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Salmeia, K. A., Baumgartner, G., Jovic, M., Gössi, A., Riedl, W., Zich, T., & Gaan, S. (2018). Industrial upscaling of DOPO-based phosphoramidates and phosphonates derivatives using Cl₂ gas as a chlorinating agent. *Organic Process Research and Development*. <https://doi.org/10.1021/acs.oprd.8b00295>

Industrial Upscaling of DOPO-based Phosphoramidates and Phosphonates Derivatives Using Cl₂ Gas as a Chlorinating Agent

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ABSTRACT: Herein, we report the industrial synthesis procedure of phosphoramidate and phosphonate derivatives via an efficient and simple chlorination of 9,10-dihydro-9-oxa-10-phosphaphenanthren-10-oxide (DOPO) with Cl₂ gas. The key step in synthesis is the conversion of P-H bond to P-Cl of DOPO by flowing Cl₂ gas into a solution of DOPO in dichloromethane, affording the key intermediate 9,10-dihydro-9-oxa-10-phosphaphenanthrene-10-chloride (DOPO-Cl) compound which is industrially not available. DOPO-Cl was isolated, characterized

and used for synthesis of DOPO-based phosphoramidates and phosphonates in relatively high yield by reaction with the corresponding amines and alcohols, respectively. The experimental results show that the chlorination reaction occurs in equimolar ratios of Cl_2 gas to DOPO compound. Subsequently, the procedure developed in laboratory scale was industrially applied for synthesis of 6,6'-(ethane-1,2-diylbis(azanediyl))bis(dibenzo[*c,e*][1,2]oxaphosphinine-6-oxide) (EDA-DOPO) compound and 6-((1-oxido-2,6,7-trioxa-1-phosphabicyclo[2.2.2]octan-4-yl)methoxy)dibenzo[*c,e*][1,2]oxaphosphinine-6-oxide (DOPO-PEPA). All synthetic compounds thus obtained were characterized and found identical to the authentic laboratory scale products.

Keywords: Cl_2 Gas, DOPO-Cl, Chlorination Reaction, Industrial Upscaling, Phosphoramidates, Phosphonates.

INTRODUCTION

In the last decades, organophosphorus compounds have been exploited due their characteristic properties and their wide range of applications.¹ Among their many applications, organophosphorus compounds have been increasingly investigated as flame retardant additives.² The invention of 9,10-dihydro-9-oxa-10-phosphaphenanthren-10-oxide (DOPO) in 1972³ as a new class of organophosphorus compound paved the way to synthesize and develop new types of flame retardant additives.⁴ DOPO-derivatives have been found to be versatile in flame retardant applications in different polymers and some derivatives have been found to be non-toxic and suitable for industrial exploitation.⁵ A great variety of P-C and P-heteroatoms containing DOPO-derivatives and their synthesis strategies have been developed over the last decades without much attention paid to their possible industrial upscaling.^{2b, 4, 6} Synthesis of two types of P-heteroatom bonds have been primarily investigated for DOPO-derivatives, namely P-O or P-N

bonds to prepare various phosphonates⁷ or phosphonamidates,⁸ respectively. Consequently, the P-H bond activation of DOPO is a crucial step to achieve P-N or P-O bond transformation and many academic publications and industrial patents are reported in the literature.^{4, 9} Therefore, the key step to synthesize the P-heteroatoms of DOPO derivatives is the transformation of P-H bond into P-Cl bond, affording 10-Chloro-9,10-dihydro-9-oxa-10-phosphaphenanthrene-10-oxide (DOPO-Cl) as depicted in **scheme 1**. The latter was synthesized via a direct Friedel-Crafts reaction of 2-phenylphenol with POCl₃ and AlCl₃ as a catalyst.¹⁰ The oxidation of 6-chloro-6*H*-dibenz[*c,e*][1,2]oxaphosphorine (DOP-Cl) using dry O₂ or in the presence of water and ozone affords DOPO-Cl which are also considered direct and easy approaches.¹¹ On the other hand, DOP-Cl₃ was investigated by the reaction of DOP-Cl with Cl₂ gas which after its hydrolysis yields DOPO-Cl.¹² The main drawback of using DOP-Cl as a raw material is that it is a very reactive substance and special handling is required during its further transformation.¹³ Another approach to synthesize DOPO-Cl involved the use of thionyl chloride (SOCl₂) as chlorinating agent and 10-Hydroxy-9,10-dihydro-9-oxa-10-phosphaphenanthrene-10-oxide (DOPO-OH) as the starting material.¹⁴



current full scale industrial exploitation is restricted as CCl_4 is toxic and is an ozone depleting substance.¹⁵ Recently, we have developed novel DOPO-based additives with high flame retardant efficacy, namely EDA-DOPO and ETA-DOPO for flexible polyurethane foams and DOPO-PEPA for polyesters (**Figure 1**).^{5b, 8a, 16}

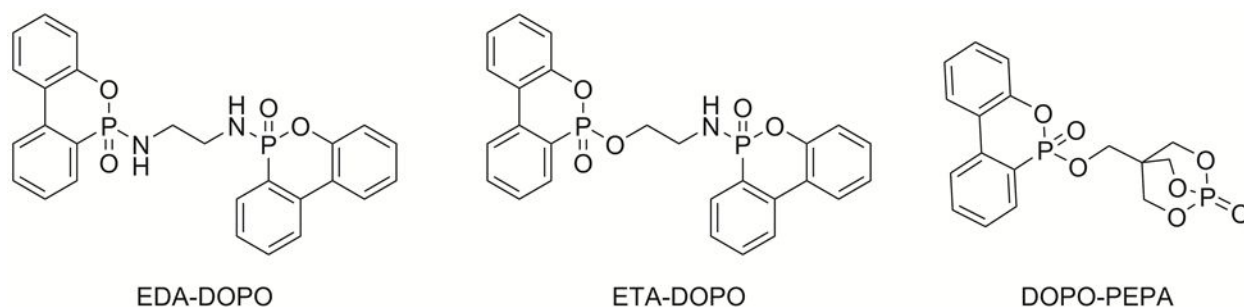


Figure 1: Chemical structure of DOPO derivatives

To further ensure their commercial exploitation for a large scale production and extensive use of these additives, preliminary toxicological assessment was conducted.⁵ Both EDA-DOPO and DOPO-PEPA flame retardant additives showed no toxicity in various in vitro toxicity assays which makes them appropriate for commercial exploitation. In addition, EDA-DOPO has been REACH registered (registration number 01-2120764996-32-0000) in April 2018. EDA-DOPO and DOPO-PEPA were produced following the Atherton-Todd reaction using CCl_4 as chlorinating agent.^{16a, 16c} Notwithstanding, CCl_4 is a carcinogen and also both ozone-depleting and greenhouse gas which prohibits its industrial usage.¹⁷ Its usage in Switzerland is banned and restricted in Europe. Accordingly, alternative synthetic methodologies were investigated to replace CCl_4 with more benign chlorinating agents, namely trichloroisocyanuric acid (TCCA)¹⁸ and *N*-chlorosuccinimide (NCS).^{8b} Nonetheless, different synthetic challenges were encountered which limit their use industrially. For example, the chlorination reaction using TCCA was found to be very exothermic which makes it difficult to scale up in industry. On the other hand, NCS

showed high efficacy for one pot synthesis of P-N bond containing derivatives at moderate temperature. On the contrary, the reaction yield of one pot synthesis of P-O bond containing derivatives in comparison to P-N bond containing derivatives was relatively low.^{5b} SO₂Cl₂ has also been investigated to transform the P-H bond into a P-Cl bond. This procedure involves, refluxing the SO₂Cl₂ with DOPO in CH₂Cl₂ which releases useful product such as Cl₂ and a byproduct SO₂.¹⁸ In-situ evolution of Cl₂ gas from thermal decomposition of SO₂Cl₂ is considered to be the key agent for chlorination of P-H bond.

To simplify the reaction procedure, avoid byproducts and reduce the overall costs we herein report the use of Cl₂ gas as a chemical feedstock for chlorination of P-H bond and thereafter the applicability of its utilization for the industrial production of phosphonamidate and phosphonate derivatives of DOPO. The fact that Cl₂ gas is industrially produced and commonly used in industry to prepare useful intermediates and final products, makes it very interesting for chlorination reaction of P-H bonds.

In this work we have investigated laboratory and industrial scale chlorination of DOPO using Cl₂ to produce useful flame retardants such as EDA-DOPO and DOPO-PEPA. The properties of EDA-DOPO and DOPO-PEPA thus synthesized were compared to those industrially produced via the Atherton-Todd reaction.

Experimental Section

Materials and Methods:

9,10-dihydro-9-oxa-10-phosphaphenanthrene-10-oxide (DOPO) was provided by Metadynea Austria GmbH (Krems, Austria) and used as received. 1-oxo-4-hydroxymethyl-2,6,7-trioxa-1-

phosphabicyclo[2.2.2]octane (PEPA) was purchased from Carbosynth Limited (Compton, United Kingdom) and dried at 80 °C prior to use. Ethanolamine (ETA), triethylamine (TEA), ethylenediamine (EDA), propylamine (PA) and all other chemicals and solvents were purchased from Sigma-Aldrich (Buchs, Switzerland) and used as received. For the lab-scale synthesis, the Cl₂ gas was produced by the redox reaction of HCl and KMnO₄. For industrial upscaling a Cl₂ gas bottle (purity ≥99.8% was purchased from Sigma-Aldrich (Vienna, Austria). Differential scanning calorimetry (DSC) analyses were performed on DSC 214 Polyma instrument (NETZSCH-Gerätebau GmbH, Germany). All DSC experiments were conducted at a controlled heating rate of 10 °C/min under nitrogen flow of 50 mL/min. Gas chromatograms were obtained on Hewlett Packard 5973 GC/MS (Quad Service, Achères, France), using He carrier gas and HP-5ms GC column (30 m x 0.25 mm x 0.25 μm). Phosphorus-contents of DOPO-derivatives were determined using OPTIMA 3000 ICP-OES (Perkin Elmer AG, Switzerland). ¹H, ³¹P{¹H} and ¹³C{¹H} NMR spectra were collected at ambient temperature using Bruker AV-III 400 spectrometer (Bruker Biospin AG, Fällanden, Switzerland). ¹H and ¹³C{¹H} chemical shifts (δ) in ppm are referenced against the residual solvent peaks. The ³¹P{¹H} chemical shifts were referenced to an external sample with neat H₃PO₄ at 0.0 ppm. EDA-DOPO and DOPO-PEPA were synthesized for comparison using CCl₄ as previously reported.^{16a, 16c, 19} In addition, ETA-DOPO (derivative of ethanolamine) was synthesized in lab-scale using Cl₂ route to prove the versatility of procedure for raw materials with mixed functional groups.

Synthesis

1) Using Cl₂ as chlorinating agent

Synthesis of DOPO-Cl:

A three-neck round-bottom flask connected to a saturated NaOH solution (500 mL) and high pressure relief valve was charged with DOPO (50 g, 231 mmol) and anhydrous CH₂Cl₂ (40 mL) under N₂ atmosphere. Cl₂ gas was then introduced to the reaction vessel at a flow rate (20 L/h) so that the reaction temperature does not exceed 20 °C. After 30 min, Cl₂ flow was stopped and the volatiles were completely removed under N₂ flow affording a white solid in quantitative yield. The product was analyzed and used without further purification. ¹H NMR (400.2 MHz, CDCl₃) δ 8.05 (ddd, *J* = 16.5, 7.6, 1.0 Hz, 1H), 8.00-7.94 (m, 2H), 7.78 (tt, *J* = 7.8, 1.3 Hz, 1H), 7.57 (ddt, *J* = 7.5, 4.4, 0.8 Hz, 1H), 7.45 (tt, *J* = 7.8, 1.5 Hz, 1H), 7.35 (m, 1H), 7.29-7.27 (m, 1H). ³¹P{¹H} NMR (162.0 MHz, CDCl₃) δ 20.0.

*Synthesis of 6,6'-(ethane-1,2-diylbis(azanediyl))bis(dibenzo[*c,e*][1,2]oxaphosphinine-6-oxide) (EDA-DOPO):*

DOPO-Cl (100 g, 399 mmol) was synthesized as described above and re-dissolved in anhydrous CH₂Cl₂ (75 mL) under N₂ atmosphere. EDA (12 g, 199.7 mmol) and TEA (44.4 g, 439 mmol) in CH₂Cl₂ (150 mL) were then added dropwise at a rate that the reaction temperature does not exceed 20 °C. After complete addition, the reaction mixture was stirred for 1 h and filtered. The solid was then washed with CH₂Cl₂, ethanol and then with water. The white product was then collected and dried in vacuum at 60 °C and 60 mbar. Yield: 88 g (90%). ¹H NMR (400.2 MHz, DMSO-*d*₆) δ 8.14 (m, 2H); 8.10 (m, 2H); 7.77 (m, 2H); 7.70 (m, 2H); 7.50 (m, 2H); 7.39 (m, 2H); 7.27 (m, 2H); 7.15 (m, 2H); 5.75 (m, 2H, NH); 2.85 (m, 4H). ¹³C{¹H} NMR (100.6 MHz, DMSO-*d*₆) δ 149.4 (d, *J*_{C-P} = 7.2 Hz); 135.9 (d, *J*_{C-P} = 6.7 Hz); 132.7; 130.4; 129.4 (d, *J*_{C-P} = 9.6 Hz); 128.3 (d, *J*_{C-P} = 14.3 Hz); 125.4 (d, *J*_{C-P} = 0.6 Hz); 125.2 (d, *J*_{C-P} = 161.9 Hz); 124.2; 124.1 (d, *J*_{C-P} = 10.7 Hz); 121.9 (d, *J*_{C-P} = 11.5 Hz); 120.0 (d, *J*_{C-P} = 5.9 Hz); 41.7 (d, *J*_{C-P} = 5.6 Hz).

$^{31}\text{P}\{^1\text{H}\}$ NMR (162.0 MHz, DMSO- d_6) δ 14.7, 14.6. Phosphorus analysis for $\text{C}_{26}\text{H}_{22}\text{N}_2\text{O}_4\text{P}_2$: calculated 12.68%; found 12.50%.

Industrial scale synthesis of EDA-DOPO

A reactor (1000 L) connected to a trap with NaOH solution (100 Kg/1000 Kg H_2O) and high pressure relief valve was charged with DOPO (73 Kg, 337.7 mol) and anhydrous CH_2Cl_2 (522 L) under N_2 atmosphere. Cl_2 gas (24 Kg, 338.5 mol) was then introduced to the reactor for 7.6 h at a rate that the reaction mixture temperature does not exceed 20 $^\circ\text{C}$. After complete feeding, the reaction was stirred for 5 h and the volatiles were then completely removed under N_2 flow, affording DOPO-Cl. DOPO-Cl was then re-dissolved in anhydrous CH_2Cl_2 (135 L). EDA (10.1 Kg, 168 mol) and TEA (51.3 Kg, 507 mol) in anhydrous CH_2Cl_2 (135 L) were then added dropwise. After complete addition, the reaction mixture was stirred at ambient temperature for 3 h. The white precipitate was collected by filtration and washed with methanol (1270 L) and water (2 x 300 L). The white product was then collected and dried in vacuum at 60 $^\circ\text{C}$ and 60 mbar. Yield: 74 Kg (90%).

Synthesis of 6-((1-oxido-2,6,7-trioxa-1-phosphabicyclo[2.2.2]octan-4-yl)methoxy)dibenzo[*c,e*][1,2]oxaphosphinine-6-oxide (DOPO-PEPA):

A three-neck round-bottom flask connected to a dropping funnel and bubbler was charged with PEPA (5.24 g, 29.1 mmol) followed by addition of anhydrous CH_2Cl_2 (15 mL) and TEA (3.24 g, 32 mmol). DOPO-Cl (7.3 g, 29.1 mmol) synthesized as described earlier was re-dissolved in anhydrous CH_2Cl_2 (20 mL) and transferred under N_2 atmosphere to the dropping funnel and

added dropwise at 0 °C. After complete addition the reaction mixture was stirred at ambient temperature overnight. The volatiles were then completely removed and the residue was washed with water. The product was then collected by filtration and dried by vacuum drying oven at 60 °C. Yield: 6.84 g (60%). ¹H NMR (400.2 MHz, DMSO-d₆) δ 8.27 (m, 1H); 8.22 (dd, *J* = 1.3, 8.0 Hz, 1H); 7.92 (m, 2H); 7.66 (m, 1H); 7.53 (m, 1H); 7.38 (m, 2H); 4.50 (d, *J*_{H-P} = 6.5 Hz, 6 H); 4.05 (m, 2H). ¹³C{¹H} NMR (100.6 MHz, DMSO-d₆) δ 148.9 (d, *J*_{C-P} = 7.9 Hz); 136.4 (d, *J*_{C-P} = 7.1 Hz); 134.4 (d, *J*_{C-P} = 2.3 Hz); 131.1; 130.1 (d, *J*_{C-P} = 9.5 Hz); 128.9 (d, *J*_{C-P} = 15.4 Hz); 126.0; 125.4; 124.9 (d, *J*_{C-P} = 11.9 Hz); 121.9 (d, *J*_{C-P} = 11.9 Hz); 120.7 (d, *J*_{C-P} = 179.5 Hz); 120.0 (d, *J*_{C-P} = 6.5 Hz); 75.0 (d, *J*_{C-P} = 5.9 Hz); 61.9 (dd, *J*_{C-P} = 5.7, 2.4 Hz); 37.5 (dd, *J*_{C-P} = 37.3, 6.7 Hz). ³¹P{¹H} NMR (162.0 MHz, DMSO-d₆) δ 10.4; -7.8. Phosphorus analysis for C₁₇H₁₆N₂O₇P₂: calculated 15.71%; found 15.63%.

Industrial scale synthesis of DOPO-PEPA

A reactor (1000 L) connected to a trap with NaOH solution (100 Kg/1000 Kg H₂O) and high pressure relief valve was charged with DOPO (77 Kg, 356.2 mol) and anhydrous CH₂Cl₂ (376 L) under N₂ atmosphere. Cl₂ gas (24 Kg, 338.5 mol) was then introduced to the reactor for 2 h at a rate that the reaction mixture temperature does not exceed 30 °C. After complete feeding, the reaction was stirred for 5 h and the volatiles were then completely removed under N₂ flow, affording DOPO-Cl. DOPO-Cl was then re-dissolved in anhydrous CH₂Cl₂ (188 L) and TEA (34 Kg, 336 mol) was dropwise added and PEPA (58 Kg, 322 mol) in CH₂Cl₂ (150 L) was pumped under N₂ at a rate that the temperature does not exceed 30 °C. After complete addition, the reaction mixture was stirred at ambient temperature for 8 h. The reactor was then cooled to about 20 °C and the reaction mixture was washed three times with a solution of Na₂CO₃ (40 Kg/ 400 L H₂O). The volatiles were then removed at 42 °C and the obtained solid was heated at 70 °C for 6

h. The solid was then washed with water (3 x 400 L). The off-white product was then collected and dried in vacuum at 60 °C and 60 mbar. Yield: 97 Kg (76%).

Synthesis of 6-(2-((6-oxidodibenzo[*c,e*][1,2]oxaphosphinin-6-yl)amino)ethoxy)dibenzo[*c,e*][1,2]oxaphosphinine-6-oxide (*ETA-DOPO*)

DOPO-Cl (50 g, 200 mmol) synthesized as described earlier was re-dissolved in anhydrous CH₂Cl₂ (190 mL) under N₂ atmosphere. ETA (6 g, 98 mmol) and TEA (22.3g, 220 mmol) in CH₂Cl₂ (150 mL) were then dropwise added at a rate that the temperature does not exceed 20 °C. After complete addition, the reaction mixture was stirred at ambient temperature overnight. The volatiles were then removed completely and the residue was dissolved in chloroform (150 mL) and washed three times with water (200 mL). The organic was then isolated and dried over anhydrous Na₂SO₄. After filtration the volatiles were then removed and the white solid was then dried in vacuum drying oven at 60 °C. Yield: 34 g (71%). ¹H NMR (400.2 MHz, DMSO-*d*₆) δ 8.24 (m, 1H); 8.18 (m, 1H); 8.14 (m, 1H); 8.12 (m, 1H); 7.89 (m, 1H); 7.83 (m, 1H); 7.71 (m, 1H); 7.65 (m, 1H); 7.61 (m, 1H); 7.45 (m, 1H); 7.44 (m, 1H); 7.40 (m, 1H); 7.32 (m, 1H); 7.28 (m, 1H); 7.27 (m, 1H); 7.12 (m, 1H); 5.83 (m, 1H, NH); 4.02 (m, 2H); 3.00 (m, 2H). ¹³C{¹H} NMR (100.6 MHz, DMSO-*d*₆) δ 149.3 (d, *J*_{C-P} = 7.1 Hz); 149.2 (d, *J*_{C-P} = 7.9 Hz); 136.2 (d, *J*_{C-P} = 7.1 Hz); 135.9 (d, *J*_{C-P} = 7.0 Hz); 134.0 (d, *J*_{C-P} = 2.4 Hz); 132.7; 130.9; 130.4; 129.9 (d, *J*_{C-P} = 9.3 Hz); 129.4 (d, *J*_{C-P} = 9.7 Hz); 128.7 (d, *J*_{C-P} = 15.1 Hz); 128.3 (d, *J*_{C-P} = 14.3 Hz); 125.9; 125.4 (d, *J*_{C-P} = 0.6 Hz); 125.3 (d, *J*_{C-P} = 162.9 Hz); 125.1; 124.6 (d, *J*_{C-P} = 11.7 Hz); 124.3; 124.1 (d, *J*_{C-P} = 10.7 Hz); 122.0 (d, *J*_{C-P} = 11.8 Hz); 121.9 (d, *J*_{C-P} = 11.6 Hz); 121.5 (d, *J*_{C-P} = 178.9 Hz); 120.1 (d, *J*_{C-P} = 5.9 Hz); 119.9 (d, *J*_{C-P} = 6.5 Hz); 66.1 ; 40.4 (d, *J*_{C-P} = 7.3 Hz). ³¹P{¹H} NMR (162.0 MHz, DMSO-*d*₆) δ 14.60; 9.79 (set of diastereomers).14.58; 9.83 (set of diastereomers). Phosphorus analysis for C₂₆H₂₁NO₃P₂: calculated 12.66%; found 12.61%.

2) Synthesis using CCl_4 as chlorination agent:

Industrial scale synthesis of EDA-DOPO:

A reactor (1000 L) was flushed with N_2 and charged with DOPO (129 Kg, 596.7 mol), EDA (18 Kg, 299.5 mol), TEA (66 Kg, 652.2 mol) and CHCl_3 (434 L). CCl_4 (101 Kg, 656.6 mol) was pumped under N_2 at a rate that the reaction mixture temperature does not exceed 18 °C. The reaction mixture was then allowed to stir at ambient temperature for 11 h. The white product was filtered off and washed with methanol (3 x 100 L) and dried in oven at 90 °C for 24 h. Yield: 131 Kg (90%).

Industrial Scale Synthesis of DOPO-PEPA

A glass-lined reactor (100 L) was flushed with N_2 and charged with DOPO (11.1 kg 51.3 mol), CH_2Cl_2 (35.0 L), and PEPA (9.4 Kg, 52.2 mol). NMI (4.3 Kg, 52.4 mol) was then slowly pumped to the reaction mixture which was then cooled to 15 °C. CCl_4 (8.6 Kg, 55.9 mol) in CH_2Cl_2 (10 L) was then dropwise added under N_2 atmosphere at a rate that the reaction mixture temperature does not exceed 20 °C. The reaction mixture was then allowed to warm up to ambient temperature and the reaction was refluxed at 45 °C. After 4 h, the reaction mixture was then cooled to 15 °C and obtained solid was collected by filtration. The solid was then washed with water (150 L) and ethanol (40 L) and dried at 95 °C and 60 mbar, affording the first crop of the product. The volatiles of the filtrate were then distilled off, affording viscous residue. Water (50 L) was added and the mixture was stirred overnight. The white precipitate was collected by filtration, washed with water (2 x 100 L) and then with ethanol (2 x 100 L) and dried in vacuum

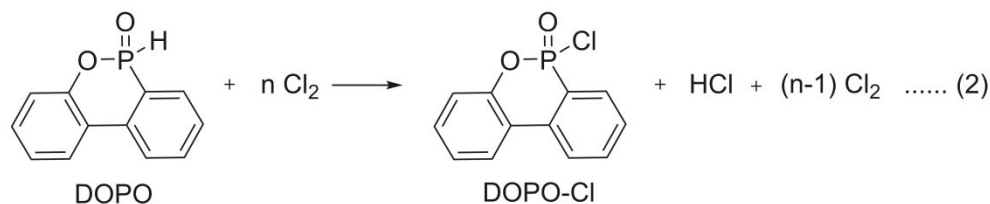
at 95 °C and 60 mbar, affording the second crop of the product. The two crops were then collected, affording 15.3 Kg (76% total yield).

Synthesis of ETA-DOPO:

A three-neck round-bottom flask (1L) connected to an additional funnel, condenser and bubbler, was charged DOPO (150 g, 694 mmol), ETA (21.2 g, 347 mmol), TEA (77.2 g, 763 mmol) and CHCl_3 (400 mL). The reaction vessel was immersed in an ice bath, and CCl_4 (117.4 g, 763 mmol) was dropwise added under N_2 at a rate that the reaction temperature does not exceed 10 °C. After the complete addition, the white suspension reaction was allowed to warm up to ambient temperature with stirring overnight. After the complete reaction, the organic volatiles were then removed by rotary evaporator. The white product was then collected on filter paper, washed with ethanol and water successively. The white product was then collected and extra dried in vacuum drying oven at 60 °C. Yield: 136 g (80%)

Results and Discussions

The preliminary assessment of chlorination procedure for P-H bond of DOPO was investigated using Cl_2 produced by the redox reaction of HCl with KMnO_4 in milligram lab-scale in two-step reaction shown below (**Scheme 2**).



Scheme 2: The chlorination reaction of DOPO compound using Cl_2 gas, produced from redox reaction of HCl with KMnO_4 .

In this reaction, the molar ratio of Cl_2 gas to DOPO compound can be controlled by changing the molar ratio of HCl to KMnO_4 using Kipp's apparatus (**Scheme 2, (1)**). The amount of Cl_2 required to achieve a full conversion of DOPO into DOPO-Cl (**Scheme 2, (2)**) was monitored by GC-MS by in-situ reaction of produced DOPO-Cl with ethanol, affording 6-ethoxydibenzo[*c,e*][1,2]oxaphosphinine-6-oxide (DOPO-OEt) (**Figure 2**). It is noteworthy to mention here that the reaction solvent needs to meet three key criteria, (1) suitable to solubilize the reactants, (2) inert to chlorination reaction and (3) can be easily recovered. Accordingly, dichloromethane was chosen as a reaction solvent.

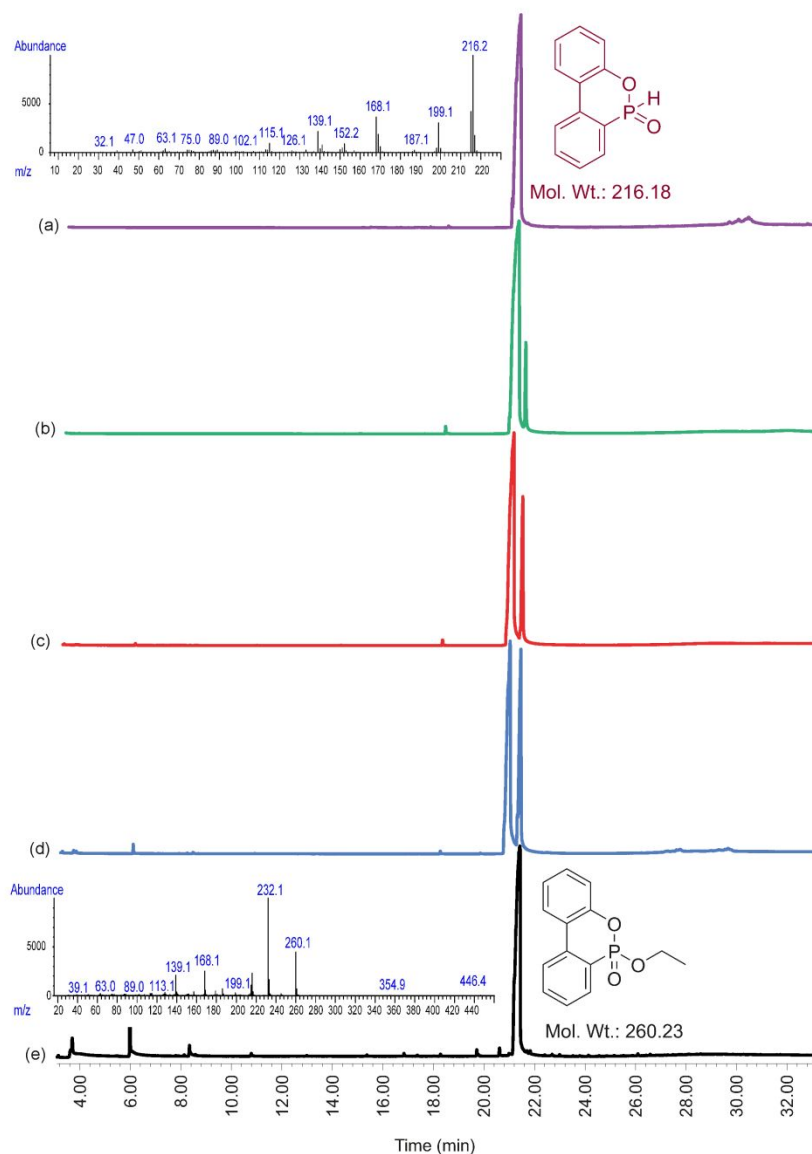


Figure 2: GC-MS chromatogram of chlorination reaction of DOPO with Cl_2 in different Cl_2 ratios to DOPO, followed by addition of ethanol to afford DOPO-OEt. (a) DOPO, (b) Cl_2 : DOPO (1.0:2.5), (c) Cl_2 : DOPO (1.0:1.2), (d) Cl_2 : DOPO (1.2:1.0), (e) Cl_2 : DOPO (1.5:1.0).

It can be presumed from these experiments that an equivalent ratio of Cl_2 to DOPO is enough to achieve the full conversion to DOPO-Cl. In the lab-scale synthesis trials a slow nitrogen flow was used as a carrier gas to introduce the Cl_2 gas into the reaction mixture to control the

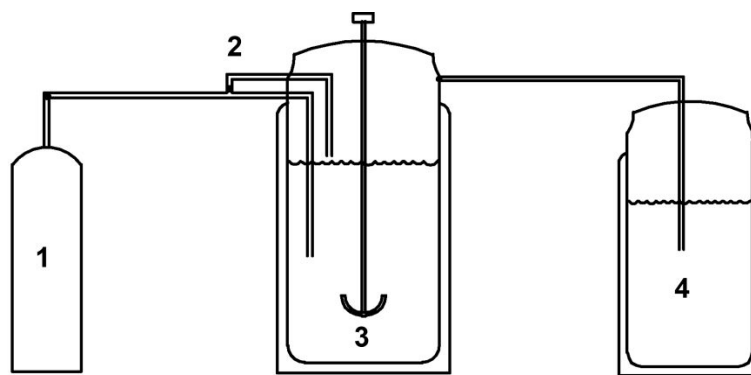
chlorination reaction and avoid wastage of Cl_2 gas. To ensure full conversion of DOPO to DOPO-Cl excess amount of Cl_2 was used in the chlorination reaction. To further optimize the chlorination reaction, the reaction of DOPO-Cl with PA, affording 6-(propylamino)dibenzo[*c,e*][1,2]oxaphosphinine-6-oxide (DOPO-PA) was conducted as a model compound and reaction parameters were controlled accordingly (**Table 1**).

Table 1: Optimization of the lab-scale chlorination reaction using DOPO-PA as a model compound ^(a)

Entry	KMnO ₄ (mol)	HCl (mol)	Calc. Cl ₂ (mol)	DOPO (mol)	PA (mol)	Yield (%)
1	0.013	0.101	0.032	0.001	0.0011	72
2	0.001	0.01	0.003	0.001	0.0011	74

^(a) DOPO and CH_2Cl_2 were charged in three-neck round-bottom flask connected to saturated NaOH solution from one side and Kipp's apparatus from the other side. Cl_2 gas was then produced in situ by dropwise addition of HCl(aq) to KMnO_4 and the evolved Cl_2 gas was carried via N_2 stream, dried in H_2SO_4 trap (to avoid the moisture) and bubbled through DOPO solution. After the complete Cl_2 evolution (pale yellow), the reaction mixture was kept under N_2 flow for additional 30 minutes. PA and an equivalent of TEA in CH_2Cl_2 (2 mL) were transferred under N_2 to a dropping funnel and added dropwise to DOPO-Cl solution. After complete addition, the solution was stirred overnight. The volatiles were then completely removed and the residue was stirred in water. The white product was collected by filtration and dried in vacuum at 60 °C overnight. The product was analyzed using NMR spectrometer (**Figures S3** and **S4**) and GC-MS (**Figure S5**).

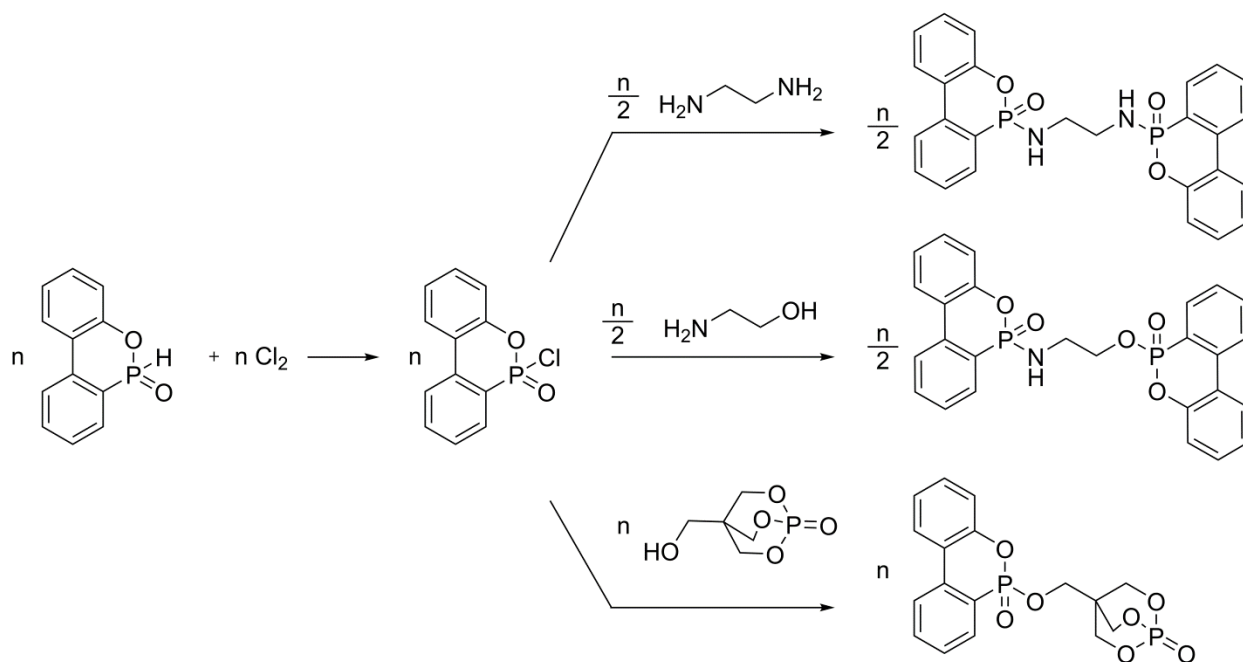
All the target compounds in this study were then synthesized in lab-scale according to recipe described in the Table 1 (Entry 2) using two molar equivalents of Cl_2 to DOPO compound. For industrial upscaling a bottle of pure Cl_2 gas was used and the accurate amount of consumed Cl_2 was controlled by monitoring the weight difference of Cl_2 gas bottle, using a setup as shown in **Figure 3**.



- 1: Cl₂ Gas Bottle
2: High Pressure Relief Valve
3: Reactor (DOPO in CH₂Cl₂)
4: Tank of NaOH Solution

Figure 3: Schematic diagram of the industrial upscaling setup for the synthesis of DOPO-Cl using Cl₂ gas.

It was therefore confirmed that 1:1 molar ratio of Cl₂ to DOPO is enough to achieve a complete chlorination reaction (**Scheme 3**).



Scheme 3: Representative synthetic scheme of the target materials using Cl₂ gas

The expected byproduct HCl is trapped in NaOH solution. HCl can also dissolve in dichloromethane therefore the complete removal of all volatiles was performed, affording DOPO-Cl as a white solid. Even though it is considered as an extra step, it allows for isolation and storage of DOPO-Cl for further reaction. For comparison, all compounds were also synthesized following the Atherton-Todd reaction and the physical properties of DOPO derivatives were investigated and summarized in Table 2.

Table 2: Summary of the physical properties of EDA-DOPO, ETA-DOPO and DOPO-PEPA with respect to the chlorination agent.

	EDA-DOPO		ETA-DOPO		DOPO-PEPA	
Chlorinating agent	CCl ₄	Cl ₂	CCl ₄	Cl ₂	CCl ₄	Cl ₂
Yield (%)	90	90	80	71	76.5	76
Appearance	White powder	White powder	White powder	White powder	White crystals	Off-White powder
Melting point (°C)	267-273	270-272	182-185	181-185	228-230	226-228
Cl-content (wt%)	≤ 0.03	0.04	≤ 0.03	≤ 0.03	≤ 0.03	≤ 0.03
Diastereomers ratio	3:2	3:2	1:1	1:1	NA ^(a)	NA ^(a)

^(a) NA: not applicable

As summarized in Table 2, all products which are synthesized using Cl₂ gas showed in general similar physical properties to those synthesized by Atherton-Todd reaction. The only difference was the appearance of DOPO-PEPA which was collected as off-white powder, using Cl₂

methodology. Low residual chloride content (≤ 0.04 wt%) in the final products is desirable for their use as flame retardant additives as it avoids the production of HCl gas upon burning. In Atherton-Todd reaction, the chlorinating agent CCl_4 turns into CHCl_3 and the only chloride source in the final product comes from triethylammonium chloride which can be easily washed off with water. In case of using Cl_2 gas, two sources of residual chloride are expected in the final products, namely HCl and triethylammonium chloride byproduct. Therefore, more washing cycles are required to achieve lower levels of Cl^- content. The diastereomers ratios of EDA-DOPO and ETA-DOPO synthesized using either CCl_4 or Cl_2 procedures were identical. This indicates that the mechanism of chlorination reaction using CCl_4 or Cl_2 could be similar. Due to the different solubility behavior of diastereomers set of ETA-DOPO they could be isolated by modifying the synthesis workup procedure. This workup includes dissolving the white residue (after the complete removal of reaction volatiles) in ethanol with vigorous stirring overnight. The white precipitate (first crop) was collected by filtration. The filtrate was then poured in water, forming a white powder (second crop) which was also collected by filtration and both ETA-DOPO crops gave the same mass yield.

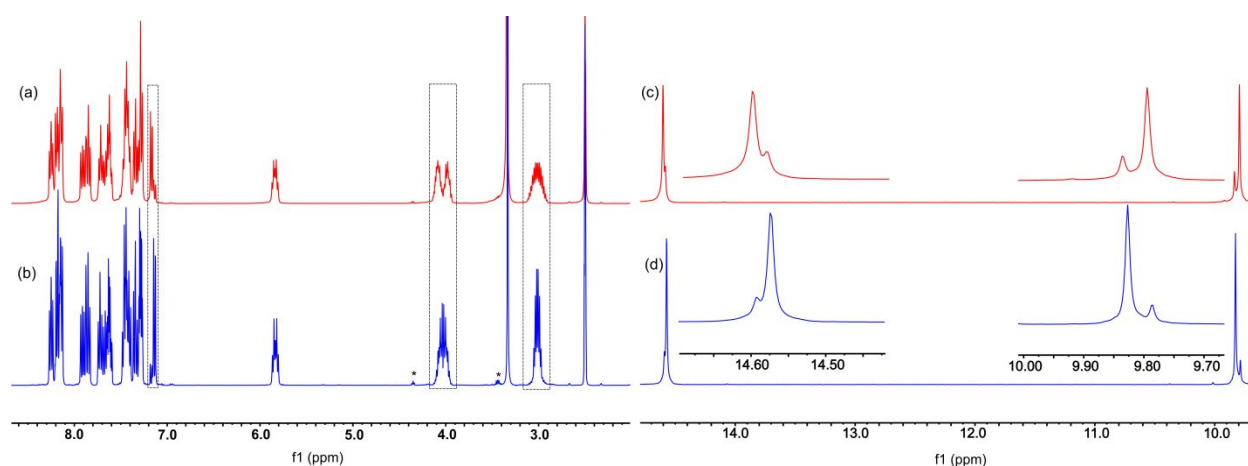


Figure 4: Differences in NMR spectra of ETA-DOPO with different diastereomeric ratio. (a) ^1H NMR spectrum of the soluble ETA-DOPO in ethanol. (b) ^1H NMR spectrum of the insoluble

ETA-DOPO in ethanol. (c) $^{31}\text{P}\{^1\text{H}\}$ NMR spectrum of soluble ETA-DOPO in ethanol. (d) $^{31}\text{P}\{^1\text{H}\}$ NMR spectrum of insoluble ETA-DOPO in ethanol.* Residual solvents.

This procedure gave about 60% diastereomeric excess and showed the influence of each set in the NMR spectra (**Figure 4**). The diastereomeric rich $^{31}\text{P}\{^1\text{H}\}$ NMR spectra (**Figure 4c** and **4d**) could help to classify the peaks of each diastereomers set, but no attempts were made to analyze the exact diastereomeric structure of each set, namely (R,S) and (S,R) set or (R,R) and (S,S) set.²⁰ The DSC study of diastereomers showed an obvious change on the melting point of ETA-DOPO which is related to the microstructure (**Figure 5**). As shown, each set of diastereomers has a clear influence on the maximum melting peak of ETA-DOPO derivative. For example, the insoluble diastereomers in ethanol showed a maximum melting peak at about 200 °C and the soluble diastereomers showed a maximum melting peak at about 152 °C. This observation can be attributed to the influence of the 60% of diastereomeric excess as calculated by $^{31}\text{P}\{^1\text{H}\}$ NMR spectra. However, small melting peaks were observed at about 189 °C for each set of the diastereomers. These melting peaks are attributed to the influence of the stereoisomers mixture: (R,R), (S,S) and (R,S), (S,R). This assumption was confirmed by studying the thermal behavior of an equimolar ratio of diastereomeric sets using DSC. It was observed that the maximum melting peak (**Figure 5**) is located between the maximum melting peaks of both diastereomeric excess of ETA-DOPO at about 185 °C. This indicates that the melting range of ETA-DOPO and EDA-DOPO can change based on the ratios of their corresponding diastereomers. However, the thermal decomposition of ETA-DOPO (≥ 230 °C) has been found same for all sets of diastereomers.

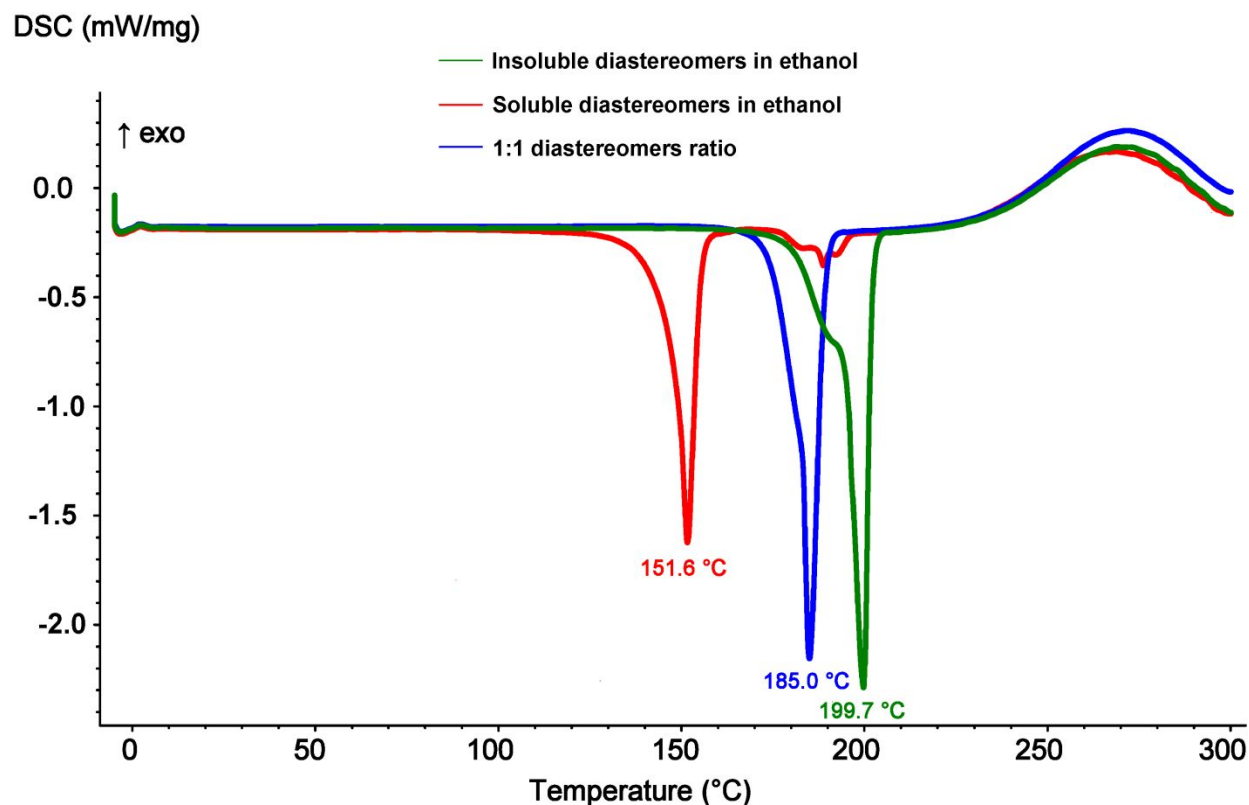


Figure 5: DSC chromatogram of ETA-DOPO with different diastereomers ratio

A first estimate of the productions cost is necessary for industrial upscaling. Therefore, the availability of raw materials and their prices are a key factor. Comparing the prices of the raw materials, namely NCS and SO_2Cl_2 for industrial utilization shows a significant low cost of Cl_2 gas. Accordingly, the first cost estimation using Cl_2 with comparison to the other chlorinating agents has a relatively inexpensive production cost. Active Cl represents 50 wt% of chlorine gas, which is approximately two times higher than other chlorinating agents (NCS and SO_2Cl_2), which accordingly reduces the disposed mass of the undesired byproducts when compared to other chlorinating agents as summarized in Table 3.

Table 3: Comparison of the qualitative economical value of Cl₂ with respect to NCS and SO₂Cl₂.

Chlorinating agent (CA)	Ratio of CA to DOPO	Weight percent of active Cl	Byproducts	produced byproducts (g) per 1 mol of CA
Cl ₂	1:1	50%	HCl	36.6 g
NCS	1:1	~27%	succinimide	99.0 g
SO ₂ Cl ₂	1:1	~27%	HCl, SO ₂	100.5 g

Conclusion:

In this work we have demonstrated the industrial feasibility of using of Cl₂ gas as a chlorinating agent for DOPO-based phosphoramidates and phosphonates synthesis. This methodology could be easily scaled up in industry, affording hundred kilograms scale of the target materials. The use of dichloromethane as the reaction solvent facilitates the ease of removal of the volatiles and further isolation and characterization of the intermediate DOPO-Cl which add a commercial benefit to this synthetic approach. The physical and thermal properties of DOPO derivatives produced via this methodology and those synthesized via Atherton-Todd reaction proved to be identical. The only drawback of this synthetic procedure is the use of dichloromethane as a reaction solvent. It has high vapor pressure and requires a special handling in large-scale synthesis and an additional recycling apparatus for its recovery from the reaction mixture. Therefore alternative solvents suitable for Cl₂ based synthesis procedure to replace dichloromethane are under further investigation.

Supporting Information

The Supporting Information is available free of charge. **Figure S1:** ^1H NMR spectrum of DOPO-Cl; **Figure S2:** $^{31}\text{P}\{^1\text{H}\}$ spectrum of DOPO-Cl; **Figure S3:** ^1H NMR spectrum of DOPO-PA; **Figure S4:** $^{31}\text{P}\{^1\text{H}\}$ NMR spectrum of DOPO-PA; **Figure S5:** GC-MS chromatogram of DOPO-PA; **Figure S6:** ^1H NMR spectrum of EDA-DOPO; **Figure S7:** $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum of EDA-DOPO; **Figure S8:** $^{31}\text{P}\{^1\text{H}\}$ spectrum of EDA-DOPO; **Figure S9:** ^1H NMR spectrum of ETA-DOPO; **Figure S10:** $^{31}\text{P}\{^1\text{H}\}$ spectrum of ETA-DOPO; **Figure S11:** ^1H NMR spectrum of DOPO-PEPA; **Figure S12:** $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum of DOPO-PEPA; **Figure S13:** $^{31}\text{P}\{^1\text{H}\}$ NMR spectrum of DOPO-PEPA.

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Funding Sources

The NMR Hardware used for measurements in this work was partially granted by the Swiss Science Foundation (SNF, grant no. 150638).

Notes

The authors declare the following competing financial interest: A patent application partially based on this work has been filed (Application No. PCT/EP2018/066946)

ACKNOWLEDGMENT

The authors would like to thank Dr. Daniel Rentsch for running the NMR measurements and Dr. Juan Carlos Cassano for proof reading the manuscript. The authors would like to thank Mr. Lucas Babiniec for his assistance in performing the first reaction using the Cl₂ gas.

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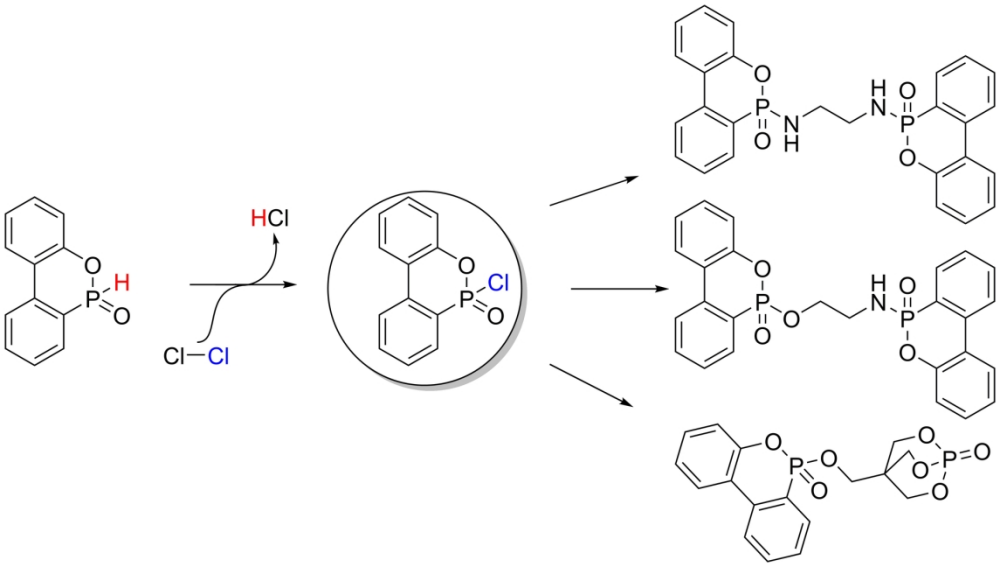


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