), 113.87 (s, CH-arom), 63.22 (d, *J* = 8.08 Hz, OCH_2CH_3), 62.28 (d, *J* = 7.07 Hz, OCH_2CH_3), 61.68 (d, *J* = 159.58 Hz, CH), 52.04 (s, OCH_3), 34.87 (s, CH_3), 16.43 (d, *J* = 6.1 Hz, OCH_2CH_3), 16.26 (d, *J* = 5.1 Hz, OCH_2CH_3) ppm. ^{31}P NMR (162 MHz, $CDCl_3$) δ 21.57 ppm. Anal. Calcd. for $C_{20}H_{26}NO_5P$: C, 61.37; H, 6.70; N, 3.58. Found: C, 60.19; H, 6.58; N, 3.40.

4.4. Use of the catalyst [$CpRu(PPh_3)_2Cl$] in several catalytic cycles

To a mixture of 4-(methylthio)benzaldehyde (1.0 mmol), aniline (1.0 mmol) and [$CpRu(PPh_3)_2Cl$] (0.5 mol %) was added $HP(O)(OEt)_2$ (2.0 mmol). The reaction mixture was stirred at 80 ºC under an air atmosphere during 15 min. The reaction mixture was cooled and the yield was determined by ^1H NMR spectroscopy using mesitylene (1.0 mmol) as internal standard. In the next catalytic cycles, 4-(methylthio)benzaldehyde (1.0 mmol), aniline (1.0 mmol), $HP(O)(OEt)_2$ (2.0 mmol) and mesitylene (1.0 mmol) was added to the reaction mixture and stirred at 80 ºC. The yields were determined by ^1H NMR spectroscopy**.**

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Highlights

[$CpRu(PPh_3)_2Cl$] is a very efficient catalyst for the direct aminophosphonylation of aldehydes

The catalyst [$CpRu(PPh_3)_2Cl$] can be use in 12 catalytic cycles with excellent activity

The reactions can be performed under solvent free conditions