Silica gel-immobilized aluminum phthalocyanine complex as a heterogeneous catalyst for the synthesis of α-amino phosphonates

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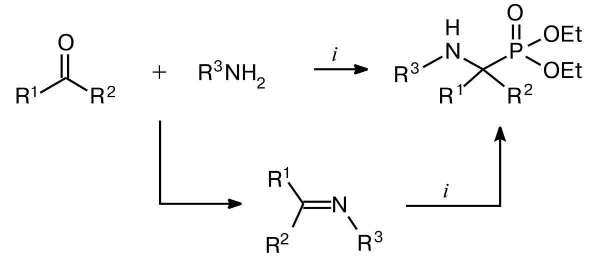
Aluminum phthalocyanine complexes immobilized onto silica gel (CPG-550 is controlled pore glass, MCM-41 is mesoporous molecular sieves) exhibited high catalytic activity and stability in the Kabachnik—Fields reaction.

Key words: α-amino phosphonates, Kabachnik—Fields reaction, (tetracarboxyphthalocyanine)aluminum chloride, (disulfophthalocyanine)aluminum chloride, heterogeneous catalysts, silica gel, aluminum complexes.

Metallophthalocyanines and porphyrines are efficient catalysts for several processes.[1—3] Earlier we developed novel catalytic procedure toward α-amino phosphonates. This method serves for the synthesis of complex biologically active compounds, *e.g.*, phosphorus-containing bioisosteric analog of selective agonists of the first subtype of glutamic receptors of 1-aminoindane-1,5-dicarboxylic acid and phosphorus-containing analogs of "memory tripeptide" (Arg—Glu—Arg).[4,5] The method involved addition of hydrophosphoryl compound to the double C=N bond in three-component (carbonyl compound, amine, and phosphite; the Kabachnik—Fields reaction) or two component (imine, azine or hydrazone, and phosphite; the Pudovik reaction) one-pot procedures in the presence of phthalocyanine as a catalyst (Scheme 1).

Scheme 1



i. $(EtO)_2P(O)H$, ^{t}PcAlCl (cat.)

R^1, R^2 = Alk, Ar; R^3 = Alk, CH(R)COOH, CH(R)COOR′, NHR, NHC(O)R, NHC(O)CH(R)NHR′

Phthalocyanine catalysis allowed extension of the scope of hydrophosphorylation. Thus, it was possible to involve ketones with complex structure, amino acids, peptides, azines, and hydrazones in the reaction. Nevertheless, in spite of efficiency of homogeneous catalysis in preparative procedures, we would like to avoid the loss of the catalyst during the products isolation and simplify the step of the separation of the catalyst from the reaction mixture.

One of the solutions of this problem is the immobilization of the catalyst on the solid support. Several fundamentally different procedures are known for the phthalocyanine immobilization. Encapsulation of phthalocyanine in the supercages of zeolites or mesoporous molecular sieves[6—8] are widely used, however, significant disadvantage of this method is impeded diffusion of reactants and products. Coordinative binding of metal complexes onto the surface of solid carriers modified with the pyridyl or imidazolyl groups[9,10] is another method of conjugation of phthalocyanine and macromolecules. The drawback of this method is flushing out of the catalyst from the carrier leading to its deactivation upon use. The same disadvantage has electrostatic binding of phthalocyanines (involving COO$^-$ or Alk$_3$N$^+$ groups on the periphery of macrocycle) at ion-exchange resin or modified silica gels.[1,11] These drawbacks deprived the physical incorporation of vinyl phthalocyanine derivatives into a macromolecular matrix,[12] however, on its turn, this method limited by the use of polystyrene as a matrix and has a number of disadvantages inherent for organic polymeric carries (*e.g.*, low temperature limits of applicability and low mechanical stability).

According to the literature data,[12] the covalent binding of phthalocyanine ring with silica gel matrix *via* different linkers is very promising. It was shown in several publications that this method allow preparation of heterogeneous catalysts with non-aggregated phthalocyanine molecules

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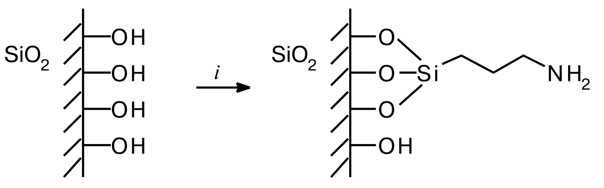
(see, *e.g.*, Ref. 13). Such catalysts exhibit comparable or even higher activity in respect of soluble homogeneous phthalocyanine catalysts for the hydroxylation of phenols,[2] photochemical oxidation,[3] and for the synthesis of cyclic carbonates from epoxides.[14]

In the present work, with the aim at preparing of heterogeneous catalysts for the synthesis of complex α-amino phosphonates, we immobilized aluminum phthalocyanine complexes on two types of silica supports and tested the activity of the resulting catalysts in the model reaction. According to the preliminary tests, no target products were formed in the reactions carried out in the presence of the unmodified supports at the same reaction time.

Mesoporous molecular sieves MCM-41 was used as a solid support. Surface of MCM-41 was modified with (3-aminopropyl)triethoxysilane (APTES).[14] For a comparison, we used similarly modified controlled pore glass (CPG-550 Å) (Scheme2).

Scheme 2



1a,b

i. $(EtO)_3SiCH_2CH_2CH_2NH_2$, PhH, 80 °C, 10 h.

1	Support
a	CPG-550
b	MCM-41

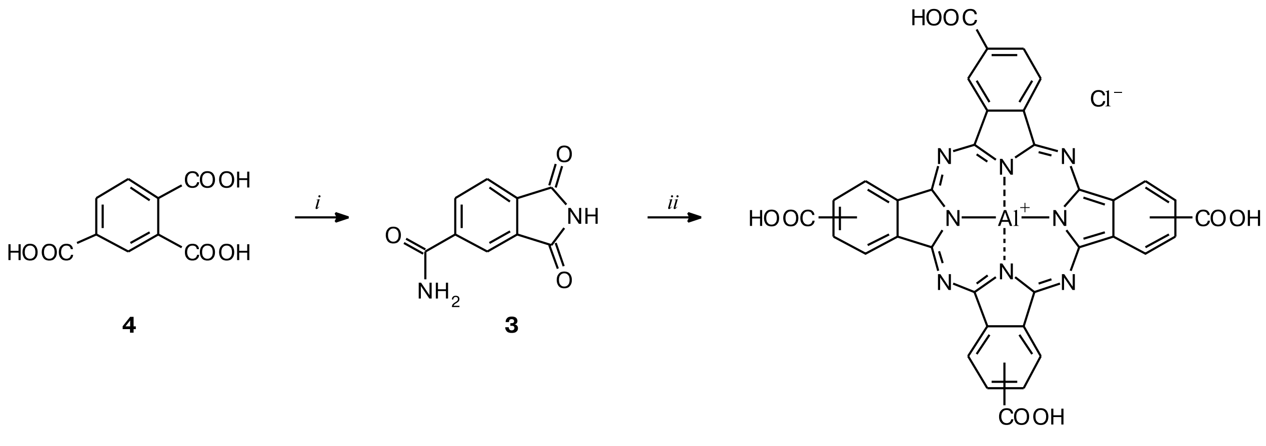
Aluminum phthalocyanine complex was grafted onto modified carrier **1** by two alternative synthetic methods, *e.g.*, *via* carbamide and sulfamide linkers. In the first case, we use (tetracarboxyphthalocyanine)aluminum chloride (**2**, TCPcAlCl),[15] which was prepared according to Scheme 3 described previously for metal tetrabromotetracaboxyphthalocyanine complexes (Co, Fe, Cu).[16] In this synthesis, amide-imide of trimellitic acid (**3**)[15] obtained preliminary by melting of acid **4** with urea was melted with aluminum chloride in the excess of urea at 270 °C in the presence of ammonium molybdate as a template catalyst.

For the immobilization onto the support, phthalocyanine **2** was, at first, converted into chloroanhydride **5** by refluxing with thionyl chloride in benzene in the presence of catalytic amount of pyridine (Scheme 4). Then, chloroanhydride **5** was grafted onto modified silica support **1** by heating in DMF. To prevent the possible influence or involvement of the free carboxy groups of phthalocyanine and free amino groups of the support on the catalytic processes, they were transformed into amide groups by subsequent treatment of the reaction mixture with diisopropylamine and acetic anhydride. Following this procedure, a number of catalysts based on phthalocyanine-aluminum chloride grafted onto solid support *via* the amide groups on the macrocycle periphery were prepared.

Alternative approach toward phthalocyanine immobilization involved formation of the sulfamide linkage. Unsubstituted phthalocyaninealuminum chloride (**9**, PcAlCl) prepared by melting of phthalimide with aluminum chloride and urea in the presence of template catalyst $(NH_4)_2MoO_4$ (see Ref. 16) was subjected to sulfonation with 30% oleum at 75 °C followed by washing with 1% aqueous HCl for the exchange of the counter-ion (Scheme 5) to give aluminum disulfophthalocyanine complex (**10**, DSPcAlCl).

Immobilization of phthalocyanine **10** onto the support was carried out in the reverse order as compared with

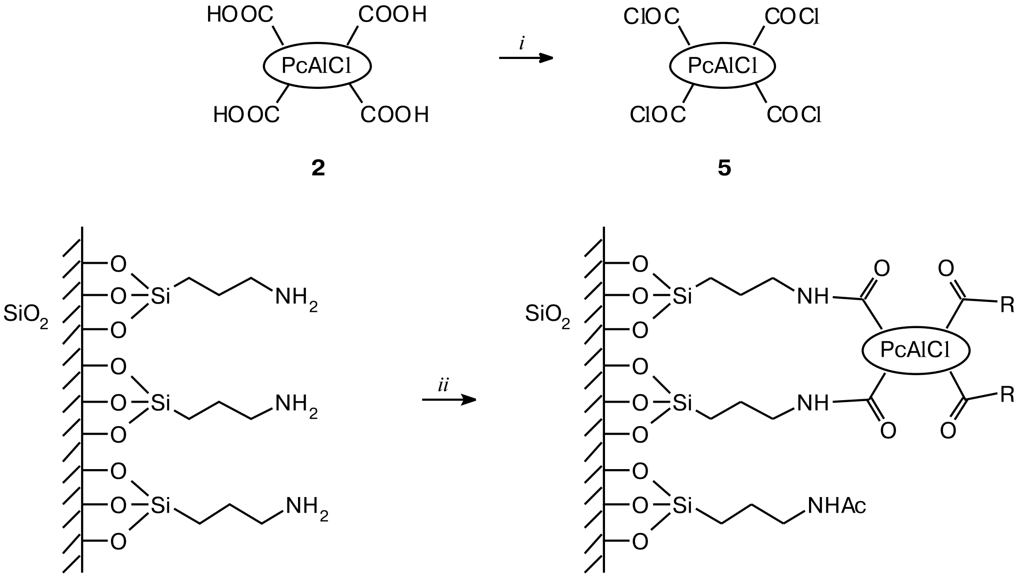
Scheme 3



2 (TCPcAlCl)

i. $H_2NC(O)NH_2$, 250 °C; *ii.* 1) $H_2NC(O)NH_2$, $AlCl_3$, $(NH_4)_2MoO_4$, 270 °C, 2) 2 *M* NaOH, 90 °C.

Scheme 4



2 **5**

1 **6—8**

R = NPr^i_2 (**6**, **7**), OH (**8**)

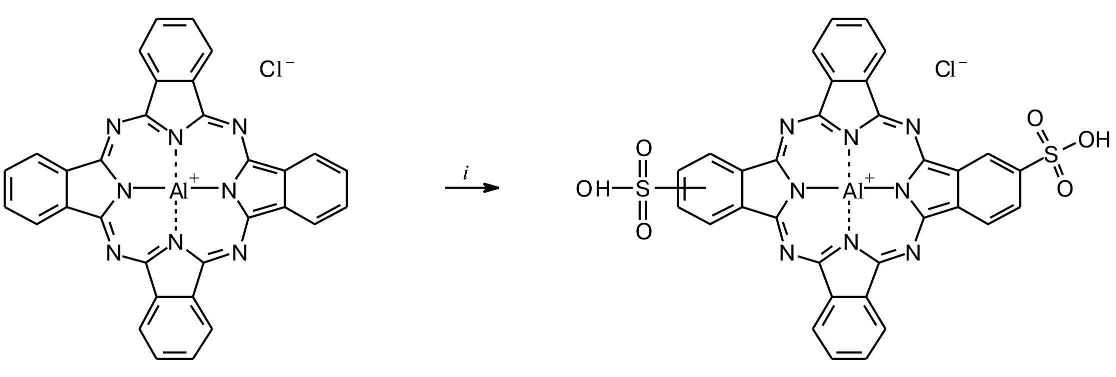
i. $SOCl_2$, PhH, Py, reflux; *ii*. 1) **5**, DMF, 50—60 °C, 24 h, 2) Pr^i_2NH, then Ac_2O (**6**, **7**) or Ac_2O (**8**).

Catalyst	R	Support	*C**
6	$N(Pr^i)_2$	CPG-550	0.055
7	$N(Pr^i)_2$	MCM-41	0.1
8	OH	CPG-550	0.055

* Content of phthalocyanine (g) on 1 g of catalyst.

phthalocyanine **5**. Namely, phthalocyanine **10** was involved in the reaction with APTES and then the resulting derivative was bonded to unmodified silica support (Scheme 6). Disulfophthalocyanine **10** (DSPcAlCl) was treated with thionyl chloride in benzene in the presence of catalytic amount of pyridine to give di(chlorosulfonyl)phthalocyanine **11**. This compound was treated with APTES in DMF in the presence of small amount of pyridine and then unmodified silica gel (MCM-41, CPG-550) was added to the reaction mixture. This immobilization

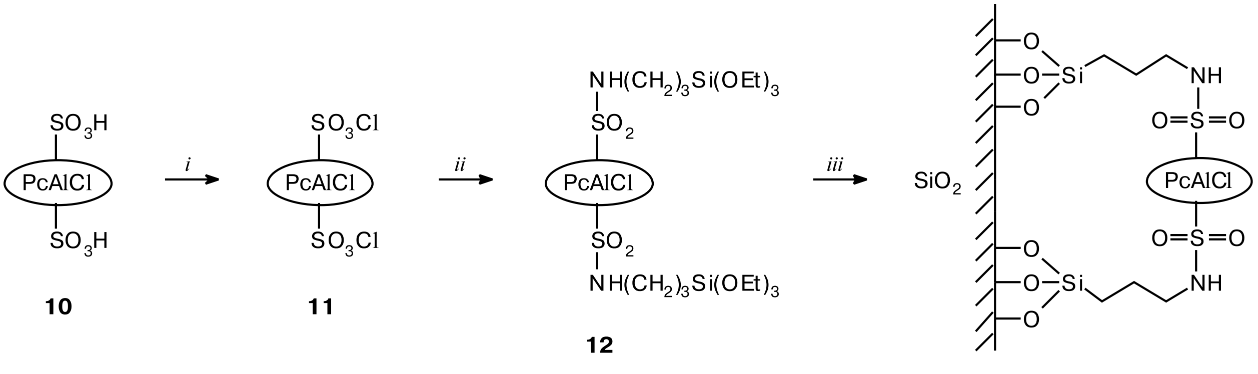
Scheme 5



9 **10** (DSPcAlCl)

i. 1) $SO_3 \cdot H_2SO_4$, 75 °C, 8 h; 2) 1% aq. HCl.

Scheme 6



13—15

i. 1) $SOCl_2$, PhH, Py, reflux, 10 h; *ii.* APTES, DMF, Py, 80 °C, 12 h; *iii.* MCM-41 or CPG-550, DMF, Py, 110 °C, 24 h.

Catalyst	Support	*C**
13	CPG-550	0.05
14	MCM-41	0.02
15	MCM-41	0.1

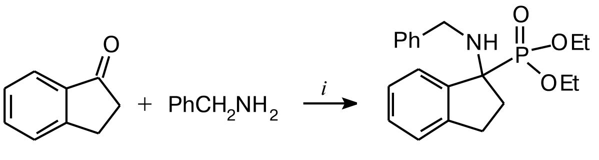
* Content of phthalocyanine (g) on 1 g of catalyst.

procedure resulted in phthalocyaninealuminum chloride bonded to the support *via* the sulfamide groups on the periphery of phthalocyanine cycle (catalysts **13**—**15**).

Thus, we synthesized two types of heterogeneous phthalocyanine catalysts immobilized on two types of carriers (MCM-41, CPG-550) with different phthalocyanine content, which depended on the reaction yield on the step of covalent bonding of phthalocyanine with solid support.

Catalytic activity of the prepared catalysts was tested under the Kabachnik—Fields reaction conditions employed earlier[4] for the synthesis of bioisosteric analog of 1-aminoindane-1,5-dicarboxylic acid (Scheme 7). Comparative yields of aminophosphonate **16** depending on the catalysts used are summarized in Tables 1—3.

Scheme 7



16

i. $(EtO)_2P(O)H$, PcAlCl, CH_2Cl_2.

Introduction of the *tert*-butyl groups on the periphery of phthalocyanine ring enhanced the solubility of ^{t}PcAlCl complex in organic solvents providing homogeneous catalytic conditions. Earlier, in the presence of [tetra(*tert*-butyl)phthalocyanine]aluminum chloride (^{t}PcAlCl, 5 mol.%), aminophosphonate **16** was synthesized in nearly quantitative yield.[4,5] For comparison of catalytic activity of phthalocyanines, this reaction was carried out in the presence of 0.125 mol.% of the following catalysts: ^{t}PcAlCl (homogeneous catalyst), PcAlCl (**9**) and TCPcAlCl (**2**) (non-immobilized heterogeneous catalysts, which were not fully soluble in the reaction mixture), and immobilized catalysts **6** and **8**. Yields of product **16** are given in Table 1. As it follows from Table 1, heterogeneous catalyst PcAlCl (**9**) is almost as effective as homogeneous analog ^{t}PcAlCl. Whereas, complex **2** is two-folds less effective with respect to unsubstituted phthalocyanine **9** due probably to the crystalline structure of these compounds. Phthalocyanine PcAlCl (**9**) forms extremely small crystals and under reaction conditions gives colloid system with large surface area, while TCPcAlCl (**2**) forms large crystals. The best results

Table 1. Yields of amino phosphonate **16** depending on the phthalocyanine catalysts used[a]

Catalyst	Yield of compound **16** (%)
^{t}PcAlCl	36
PcAlCl (**9**)	31
TCPcAlCl (**2**)	15
TCPcAlCl/CPG-550 (**8**)[b]	43
TCPcAlCl/CPG-550 (**6**)[c]	43

[a] Reaction conditions: 1-indanone (0.5 mmol), benzylamine (0.55 mmol), $(EtO)_2P(O)H$ (0.62 mmol), catalyst (0.125 mol.%), CH_2Cl_2 (1 mL), 30 °C, 24 h.

[b] With free carboxy groups (R = OH).

[c] With NPr^i_2 groups on periphery.

Table 2. Yields of amino phosphonate **16** depending on the amount of the phthalocyanine catalyst

Catalyst	Amount of phthalocyanine/mol.%	Yield of compound **16** (%)
^{t}PcAlCl	0.625	95
6	0.375	70
6	0.625	85
7	0.375	50
7	0.625	60
13	0.625	65
14	0.375	65
15	0.375	80

were obtained for the immobilized heterogeneous catalysts **6** and **8** since the solid support provided maximum surface area.

After the efficiency of the immobilized heterogeneous catalysis in the synthesis of aminophosphonates was shown, we carried out comparative study of catalytic activity of novel catalysts **6**, **7**, and **13—15** (0.375 and 0.625 mol.%, based on phthalocyaninealuminum chloride) in the synthesis of aminophosphonate **16** (Table 2). Catalysts **6** and **15** exhibited the highest catalytic activity. The obtained results indicate that the catalytic activity is almost independent on the linker structure and the solid support nature.

Important parameter for any catalyst is its stability under reaction conditions, which is characterized by a number of catalytic cycles. We tested most efficient catalysts **6b** and **15** in 3 catalytic cycles (Table 3). After the first cycle, a small loss in the activity was indicated and, on the next cycles, this level of the activity remained constant.

In summary, in the present work, phthalocyanines covalently bonded onto silica support were prepared; they turned to be effective catalysts in hydrophosphorylation of the imine bond and their activity is virtually the same as for homogeneous catalyst ^{t}PcAlCl. The catalytic activity of the supported catalysts is almost independent on the support nature and the immobilization type. Catalysts retained their high catalytic activity in three catalytic cycles.

Table 3. Yields of amino phosphonate **16** in three catalytic cycles of phthalocyanine catalysts

Catalyst	Cycle	Yield of compound **16** (%)
^{t}PcAlCl	1	95
6	1	85
6	2	75
6	3	75
15	1	80
15	2	75
15	3	75

Experimental

NMR spectra were run on a Bruker Avance 400 instrument (400.13 (^{1}H), 100.61 (^{13}C), and 161.98 MHz (^{31}P)) in $CDCl_3$ relative to Me_4Si (^{1}H, ^{13}C, internal standard) and 85% aqueous H_3PO_4 (^{31}P, external standard). MALDI-TOF mass-spectra were recorded on an Autoflex II mass spectrometer (Bruker Daltonics) with dihydroxybenzoic acid as a matrix. The course of the reactions and the purity of compounds were monitored by TLC.

Modification of supports MCM-41 (mesostructured silica, hexagonal, Aldrich) and CPG-550 (controlled pore glass, 550 Å, Fluka) was carried out according to the known procedure.[14]

AP-CPG-550 (1a). To a suspension of freshly activated CPG-550 (3 g) in boiling toluene, (3-aminopropyl)triethoxysilane (APTES, 2 g, 2.4 mL) were added and the mixture was stirred for 10 h. After removal of the volatiles *in vacuo*, the heating and removal of the solvent were repeated three times. Modified AP-CPG-550 was filtered off, washed with CH_2Cl_2 (5×10 mL), and dried *in vacuo* at 90 °C. Yield was 3.8 g (76%), white powder.

AP-MCM-41 (1b) was synthesized according to the procedure described for **1a** using mesoporous molecular sieves MCM-41. Yield was 4.1 g (81%) of white friable product.

Trimellitic acid amide-imide (3). A mixture of trimellitic acid (**4**) (10 g, 0.05 mol) and urea (9 g, 0.15 mol) was heated at 250 °C for 2 h. Hot mixture was poured into glass beaker and cooled to ambient temperature. The resulting solid was ground and triturated with water (2×100 mL). The product was dried on air, the yield of compound **3** was 7.2 g (80%), white powder, m.p. 138—140 °C.

Physicochemical and spectral data of amide **3** are in good agreement with that given in literature.[15]

(Tetracarboxyphthalocyanine)aluminum chloride (2). A mixture of trimellitic acid amide-imide (**3**) (2 g, 10.53 mmol), aluminum chloride (350 mg, 2.63 mmol), urea (6 g, 100 mmol), and catalytic amount of ammonium molybdate was heated at 270 °C for 2 h. The resulting solid was ground and dissolved in water (200 mL). The insoluble residue was filtered off and treated with a solution of NaCl (36 g) in 2 *M* NaOH (90 mL) with stirring at 90 °C for 5 h. Then the hydrolysis was completed, the resulting dark-blue solution was acidified with 2 *M* HCl to pH 4. The residue that formed was filtered off and re-precipitated twice with 2 *M* HCl from a solution in 2 *M* NaOH. The product was dried *in vacuo* at 90 °C, the yield of phthalocyanine **2** was 600 mg (30%), crystalline dark-blue compound. MS, *m/z*: 715 $[M]^+$.

Physicochemical and spectral data of phthalocyanine **2** are consistent with that given in literature.[15]

CPG-550-CO-PcAlCl-(CONPr$^i_2$) (6). A mixture of TCPcAlCl (**2**) (170 mg, 0.22 mmol), thionyl chloride (3 mL), benzene (9 mL), and few drops of pyridine was refluxed for 10 h. The precipitate that formed was filtered off, washed with benzene and dried *in vacuo* at 90 °C. The resulting chloroanhydride **5** was dissolved in DMF (10 mL) and AP-CPG-550 (**1a**) (1 g) was suspended in the obtained solution. The suspension was stirred at 50—60 °C for 24 h, then diisopropylamine (0.2 mL) was added and stirring was continued for 30 min, afterwards acetic anhydride (3 mL) was added, and the reaction mixture was stirred for another 30 min. The product was filtered off, washed thoroughly with DMF and CH_2Cl_2, and dried *in vacuo* at 90 °C.

MCM-41-CO-PcAlCl-(CONPr$^i_2$) (7) was prepared as described for **6** using AP-MCM-41 (**1b**) as a matrix.

CPG-550-CO-PcAlCl-(COOH) (8) was prepared analogously to catalyst **6** with the exception that addition of diisopropylamine was omitted.

(Disulfophthalocyanine)aluminum chloride (10). A mixture of phthalocyaninealuminum chloride (**9**) (0.5 g, 0.87 mmol) and oleum (70% H_2SO_4, 30% SO_3, 5 mL) was stirred at room temperature for 16 h. The reaction mixture was cooled to ambient temperature and poured onto ice. The precipitate that formed was filtered off, washed with 1% aqueous HCl, water, and dried *in vacuo* at 90 °C. Compound **10** was obtained in the yield of 0.58 g (91%) as dark-blue crystals. MS, *m/z*: 699 $[M]^+$. Physicochemical and spectral parameters of phthalocyanine **10** are consistent with that given in literature.[14]

CPG-550-SO$_2$-PcAlCl (13). A mixture of complex **10** (250 mg, 0.34 mmol), thionyl chloride (2 mL), benzene (5 mL), and few drops of pyridine was refluxed for 10 h. The precipitate that formed was filtered off, washed with benzene and dried *in vacuo* at 90 °C. The resulting sulfonyl chloride **11** (250 mg, 0.32 mmol) was dissolved in DMF (15 mL) and a mixture of APTES (0.075 mL, 72 mg, 0.64 mmol) and catalytic amount of pyridine was added dropwise at 80 °C with stirring. After 12 h of stirring, CPG-550 (1 g) was added and stirring was continued for 24 h at 110 °C. The product was filtered off, washed thoroughly with DMF, CH_2Cl_2, and dried *in vacuo* at 90 °C. Catalysts **13** was obtained in the yield of 1.05 g.

MCM-41-SO$_2$-PcAlCl (14, 15) was obtained as described for **13** using MCM-41 as a support.

Diethyl (1-benzylamino-2,3-dihydro-1*H*-inden-1-yl)phosphonate (16). Benzylamine (0.06 mL, 0.55 mmol), diethyl phosphite (0.08 mL, 0.62 mmol), molecular sieves 4 Å (dried prior to use), and the corresponding catalyst were added to a solution of 1-indanone (66 mg, 0.5 mmol) in CH_2Cl_2 (1 mL). The reaction mixture was stirred in the sealed vessel at 30 °C for 24 h. Molecular sieves and the catalyst were filtered off and washed with $CHCl_3$—MeOH, 5 : 1 (3×2 mL). The solvent was removed *in vacuo*, the residue was dissolved in small amount of $CHCl_3$—MeOH, 50 : 1, and purified by column chromatography on silica gel (column length 100 mm, column diameter 15 mm, elution with $CHCl_3$—MeOH (from 80 : 1 to 20 : 1)). R_f 0.24 (CH_2Cl_2—EtOH, 35 : 1). NMR ^{31}P, δ: 27.82 (see Ref.[4]).

Yields of compound **16** (orange oil) are given in Tables 1—3.

Recycling of the catalysts. A mixture of molecular sieves and heterogeneous catalyst obtained in the reaction work-up (see above) was mechanically separated on a filter (porosity 1 mm). The catalyst was stirred in chloroform for 10 min, filtered off, the washings was repeated one more time with chloroform and twice with MeOH. Recovered catalysts was dried *in vacuo* at 70 °C.

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