

TITLE OF THE INVENTION

A Selective Synthesis of Organophosphites

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part of U.S. 10/454,043, filed
5 on June 4, 2003, which, in turn, claims the benefit of the filing date of
provisional application 60/430,426 filed on December 2, 2002, in the name
of Joachim Ritter.

FIELD OF THE INVENTION

This application relates to processes for the synthesis of mono-, di-
10 and tri-organophosphites.

BACKGROUND OF THE INVENTION

Organophosphites of the general structure $(R^1O)P(OR^2)(OR^3)$ are
used in a number of commercially important applications including their
use as antioxidants, stabilizers, anti-wear additives and as ligands for
15 various catalytic processes. Organophosphites are generally produced
from PX_3 ($X = Cl, Br, I$) and alcohols. The reaction occurs stepwise by
displacement of X of PX_3 with OR of alcohol ROH and results in the
formation of mono-, di- and tri-organophosphite esters e.g., $(R^1O)PX_2$,
 $(R^1O)(R^2O)PX$, and $(R^1O)P(OR^2)(OR^3)$ and acid HX . The acid can be
20 removed by means of physical separation or by means of acid base
reaction using organic or inorganic bases.

Several methods for making organophosphites, described in
Houben-Weyl, Bd. XXII/2 pages 12-17, G. Thieme Verlag, Stuttgart 1964,
and supplement E1, pages 413-421 Stuttgart, New York 1982, are known
25 for the production of phosphites using readily available PCl_3 and the
corresponding alcohols. However, the selectivity of the displacement of Cl
by the alcohol to give the corresponding phosphorous dichloridite
 $(R^1O)P(Cl)_2$ and chloridite $(R^1O)P(OR^2)(Cl)$, respectively, is generally low.
This limits the formation of any specific phosphite of the general structure
30 $(R^1O)P(OR^2)(OR^3)$ to low yields, except when R^1 , R^2 and R^3 are the same.
Though for some applications this low selectivity is acceptable, for others,
selectivity to a specific structure with different R groups is highly desirable.

In Houben-Weyl, Bd. XXII/2 pages 12-17, G. Thieme Verlag,
Stuttgart 1964, it is summarized that a large excess of PCl_3 is needed to

preferably form a dichloridite from aliphatic or aromatic alcohols suppressing the second displacement reaction and distillation of the crude dichloridite is obligatory to separate the excess PCl_3 . Similarly the formation of chloridite from dichloridite and alcohol shows low selectivity, and extensive purification by distillation is needed.

WO 01/32666 describes a high yield process for the synthesis of $\text{PCl}(\text{O-m-tolyl})_2$ however, due to low selectivities, a time consuming process consisting of a) distillation to separate from by-products dichloridite $\text{PCl}_2(\text{O-m-tolyl})$ and triarylphosphite $\text{P}(\text{O-m-tolyl})_3$ and b) subsequent recycle of the by-products is needed.

From WO96/22968 it is known that higher selectivity for the synthesis of chloridites and dichloridites can be achieved by a stepwise protective group approach, however this reaction sequence requires two additional reaction steps for each RO group introduced adding considerable cost to the overall process.

Selectivities to form chloridite and/or dichloridite from PCl_3 and ROH are generally higher if organic tertiary amines are used in equimolar amounts. For example US 4,120,917 describes the use of tertiary amines as acid scavengers for the production of alkylphosphorodichloridites. A mixture of amine and alcohol is added to an excess of PCl_3 in an organic solvent to produce the corresponding dichloridites in moderate yields. However, a five-fold excess of PCl_3 is needed to suppress the formation of chloridite. In addition, subsequent filtration of the ammonium salt is required and PCl_3 has to be removed by distillation before a mixed phosphite can be produced. Both filtration and PCl_3 distillation are significant cost factors.

US 6,069,267 and EP 1234831 disclose that yields for phosphorous dichloridite $(\text{R}^1\text{O})\text{P}(\text{Cl}_2)$ and chloridite $(\text{R}^1\text{O})\text{P}(\text{OR}^2)(\text{Cl})$ derived from aromatic alcohols, PCl_3 , and trialkylamines are satisfactory only if temperatures below 0°C between 0°C and -20°C are deployed. Low temperature and viscosity of the product mixture within this temperature range add significantly to operating cost and process complexity.

Furthermore, US 6,069,267 describes a process for the selective synthesis of organodiphosphite compounds using PCl_3 and aryl alcohols.

However, the procedure only gives acceptable yields with phenols containing bulky ortho-substituents as alcohols and does not provide high yields for a general range of mixed triarylphosphites within a commercially favorable temperature range.

- 5 A selective commercial production of organophosphites of the general formula $(R^1O)P(OR^2)(OR^3)$ requires a method by which the displacement of X by the alcohol in PX_3 and in $ROPX_2$ occurs with high selectivity under commercially feasible conditions. It would be desirable to have high yield, highly selective processes for the production of $(R^1O)PX_2$,
 10 $(R^1O)(R^2O)PX$ and $(R^1O)P(OR^2)(OR^3)$ that are not restricted to low temperatures and at a cost that is commercially feasible. The invention described herein is such a process.

SUMMARY OF THE INVENTION

- In this invention, it has been discovered that the selectivity in the displacement reaction of X in PX_3 by the OR^1 group of an alcohol R^1OH
 15 and in the displacement reaction of X in $(R^1O)PX_2$ by the OR^2 group of an alcohol R^2OH in the presence of a triorganoamine $(R')(R'')(R''')N$ resulting in the formation of, respectively, the mono-, and di- organophosphite esters e.g., $(R^1O)PX_2$ and $(R^1O)(R^2O)PX$ strongly depends on the method
 20 of the addition of the triorganoamine and the respective alcohol. The compound $(R^1O)PX_2$ can be made with increased selectivity by the reaction of PX_3 , alcohol R^1OH and a triorganoamine $(R')(R'')(R''')N$, and the compound $(R^1O)(R^2O)PX$ can be made with increased selectivity by the reaction of $(R^1O)PX_2$, an alcohol R^2OH and a triorganoamine
 25 $(R')(R'')(R''')N$ if the triorganoamine and the respective alcohol are added (i) to PX_3 for making $(R^1O)PX_2$ and (ii) to $(R^1O)PX_2$ for making $(R^1O)(R^2O)PX$, such that the additions of the triorganoamine and the alcohol R^1OH to PX_3 for making $(R^1O)PX_2$ or the additions of the triorganoamine and the alcohol R^2OH to $(R^1O)PX_2$ for making
 30 $(R^1O)(R^2O)PX$ are done in a separate but concurrent fashion or in a separate and in alternating portions of the triorganoamine and the respective alcohol. The method of addition to the reaction mixture allows the triorganoamine and the respective alcohol to be present in low concentrations and in a low molar ratios relative to PX_3 and $(R^1O)PX_2$ for

making $(R^1O)PX_2$ and $(R^1O)PX_2$ and $(R^1O)(R^2O)PX$ for making $(R^1O)(R^2O)PX$ during the largest part of the addition period without using excessive PX_3 for making $(R^1O)PX_2$, $(R^1O)PX_2$ for making $(R^1O)(R^2O)PX$ or excessive solvent for alcohol and triorganoamine. The method of this

- 5 invention allows a wider range of reaction temperatures including significantly higher reaction temperatures as well as higher yields as previously reported in the art. The present invention is, therefore:

a method for making a composition comprising a compound of the formula $(R^1O)PX_2$, wherein X is selected from the group consisting of Cl, Br, and I, R^1 is a C_1 to C_{18} alkyl, a C_6 to C_{18} aryl radical, or a C_3 to C_{18} cycloalkyl radical, wherein said method comprises: contacting a first solution comprising a predetermined amount of PX_3 dissolved in an aprotic solvent with (i) a second solution comprising a predetermined amount of an alcohol R^1OH , and a predetermined amount of a triorganoamine $(R')(R'')(R''')N$, wherein R' , R'' and R''' are independently selected from the group consisting of C_1 to C_{18} alkyl, C_6 to C_{18} aryl and C_4 to C_{18} heteroaryl radicals, and wherein the molar ratio of the alcohol to the triorganoamine is greater than 5, and (ii) a third solution comprising a predetermined amount of the triorganoamine and a predetermined amount of the alcohol, wherein the molar ratio of the triorganoamine to the alcohol is greater than 5, and wherein in said method the second and third solutions are added to the first solution separately by either

(a) adding each of the second and third solutions concurrently and continuously into the first solution at a rate of no greater than 4 molar equivalents of each of the alcohol and triorganoamine, relative to the PX_3 , per hour until the predetermined amounts of each of the alcohol and triorganoamine have been added to the first solution, provided that at any given time, the total molar amount of alcohol added does not exceed the total molar amount of triorganoamine added by more than 25% of the total molar amount of the triorganoamine added; or

(b) adding each of the second and third solutions concurrently and discontinuously into the first solution at a rate of no greater than 4 molar equivalents of each of the alcohol and triorganoamine, relative to the PX_3 , per hour in aliquots of the second solution containing no more than 0.5

molar equivalents of alcohol and in aliquots of the third solution containing no more than 0.5 equivalents of triorganoamine, until the predetermined amounts of each of the alcohol and triorganoamine have been added to the first solution; or

- 5 (c) adding each of the second and third solutions discontinuously into the first solution at a rate of no greater than 4 molar equivalents of each of the alcohol and triorganoamine, relative to the PX_3 , per hour in aliquots of the second solution containing no more than 0.5 molar equivalents of alcohol and in aliquots of the third solution containing no more than 0.5 equivalents of triorganoamine, until the predetermined amounts of each of the alcohol and triorganoamine have been added to the first solution by repetitively adding an aliquot of either the triorganoamine followed sequentially by an aliquot of the alcohol, or an aliquot of the alcohol followed by an aliquot of the triorganoamine, until the predetermined amounts of each of the alcohol and triorganoamine have been added to the first solution;

to produce the composition comprising the compound of the formula R^1OPX_2 , provided that in either of the alternatives (b) or (c), for any given additions, whether concurrent or sequential, within a series of discontinuous additions, the molar difference between the triorganoamine added and the alcohol added does not exceed 0.5 equivalent, relative to the PX_3 ; and

a method for making a composition comprising a compound of the formula $(R^1O)(R^2O)PX$, wherein X is selected from the group consisting of Cl, Br, and I, R^1 and R^2 are independently selected from the group consisting of C_1 to C_{18} alkyl, C_6 to C_{18} aryl, and C_3 to C_{18} cycloalkyl radicals, wherein said method comprises: contacting a first solution comprising a predetermined amount of R^1OPX_2 dissolved in an aprotic solvent with (i) a second solution comprising a predetermined amount of an alcohol R^2OH , and a predetermined amount of a triorganoamine $(R')(R'')(R''')N$, wherein R' , R'' and R''' are independently selected from the group consisting of C_1 to C_{18} alkyl, C_6 to C_{18} aryl and C_4 to C_{18} heteroaryl radical, and wherein the molar ratio of the alcohol to the triorganoamine is greater than 5, and (ii) a third solution comprising a predetermined amount

of the triorganoamine and a predetermined amount of the alcohol, wherein the molar ratio of the triorganoamine to the alcohol is greater than 5, and wherein in said method the second and third solutions are added to the first solution separately by either

5 (a) adding each of the second and third solutions concurrently and continuously into the first solution at a rate of no greater than 4 molar equivalents of each of the alcohol and triorganoamine relative to the $(R^1O)PX_2$, per hour until the predetermined amounts of each of the alcohol and triorganoamine have been added to the first solution, provided that at
10 any given time, the total molar amount of alcohol added does not exceed the total molar amount of triorganoamine added by more than 25% of the total molar amount of the triorganoamine added; or

(b) adding each of the second and third solutions concurrently and discontinuously into the first solution at a rate of no greater than 4 molar
15 equivalents of each of the alcohol and triorganoamine, relative to the $(R^1O)PX_2$, per hour in aliquots of the second solution containing no more than 0.5 molar equivalents of alcohol and in aliquots of the third solution containing no more than 0.5 equivalents of triorganoamine, until the predetermined amounts of each of the alcohol and triorganoamine have
20 been added to the first solution; or

(c) adding each of the second and third solutions discontinuously into the first solution at a rate of no greater than 4 molar equivalents of each of the alcohol and triorganoamine, relative to the $(R^1O)PX_2$, per hour in aliquots of the second solution containing no more than 0.5 molar
25 equivalents of alcohol and in aliquots of the third solution containing no more than 0.5 equivalents of triorganoamine, until the predetermined amounts of each of the alcohol and triorganoamine have been added to the first solution by repetitively adding an aliquot of either the triorganoamine followed sequentially by an aliquot of the alcohol, or an
30 aliquot of the alcohol followed by an aliquot of the triorganoamine, until the predetermined amounts of each of the alcohol and triorganoamine have been added to the first solution;

to produce the composition comprising the compound of the formula $(R^1O)(R^2O)PX$, provided that in either of the alternatives (b) or (c),

for any given additions, whether concurrent or sequential, within a series of discontinuous additions, the molar difference between the triorganoamine added and the alcohol added does not exceed 0.5 equivalent, relative to the R^1OPX_2 .

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DETAILED DESCRIPTION

The present invention describes methods for the synthesis of the compounds $(R^1O)PX_2$, $(R^1O)(R^2O)PX$, $(R^1O)(R^2O)_2P$, and $(R^1O)P(OR^2)(OR^3)$, wherein X is selected from the group consisting of Cl, Br and I, and wherein R^1 , R^2 , and R^3 can be independently selected from the group consisting of C_1 to C_{18} alkyl, C_6 to C_{18} aryl, and C_3 to C_{18} cycloalkyl radicals.

For the synthesis of the compound $(R^1O)PX_2$, a first solution comprising a predetermined amount of PX_3 dissolved in an aprotic solvent is contacted with (i) a second solution comprising a predetermined amount of an alcohol R^1OH , and a predetermined amount of a triorganoamine $(R')(R'')(R''')N$, wherein R' , R'' and R''' are independently selected from the group consisting of C_1 to C_{18} alkyl, C_6 to C_{18} aryl and C_4 to C_{18} heteroaryl radicals, and wherein the molar ratio of the alcohol to the triorganoamine is greater than 5, and (ii) a third solution comprising a predetermined amount of the triorganoamine and a predetermined amount of the alcohol, wherein the molar ratio of the triorganoamine to the alcohol is greater than 5, to produce the composition comprising the compound of the formula $(R^1O)PX_2$.

For the synthesis of the compound $(R^1O)(R^2O)PX$, a first solution comprising a predetermined amount of R^1OPX_2 dissolved in an aprotic solvent is contacted with (i) a second solution comprising a predetermined amount of an alcohol R^2OH , and a predetermined amount of a triorganoamine $(R')(R'')(R''')N$, wherein R' , R'' and R''' are independently selected from the group consisting of C_1 to C_{18} alkyl, C_6 to C_{18} aryl and C_4 to C_{18} heteroaryl radical, and wherein the molar ratio of the alcohol to the triorganoamine is greater than 5, and (ii) a third solution comprising a predetermined amount of the triorganoamine and a predetermined amount of the alcohol, wherein the molar ratio of the triorganoamine to the alcohol

is greater than 5, to produce the composition comprising the compound of the formula $(R^1O)(R^2O)PX$.

The second and third solutions can be added into the first solution separately but concurrently and continuously at a rate of no greater than 4 molar equivalents of each of the alcohol and triorganoamine, relative to the PX_3 for making $(R^1O)PX_2$, or relative to $(R^1O)PX_2$ for making $(R^1O)(R^2O)PX$, per hour until the predetermined amounts of each of the alcohol and triorganoamine have been added to the first solution, provided that at any given time, the total molar amount of alcohol added does not exceed the total molar amount of triorganoamine added by more than 25% of the total molar amount of the triorganoamine added.

The second and third solutions can be added into the first solution separately and concurrently but discontinuously at a rate of no greater than 4 molar equivalents of each of the alcohol and triorganoamine, relative to the PX_3 for making $(R^1O)PX_2$, or relative to $(R^1O)PX_2$ for making $(R^1O)(R^2O)PX$, per hour in aliquots of the second solution containing no more than 0.5 molar equivalents of alcohol and in aliquots of the third solution containing no more than 0.5 equivalents of triorganoamine, until the predetermined amounts of each of the alcohol and triorganoamine have been added to the first solution.

The second and third solutions can be added into the first solution separately and discontinuously at a rate of no greater than 4 molar equivalents of each of the alcohol and triorganoamine, relative to the PX_3 for making $(R^1O)PX_2$, or relative to $(R^1O)PX_2$ for making $(R^1O)(R^2O)PX$, per hour in aliquots of the second solution containing no more than 0.5 molar equivalents of alcohol and in aliquots of the third solution containing no more than 0.5 equivalents of triorganoamine, until the predetermined amounts of each of the alcohol and triorganoamine have been added to the first solution by repetitively adding an aliquot of either the triorganoamine followed sequentially by an aliquot of the alcohol, or an aliquot of the alcohol followed by an aliquot of the triorganoamine, until the predetermined amounts of each of the alcohol and triorganoamine have been added to the first solution;

In either of the alternatives above for discontinuous additions, for any given additions, whether concurrent or sequential, within a series of discontinuous additions, the molar difference between the triorganoamine added and the alcohol added does not exceed 0.5 equivalent, relative to the PX_3 for making $(R^1O)PX_2$, or relative to $(R^1O)PX_2$ for making $(R^1O)(R^2O)PX$.

The composition comprising the compound of the formula $(R^1O)PX_2$ made by the method described above can be used as the first solution for making $(R^1O)PX_2$. One can use the product of reaction of PX_3 with an alcohol R^1OH and any triorganoamine by a method different from that described above. For example, $(R^1O)PX_2$ prepared by less selective methods described in the prior art and dissolved in an aprotic solvent can also be used.

The above methods can be used for successive replacement of X of PX_3 by a polyalcohol to produce products of the general formula $A(OPX_2)_n$, $B[(R^1O)(X)PO]_n$, etc., where A and B can be independently selected from the group consisting of C_2 to C_{18} alkyl, C_3 to C_{18} cycloalkyl, and C_6 to C_{18} aryl di-, tri- or tetra-radicals corresponding to $n=2$, $n=3$ and $n=4$.

It is critical to add the triorganoamine and the alcohol separately in such a way that both materials exhibit low concentration in the reaction mixture where the formation of the products occurs. Furthermore it is important that the triorganoamine and the alcohol concentration relative to PX_3 and $(R^1O)PX_2$ for making $(R^1O)PX_2$ and $(R^1O)PX_2$ and $(R^1O)(R^2O)PX$ for making $(R^1O)(R^2O)PX$ are low during the largest part of the addition period. This can be achieved in the above described ways, for example by either separate and concurrent both continuous and discontinuous addition of triorganoamine and alcohol or by separate and discontinuous repetitive additions of small aliquot portions one followed by the other of the triorganoamine and the alcohol. The separate and concurrent, both continuous and discontinuous additions can be achieved by using one or more separate feed lines for each the triorganoamine and the alcohol attached either directly to the reaction vessel at different locations, or to an external recirculation pipe. In a preferred mode of the separate and

discontinuous repetitive additions of aliquot portions one followed by the other of the triorganoamine and the alcohol, the addition begins with the addition of an aliquot portion of the triorganoamine. In a more preferred version of this addition mode at least two alternating additions are
5 employed. Most preferred is the separate but concurrent addition mode.

The preferred amount of each alcohol OH group added per equivalent X attached to P is important for the product distribution and depends on the individual selectivity of the substrates in the displacement reaction and the target distribution of the corresponding phosphite.

10 Generally 0.8 to 1.2 molar equivalents of alcohol OH groups per molar equivalent of phosphorous bound X groups are suitable. More preferred but not restrictive are 1.00 to 1.05 mol equivalents of alcohol OH groups per phosphorous bound X groups to be substituted.

The ratio between added triorganoamine and alcohol at any given
15 time of the process is important for the selectivity of the displacement reaction of X by R^1O or by R^2O . For polyalcohols each alcohol OH group represents a molar equivalent of OH in the displacement reaction of X. It is preferred to keep the difference in the amount of added molar equivalents of triorganoamine and molar equivalents of alcohol OH groups
20 at any given time of the addition between 0.0 and 1.0 equivalents. In a more preferred version of this method the difference in the amount of added molar equivalents of triorganoamine and molar equivalents of alcohol OH groups at any given time of the addition is kept between 0.0 and 0.05 equivalents. Furthermore it is preferred to keep conditions where
25 the amount of added molar equivalents of triorganoamine exceeds the amount of added molar equivalents of alcohol OH groups at any given time of the addition by 0.0-0.05 equivalents. In a most preferred version of this invention triorganoamine and alcohol are added in a separate but concurrent fashion in equimolar amounts such that the amount of molar
30 equivalents of added alcohol OH groups does not exceed the molar equivalent amount of added triorganoamine at any given time.

The composition comprising the compound of the formula $(R^1O)(R^2O)PX$, made by the methods described above, can be contacted with additional amount of the alcohol R^2OH and a triorganoamine to

produce a product comprising the compound of the formula $(R^1O)(R^2O)_2P$.

The composition comprising the compound of the formula $(R^1O)(R^2O)PX$, made by the methods described above, can be contacted with an alcohol R^3OH and a triorganoamine to produce a product comprising the

5 compound of the formula $(R^1O)P(OR^2)(OR^3)$.

During the addition of the alcohol and the triorganoamine, good agitation using methods known by those skilled in the art is important to provide sufficient heat removal and to avoid areas of highly concentrated triorganoamine or alcohol. This invention is especially useful for the
10 production of mixed compounds, e.g., compounds $(R^1O)(R^2O)_2P$ and $(R^1O)P(OR^2)(OR^3)$. At any given time of the concurrent alcohol and triorganoamine addition, the alcohol feed may be changed to a different alcohol. Mixed phosphites, $(R^1O)(R^2O)PX$ can be synthesized in high selectivity by first adding approximately one equivalent of alcohol R^1OH
15 and triorganoamine, separately and concurrently, followed by approximately one equivalent of alcohol R^2OH and triorganoamine.

The triorganoamine, $(R^1)(R^2)(R^3)N$ used in the methods of this invention should be as dry as possible to minimize hydrolysis of phosphorus reactants and products and are independently selected from
20 the group consisting of aliphatic, aromatic and hetero aromatic amines, or combinations thereof. The triorganoamine used may be substituted or unsubstituted. It is preferred, however, that the corresponding triorganoammonium salt exhibits no acidic reactivity in the reaction medium to avoid undesired rearrangement reactions of the phosphite products.
25 Preferred amines are amines selected from the group consisting of trialkylamines wherein the alkyl groups are linear, branched or cyclic, have 1 to 12 carbon atoms and may be linked together. More preferred amines are chosen from the group of trimethylamine, dimethylethylamine, diethylmethylamine, triethylamine, dimethylpropylamine and
30 dimethylisopropylamine.

Aprotic solvents are suitable provided they do not react with PX_3 , triorganoamine, alcohol and triorgano-ammonium salts. The solvent should not have the ability to dissolve the triorganoammonium salt produced during the reaction if the acidity associated with dissociated

triorganoammonium salts can cause undesired rearrangement reactions. Furthermore, a solvent with a melting point below the desired reaction temperature is preferred. Preferred solvents are selected from the group of organic aprotic solvents or mixtures thereof. More preferred are
5 solvents or solvent mixtures selected from the group of aliphatic and aromatic solvents. Most preferred solvents or solvent mixtures are aromatic solvents selected from the group consisting of toluene, xylenes, 1,2,3,4-tetrahydronaphthalene, and ethylbenzene.

The rates of addition of triorganoamine and alcohol are generally
10 limited by the mixing and cooling capabilities of the equipment. Practical addition times range from 15 minutes to 12 hours. A preferred range is 1 to 6 hours.

Reagent and product concentrations are generally limited by the ability to effectively mix the resulting slurry of triorganoamine-HX. The
15 concentrations of the phosphorous species, the triorganoamine, and the alcohol can be independently chosen only limited by density and solubility as long as the above and below mentioned process conditions described herein are maintained. The alcohols and the amines may be fed neat or diluted with solvent. The alcohol feed may contain triorganoamine and the
20 triorganoamine feed may contain alcohol, however, for the alcohol feed the molar ratio of alcohol to the triorganoamine should be greater than 5, preferably greater than 9, and, for the triorganoamine feed the molar ratio of the triorganoamine to the alcohol should be greater than 5, preferably greater than 9. It is most preferred that the feed containing alcohol
25 contains no triorganoamine and the feed containing triorganoamine contains no alcohol. A preferred concentration range for the triorganoamine and alcohol feed is 1 to 4 mol/l in feed solutions. The final concentration of phosphorus-containing product in the reactor may range from about 1% to 35%. The preferred concentration of the phosphorous
30 containing product in the reactor ranges from 7% to 25% by weight.

In the process of this invention, water in the solvent, triorganoamine, alcohol, and reaction vessel can decrease yields to the desired monophosphite, diphosphite, and triphosphite products. Hence, it is necessary to reduce the water content in the solvent, reagents, and

vessel to concentrations that generate acceptable yields on an economic basis and conduct the reaction under an inert atmosphere.

Suitable PX_3 compounds are those where X is capable of exchange reactions with alcohols in the presence of a triorganoamine to form a P-O bond and a salt of HX-triorganoamine. Preferred groups for X are Cl, Br, I. Most preferred is Cl.

In principle, all alcohols capable of reacting with PX_3 in the presence of a base are suitable substrates for the present invention. Aromatic as well as aliphatic alcohols show significantly higher selectivities in the displacement reaction with PX_3 and $(R^1O)PX_2$ if the above mentioned process is applied. Non-exclusive examples for suitable alcohols are primary, secondary and tertiary aliphatic alcohols including diols and polyols. Further nonexclusive examples include aromatic alcohols, diols and polyols from the group of substituted and unsubstituted phenols, naphthols, hydroxyphenanthrenes and hydroxyanthracenes, hydroxy-substituted heteroaromatic compounds.

The preferred reaction temperature for a given displacement of X in PX_3 depends on the steric and electronic nature of the alcohol and the decomposition temperature of the corresponding products. However, this invention is not restricted to the low temperature range as previously described in the prior art. Aromatic alcohols give good selectivity to the corresponding phosphorodichloridites and chloridites over a wide range of temperatures even at 55°C. In most cases, sterically demanding alcohols such as ortho-substituted phenols give better yields to the corresponding dichloridites and chloridites compared to less-hindered alcohols such as unsubstituted or meta- and para-substituted aromatic alcohols lacking ortho-substitution. If the reactivity of the alcohol is low, a reaction temperature high enough to provide a reaction rate equal to or faster than the addition rate is preferred. Since under commercial operation the temperature range achievable is subject to limits of the equipment available, temperatures above -25°C are generally preferred. A preferred but not limiting temperature range for this process is -25°C to +65°C.

The reaction is relatively insensitive to pressure and is limited only by practical considerations. For practical reasons, preferred reaction pressure ranges from 10 psia (69 kPa) to 50 psia (345 kPa).

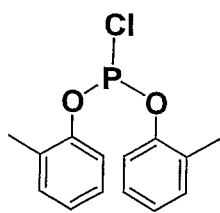
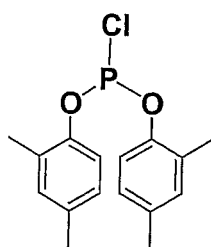
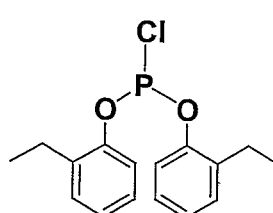
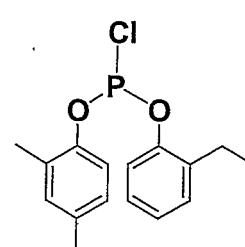
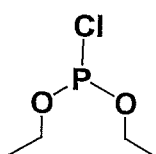
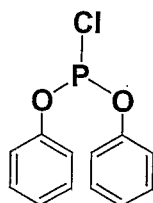
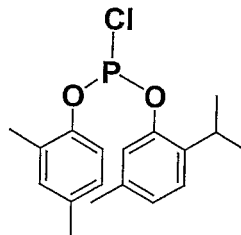
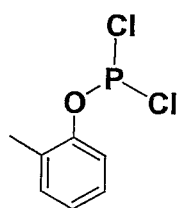
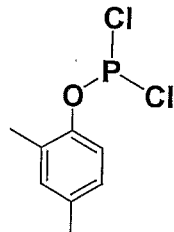
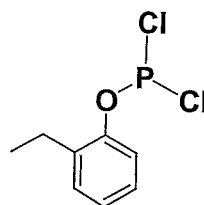
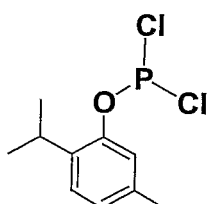
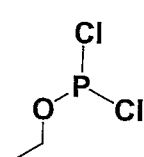
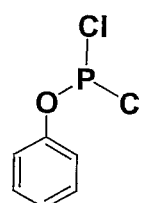
Compounds $(R^1O)PX_2$ and $(R^1O)(R^2O)PX$ formed by the processes described above can be transformed conveniently in the same or a separate vessel to the corresponding phosphites $(R^1O)P(OR^2)(OR^3)$ and $(R^1O)(R^2O)_2P$, respectively, thiophosphites $(R^1O)P(OR^2)(SR^4)$, $(R^1O)P(SR^4)(SR^5)$, or amidites $(R^1O)P(OR^2)(NR^6R^7)$, $(R^1O)P(NR^6R^7)(NR^8R^9)$ by displacing the remaining X's of $(R^1O)PX_2$ or $(R^1O)(R^2O)PX$ with one or more of the groups OR^2 , OR^3 , SR^4 , SR^5 , NR^6R^7 , and NR^8R^9 groups wherein R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 and R^9 can be independently selected from the group consisting of C_1 to C_{18} alkyl, C_6 to C_{18} aryl, and C_3 to C_{18} cycloalkyl radicals. Compound $(R^1O)(R^2O)PX$ can be hydrolyzed to $(R^1O)(R^2O)POH$. For $(R^1O)P(OR^2)(OR^3)$, this reaction product can be obtained by adding about one molar equivalent of triorganoamine followed by one equivalent of alcohol R^3OH to $(R^1O)PX_2$. For $(R^1O)P(OR^2)_2$, this reaction product can be obtained by adding about two molar equivalents of triorganoamine followed by two equivalents alcohol HOR^2 to $(R^1O)(R^2O)PX$. In contrast to the formation of $(R^1O)PX_2$ and $(R^1O)(R^2O)PX$, for transformation to $(R^1O)P(OR^2)(OR^3)$ and derivatives described above, the alcohols and amines may be fed as a mixture, if so desired. Likewise, thiophosphites e.g., $(R^1O)P(OR^2)(SR^4)$, $(R^1O)P(SR^4)(SR^5)$, and amidites e.g., $(R^1O)P(OR^2)(NR^6R^7)$, $(R^1O)P(NR^6R^7)(NR^8R^9)$ can be produced from $(R^1O)PX_2$ or $(R^1O)(R^2O)PX$ and secondary amines and thiols, respectively.

The process described herein can be carried out as a continuous process whereby the triorganoamine and the alcohol are added concurrently but separately into a continuous type reactor, such as a continuous flow stirred tank reactor (CSTR). Simultaneously, PX_3 is added separately or together with the triorganoamine, and the triorganoamine and the alcohol are fed separately and concurrently. This embodiment of the present invention has the advantage of smaller reaction volumes with improved mixing and heat transfer. In a more preferred variation of a continuous process a series of 2 to 10 CSTR's are

used whereby the PX_3 is fed into the first reactor only and the triorganoamine and the alcohol are fed separately and concurrently in portions into each subsequent reactor. In the most preferred version of a continuous reactor a plug-flow reactor is employed where PX_3 is fed into
5 an entry port at the beginning of the plug-flow reactor and the triorganoamine and the alcohol are added concurrently but separately in equimolar portions into multiple entry ports along the length of the plug-flow reactor.

EXAMPLES

Structures of Phosphorochloridites and Phosphorodichloridites:

**1a****1b****1c****1d****1e****1f****1g****2a****2b****2c****2d****2e****2f**

Examples 1, 15, 18, and 24 show that a chloridite and dichloridite derived from an aromatic alcohol (ArOH) with little steric hindrance can be produced in high selectivity. All ^{31}P NMR chemical shifts δ (75 MHz) are given in ppm in reference to triphenylphosphineoxide (δ 25.6). Unless otherwise noted all ^{31}P NMR samples were prepared by mixing 0.4 ml of the reaction volume with 0.8 ml of 0.1 molar triphenylphosphineoxide in C_6D_6 . All reactions and sampling procedures were performed under the exclusion of air and moisture.

10

Example 1: Synthesis of phosphorochloridite **1a** and phosphorodichloridite **2a**

In a temperature controlled 250 ml baffled flask charged with 50 ml of 1.0 molar PCl_3 in toluene, a solution of 25 ml 2.0 molar triethylamine in toluene, and a solution of 25 ml 2.0 molar o-cresol in toluene were added separately and concurrently under vigorous stirring via a dual syringe pump over a period of 90 min. During the addition period, the reaction temperature was maintained at -5°C . The ^{31}P NMR analysis showed clean transformation to the corresponding dichloridite **2a** (δ 182.7) in 97% selectivity. A second 25 ml of each 2.0 molar triethylamine solution in toluene and 2.0 molar o-cresol solution in toluene were added separately and concurrently via a dual syringe pump over a period of 90 min. The ^{31}P NMR analysis showed clean transformation to the corresponding chloridite **1a** (δ 161.9) in 91% overall selectivity.

25

Examples 2-5: demonstrate the temperature effect on the yield of **1a** and **2a** between -15°C and $+15^\circ\text{C}$. These examples were carried out under the same conditions as Example 1 but at different temperatures. Results as derived from ^{31}P NMR analysis are shown in Table 1.

Table 1: Effect of temperature on the yield of 1a and 2a in the range of – 15°C and + 15°C.

All examples were carried out under the same conditions as Example 1 but at different temperatures. Results are derived from ^{31}P NMR analysis an given as the molar equivalent fraction of each of the components in the reaction mixture

Example	Temp (°C)	Equivalents ArOH and NEt_3 added	% 1a	% 2a	% PCl_3	% (o-tolyl-O) $_3\text{P}$
2	-5	1.0	3	97	0	0
		2.0	91	4	0	5
3	+5	1.0	4	94	2	0
		2.0	91	3	0	6
4	-15	1.0	2	97	1	0
		2.0	92	3	0	5
5	+15	1.0	4	88	8	0
		2.0	90	5	0	5

Examples 6-10: demonstrate the temperature effect on the yield of **1a** and **2a** between – 20°C and + 55°C. All examples were carried out under the same conditions as Example 6 but at different temperatures. Results as derived from ^{31}P NMR analysis are shown in Table 2.

Example 6: Synthesis of phosphorochloridite **1a** and phosphorodichloridite **2a**

In a temperature controlled 500 ml baffled, jacketed, glass reactor with overhead stirrer charged with 200 ml of 1.0 molar PCl_3 in toluene, a solution of 100 ml 2.0 molar triethylamine in toluene, and a solution of 100 ml 2.0 molar o-cresol in toluene were added separately and concurrently under vigorous stirring via a peristaltic pump over a period of 45 min. During the addition period the reaction temperature was maintained at -20 °C. The ^{31}P NMR analysis showed clean transformation to the corresponding dichloridite **2a** in 94% selectivity. A second 100 ml of each 2.0 molar triethylamine solution in toluene and 2.0 molar o-cresol solution

in toluene were added separately and concurrently via a peristaltic pump over a period of 45 min. The ^{31}P NMR analysis showed clean transformation to the corresponding chloridite in 93% overall selectivity.

5 Table 2: Effect of temperature on the yield of 1a and 2a in the range of -20°C and +55°C.

All examples were carried out under the same conditions as Example 6 but at different temperatures. Results are derived from ^{31}P NMR analysis and given as the molar equivalent fraction of each of the components in
10 the reaction mixture.

Example	Temp (°C)	Equivalents ArOH and NEt ₃ added	% 1a	% 2a	% PCl ₃	% (o-tolyl-O) ₃ P
6	-20	1.0	3	94	3	0
		2.0	93	2	0	5
7	-5	1.0	3	93	4	0
		2.0	91	4	0	5
8	+15	1.0	4	93	3	0
		2.0	90	4	0	6
9	+35	1.0	6	88	6	0
		2.0	89	4	0	7
10	+55	1.0	5	91	4	0
		2.0	89	4	0	7

Example 11: This example shows the effect of a two-fold concentration increase of reactants on the yields of **1a** and **2a** as compared to Example
15 9 in Table 3.

In a temperature controlled 500 ml baffled, jacketed, glass reactor with overhead stirrer charged with 200 ml of 2.0 molar PCl₃ in toluene, a solution of 100 ml 4.0 molar triethylamine in toluene, and a solution of 100 ml 4.0 molar o-cresol in toluene were added separately and concurrently
20 under vigorous stirring via a peristaltic pump over a period of 80 min. During the addition period the reaction temperature was maintained at 35°C. The ^{31}P NMR analysis showed clean transformation to the

corresponding dichloridite **2a** in 91% selectivity. A second 100 ml of each 4.0 molar triethylamine solution in toluene and 4.0 molar o-cresol solution in toluene were added separately and concurrently via a peristaltic pump over a period of 80 min. The ^{31}P NMR analysis showed clean

5 transformation to the corresponding chloridite **1a** in 90% overall selectivity.

Table 3: Effect of a two-fold concentration increase of reactants on the yields of 1a and 2a as compared to Example 9.

Results are derived from ^{31}P NMR analysis and given as the molar

10 equivalent fraction of each of the components in the reaction mixture.

Example	Temp (°C)	Equivalents and concentration of ArOH and NEt_3 added	% 1a	% 2a	% PCl_3	% (o-tolyl-O) $_3\text{P}$
9	+35	1.0 (2 Molar)	6	88	6	0
		2.0 (2 Molar)	89	4	0	7
11	+35	1.0 (4 Molar)	5	91	4	0
		2.0 (4 Molar)	90	4	0	6

Examples 12-14: demonstrate the effect of feed rates on the yield of **1a**

15 and **2a**. Results are given in Table 4. These examples were carried out under the same conditions as Example 1 but at different feed rates. Results as derived from ^{31}P NMR analysis are shown in Table 4.

Table 4: Effect of feed rates on the yield of 1a and 2a.

These examples were carried out under the same conditions as Example 1 but at different feed rates. Results are derived from ^{31}P NMR analysis and given as the molar equivalent fraction of each of the components in the reaction mixture.

Example	Feed rate equiv / hr	Equivalents ArOH and NEt_3 added	% 1a	% 2a	% PCl_3	% (o-tolyl-O) $_3\text{P}$
12	0.67	1.0	3	97	0	0
		2.0	91	4	0	5
13	1.20	1.0	4	93	3	0
		2.0	94	0	0	6
14	2.4	1.0	2	92	6	0
		2.0	88	3	0	9

Example 15: Synthesis of phosphorochloridite **1b** and phosphorodichloridite **2b**

In a temperature controlled 250 ml baffled, flask charged with 50 ml of 1.0 molar PCl_3 in toluene, a solution of 25 ml 2.0 molar triethylamine in toluene, and a solution of 25 ml 2.0 molar 2,4-xyleneol in toluene were added separately and concurrently under vigorous stirring via a dual syringe pump over a period of 90 min. During the addition period, the reaction temperature was maintained at -5°C . The ^{31}P NMR analysis exhibited clean transformation to the corresponding dichloridite **2b** (δ 183.0) in 98% selectivity. Another 26.0 ml of each 2.0 molar triethylamine solution in toluene and 2.0 molar 2,4-xyleneol solution in toluene were added separately and concurrently via a dual syringe pump over a period of 90 min. The ^{31}P NMR analysis exhibited clean transformation to the corresponding chloridite **1b** (δ 162.3) in 93% overall selectivity.

Examples 16 and 17: Synthesis of phosphorochloridite **1b** and phosphorodichloridite **2b** demonstrate the temperature effect on the yield at -5°C and $+35^\circ\text{C}$ 0.4 mol PCl_3 scale.

Example 16: In a temperature controlled 2000 ml baffled, jacketed, glass reactor with overhead stirrer charged with 400 ml of 1.0 molar PCl_3 in toluene, a solution of 200 ml 2.0 molar triethylamine in toluene, and a solution of 200 ml 2.0 molar 2,4-dimethylphenol in toluene were added separately and concurrently under vigorous stirring via a peristaltic pump over a period of 133 min. During the addition period, the reaction temperature was maintained at -5°C . The ^{31}P NMR analysis showed clean transformation to the corresponding dichloridite **2b** in 96% selectivity. A second 200 ml of each 2.0 molar triethylamine solution in toluene and 2.0 molar 2,4-dimethylphenol solution in toluene were added separately and concurrently via a peristaltic pump over a period of 133 min. The ^{31}P NMR analysis showed clean transformation to the corresponding chloridite **1b** in 94% overall selectivity

Example 17: In a temperature controlled 2000 ml baffled jacketed glass reactor with overhead stirrer charged with 400 ml of 1.0 molar PCl_3 in toluene, a solution of 200 ml 2.0 molar triethylamine in toluene, and a solution of 200 ml 2.0 molar 2,4-dimethylphenol in toluene were added separately and concurrently under vigorous stirring via a peristaltic pump over a period of 85 min. During the addition period, the reaction temperature was maintained at $+35^\circ\text{C}$. The ^{31}P NMR analysis showed clean transformation to the corresponding dichloridite **2b** in 92% selectivity. A second 206 ml of each 2.0 molar triethylamine solution in toluene and 2.0 molar 2,4-dimethylphenol solution in toluene were added separately and concurrently via a peristaltic pump over a period of 88 min. The ^{31}P NMR analysis showed clean transformation to the corresponding chloridite **1b** in 95% overall selectivity.

Example 18: Synthesis of phosphorochloridite **1c** and phosphorodichloridite **2c**

In a temperature controlled 250 ml baffled flask charged with 50 ml of 1.0 molar PCl_3 in toluene, a solution of 26 ml 2.0 molar triethylamine in toluene, and a solution of 26 ml 2.0 molar o-ethylphenol in toluene were

added separately and concurrently under vigorous stirring via a dual syringe pump over a period of 90 min. During the addition period the reaction temperature was maintained at -5° deg. C. The ^{31}P NMR analysis exhibited clean transformation to the corresponding dichloridite **2c** (δ 183.2) in 96% selectivity. Another 24.0 ml of each 2.0 molar triethylamine solution in toluene and 2.0 molar o-ethylphenol solution in toluene were added separately and concurrently via a dual syringe pump over a period of 90 min. The ^{31}P NMR analysis exhibited clean transformation to the corresponding chloridite **1c** (δ 161.5) in 93% overall selectivity

10

Example 19: This example shows that the selectivity of the displacement reaction of chloride by phenolate in PCl_3 during the synthesis of dichloridite **2c** decreases significantly if the amount of alcohol added exceeds the amount of triorganoamine added during the addition procedure.

15

In a temperature controlled 250 ml baffled flask charged with 50 ml of 1.0 molar PCl_3 in toluene, a solution of 25 ml 2.0 molar triethylamine in toluene, and a solution of 25 ml 2.5 molar o-ethylphenol in toluene were added separately and concurrently under vigorous stirring via a dual syringe pump over a period of 90 min. During the addition period, the reaction temperature was maintained at -5°C. The ^{31}P NMR analysis exhibited transformation to the corresponding dichloridite **2c** in 82% selectivity, a 14% drop in selectivity compared to Example 18.

20

Example 20: Synthesis of mixed phosphorochloridite **1d** and phosphorodichloridite **2b**. This example shows that a mixed chloridite derived from aromatic alcohols (ArOH) with little steric hindrance can be produced in high selectivity reaching a final chloridite concentration of 0.167 mol/l.

25

A solution of 60 ml of 1.0 molar PCl_3 in toluene and 0.6 ml 1.0 molar triethylamine in toluene were charged to a temperature-controlled 1000 ml baffled-flask equipped with an overhead stirrer. Under vigorous stirring, a solution of 59 ml 1.0 molar triethylamine in toluene and a solution of 59 ml 1.0 molar 2,4-xyleneol in toluene were added separately and concurrently

30

via two peristaltic pumps at 1.5 ml / min. During the addition period the reaction temperature was maintained at -10 °C. The ^{31}P NMR analysis exhibited clean transformation to the corresponding dichloridite **2b** in 96% selectivity. Then 59.0 ml of each 1.0 molar triethylamine solution in toluene and 1.0 molar o-ethylphenol solution in toluene were added separately and concurrently via two peristaltic pumps at 1.5 ml/min. The ^{31}P NMR analysis exhibited clean transformation to the corresponding mixed chloridite **1d** (δ 162.5) in 95 % overall selectivity.

10 Example 21: Synthesis of mixed phosphorochloridite **1d** and phosphorodichloridite **2c**. This example shows that a mixed chloridite derived from aromatic alcohols with little steric hindrance can be produced in high selectivity reaching a final chloridite concentration of 0.333 mol/l.

In a temperature controlled 1000 ml baffled flask equipped with an overhead stirrer charged with 200mL of 1.0 molar PCl_3 in toluene and 2.0 ml 2.0 molar triethylamine in toluene, a solution of 98 ml 2.0 molar triethylamine in toluene and under vigorous stirring a solution of 98 ml 2.0 molar o-ethylphenol in toluene were added separately and concurrently via two peristaltic pumps at 2.0 ml/min. During the addition period the reaction temperature was maintained at -10 °C. The ^{31}P NMR analysis showed clean transformation to the corresponding dichloridite **2c** in 95% selectivity. Then 98 ml of each 2.0 molar triethylamine solution in toluene and 2.0 molar 2,4-xylenol solution in toluene were added separately and concurrently via two peristaltic pumps at 2 ml/min. The ^{31}P NMR analysis exhibited clean transformation to the corresponding mixed chloridite **1d** in 96% overall selectivity.

Example 22: Synthesis of a mixed phosphorochloridite **1g** and phosphorodichloridite **2d**. This example shows that a mixed chloridite derived from aromatic alcohols with little steric hindrance can be produced in high selectivity reaching a final chloridite concentration of 0.333 mol/l.

A temperature controlled 1000 ml baffled glass reactor with overhead stirrer was charged with 200 ml of 1.0 molar PCl_3 in toluene and

2 ml 2.0 molar triethylamine in toluene. Under vigorous stirring a solution of 100 ml of 2.0 molar triethylamine in toluene and 100 ml of 2.0 molar thymol in toluene were added separately and concurrently via two peristaltic pumps over a period of 50 min. During the addition period, the reaction temperature was maintained at -10 °C. The ^{31}P NMR analysis showed clean transformation to the corresponding dichloridite **2d** (δ 181.2) in 95% selectivity. Then 100 ml of each 2.0 molar triethylamine solution in toluene and 100 ml 2.0 molar 2,4-xyleneol solution in toluene were added separately and concurrently via a dual syringe pump over a period of 50 min. The ^{31}P NMR analysis showed clean transformation to the corresponding chloridite **1g** (δ 159.9) in 96% overall selectivity.

Example 23: Synthesis of phosphorochloridite **1e** and phosphorodichloridite **2e**. This example shows that aliphatic phosphorochloridites and phosphorodichloridites can be produced in good selectivity.

A temperature controlled 300 ml baffled round bottom flask was charged with a solution of 25 ml 2.0 molar PCl_3 in toluene. Under vigorous stirring a solution of 25 ml 2.0 molar triethylamine in toluene and a solution of 25 ml 2.0 molar ethyl alcohol in toluene were added separately and concurrently via a dual syringe pump over a period of 100 min. During the addition period the reaction temperature was maintained at -10 °C. The ^{31}P NMR analysis exhibited transformation to the corresponding dichloridite **2e** in 94% selectivity. Another 25 ml of each 2.0 molar triethylamine solution in toluene and 2.0 molar ethyl alcohol solution in toluene were added separately and concurrently via dual syringe pump over a period of 100 min. The ^{31}P NMR analysis exhibited transformation to the corresponding chloridite **1e** in 70% overall selectivity. Another 4.7 ml of each 2.0 molar triethylamine solution in toluene and 2.0 molar ethyl alcohol solution in toluene were added separately and concurrently via a dual syringe pump. The final product distribution was 82% phosphorochloridite **1e** and 18% triethylphosphite. No ethyl chloride was formed.

Example 24: Synthesis of a phosphorochloridite **1f** and phosphorodichloridite **2f**. This example shows that a phosphorochloridite and phosphorodichloridite derived from a phenol without ortho-substituent
5 can be produced in good selectivity.

A temperature controlled 300 ml baffled round bottom flask was charged with 25 ml of 2.0 molar PCl_3 in toluene. Under vigorous stirring a solution of 25 ml 2.0 molar triethylamine in toluene and a solution of 25 ml 2.0 molar phenol in toluene were added separately and concurrently via a
10 dual syringe pump over a period of 100 min. During the addition period the reaction temperature was maintained at -10°C . The ^{31}P NMR analysis exhibited transformation to the dichloridite **2f** in 92% selectivity. A second addition of 25 ml of each 2.0 molar triethylamine solution in toluene and 2.0 molar phenol solution in toluene were added separately and
15 concurrently via a dual syringe pump over a period of 100 min.. The ^{31}P NMR analysis exhibited transformation to the corresponding chloridite **1f** in 80 % overall selectivity.

Examples 25-40: Synthesis of mixed phosphites. These examples show
20 the selective synthesis of mixed aromatic and aliphatic phosphites from phosphorochloridites **1a**, **1c**, **1d** and **1e** synthesized as described in examples 1, 18, 21 and 23.

To a 1 g aliquot of the corresponding crude phosphorochloridite and triethylammonium chloride suspension in toluene as prepared in Examples
25 1, 18, 21 and 23, about 1.2 equiv. of 2.0 molar NEt_3 in toluene was added. The mixture was stirred at 5°C and 1.0 equiv. of the respective alcohol or 0.5 equiv. of the respective diol was added. Of this product suspension, 0.4 ml of the reaction volume were combined with 0.8 ml of 0.1 molar triphenylphosphine oxide in C_6D_6 and the mixture was analyzed by ^{31}P
30 NMR. Results are given in Table 5. All NMR chemical shifts are given in ppm in reference to triphenylphosphineoxide (δ 25.6).

Table 5: Yields for the synthesis of mixed phosphites**(R¹O)(R²O)(R³O)P and (R¹O)(R²O)₂P:**Results are derived from ³¹P NMR analysis and given as the molar

5 equivalent fraction of each of the components in the reaction mixture.

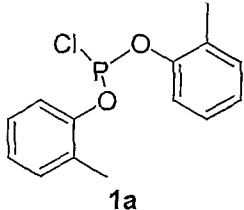
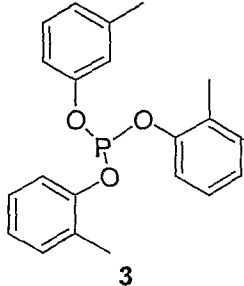
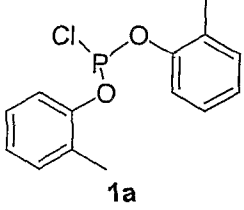
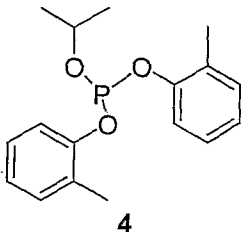
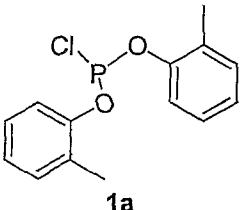
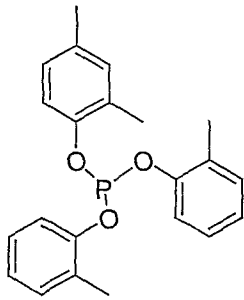
Examp le	chloridite purity		overall yield
	chloridite	alcohol	target phosphite
	³¹ P NMR δ		³¹ P NMR δ
25	94%		94%
	 1a	m-Cresol	 3
	161.9		128.6
26	94%		94%
	 1a	iso-Propanol	 4
	161.9		131.2
27	94%		94%
	 1a	2,4-Xylenol	 5
	161.9		131.1

Table 5 cont.

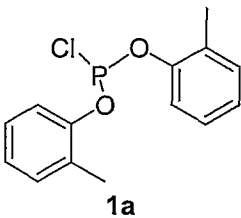
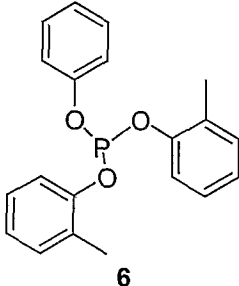
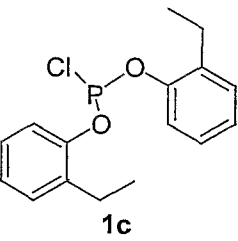
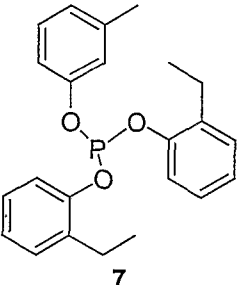
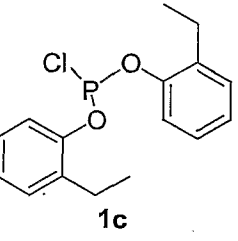
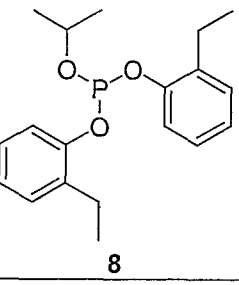
Exempl e	chloridite purity		Overall yield
	chloridite	alcohol	target phosphite
	^{31}P NMR δ		^{31}P NMR δ
28	94%	Phenol	94%
	 1a		 6
	161.9		131.5
29	92%	m-Cresol	92%
	 1c		 7
	161.5		127.8
30	92%	iso-Propanol	92%
	 1c		 8
	161.5		130.9

Table 5 cont.

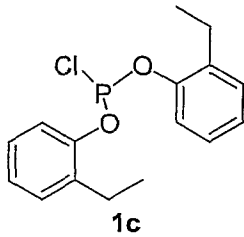
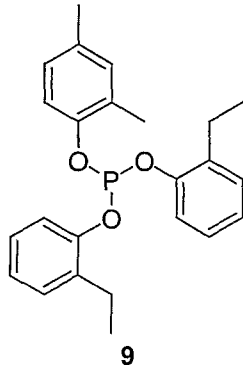
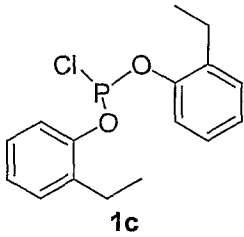
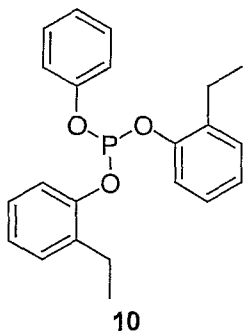
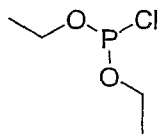
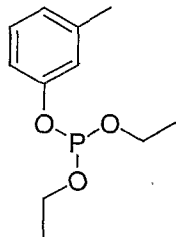
Example	chloridite purity		overall yield
	chloridite	alcohol	target phosphite
	^{31}P NMR δ		^{31}P NMR δ
31	92%	2,4-Xylenol	92%
	 1c		 9
	161.5		129.3
32	92%	Phenol	92%
	 1c		 10
	161.5		127.3
33	82%	m-Cresol	82%
	 1e		 11
	167.4		134.0

Table 5 cont.

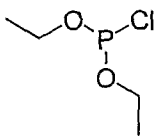
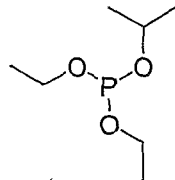
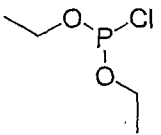
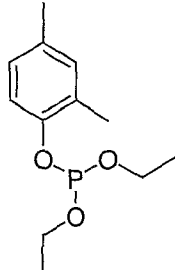
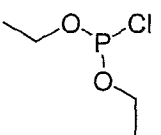
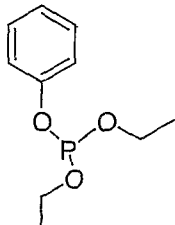
Example	chloridite purity		overall yield
	chloridite	alcohol	target phosphite
	³¹ P NMR δ		³¹ P NMR δ
34	82%		82%
	 1e	iso-Propanol	 12
	167.4		139.3
35	82%		82%
	 1e	2,4-Xylenol	 13
	167.4		134.3
36	82%		82%
	 1e	Phenol	 14
	167.4		133.9

Table 5 cont.

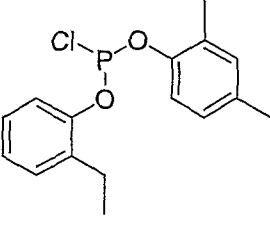
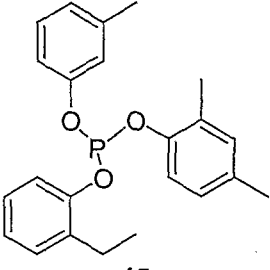
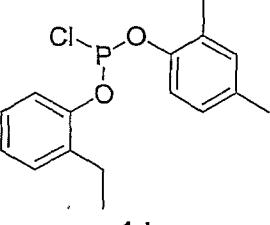
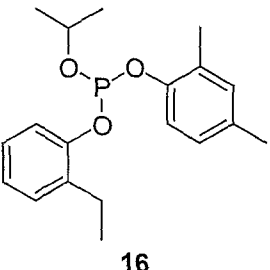
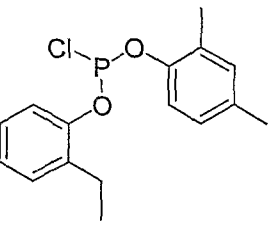
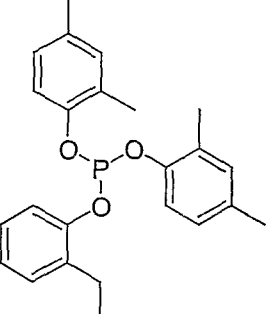
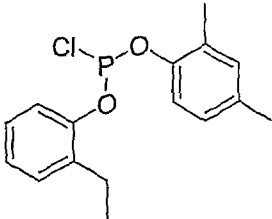
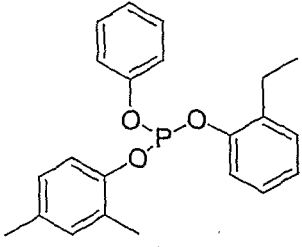
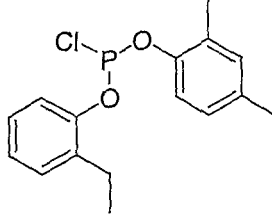
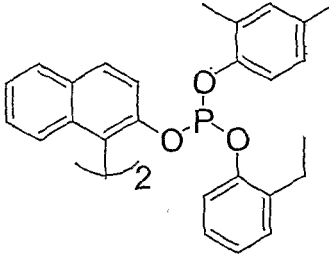
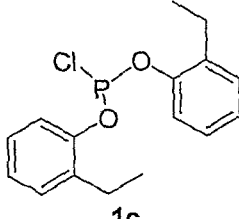
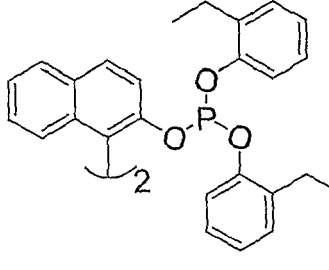
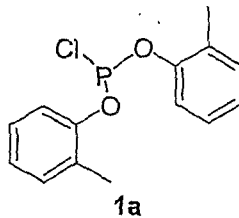
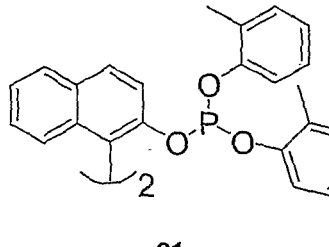
Example	chloridite purity		overall yield
	chloridite	alcohol	target phosphite
	^{31}P NMR δ		^{31}P NMR δ
37	94%		94%
	 1d	m-Cresol	 15
	162.5		130.0
38	94%		94%
	 1d	iso-Propanol	 16
	162.5		131.4
39	94%		94%
	 1d	2,4-Xylenol	 17
	162.5		131.6

Table 5 cont.

Example	chloridite purity		overall yield
	chloridite	alcohol	target phosphite
	^{31}P NMR δ		^{31}P NMR δ
40	94%		94%
	 1d	Phenol	 18
	162.5		131.1
41	94%		90%
	 1d	Bisnaphthol	 19
	162.5		130.0
42	92%		88%
	 1c	Bisnaphthol	 20
	161.5		129.6
43	94%		90%
	 1a	Bisnaphthol	 21
	161.9		129.0

COMPARATIVE EXAMPLES

Comparative Example A: Synthesis of phosphorochloridite **1a** and phosphorodichloridite **2a** under conditions where a mixture of triorganoamine and alcohol was added to PCl_3 at 0.67 mol equiv / hr.

- 5 A temperature controlled 250 ml baffled flask was charged with 50 ml of 1.0 molar PCl_3 in toluene. Under vigorous stirring, a mixture of 25 ml 2.0 molar triethylamine in toluene and 25 ml 2.0 molar o-cresol in toluene was added via a single syringe pump over a period of 90 min. During the addition period the reaction temperature was maintained at -5°C . The ^{31}P
- 10 NMR analysis showed transformation to the corresponding dichloridite **2a** in only 16% selectivity. The distribution was PCl_3 56 %; dichloridite 7 %; chloridite 9 %; triarylphosphite 28%. Another mixture of 25 ml 2.0 molar triethylamine in toluene and 25 ml 2.0 molar o-cresol in toluene was added under vigorous stirring via a single syringe pump over a period of 90 min.
- 15 During the addition period the reaction temperature was maintained at -5°C . The ^{31}P NMR analysis showed transformation to the corresponding chloridite **1a** in only 14 % overall selectivity. The distribution was PCl_3 21 %; dichloridite 7 %; chloridite 14 %; triarylphosphite 58 %.

- 20 Comparative Example B: Synthesis of a phosphorochloridite **1a** and phosphorodichloridite **2a** under conditions where a mixture of triorganoamine and alcohol was added to PCl_3 at 0.3 mol equiv. / hr.

- A temperature controlled 300 ml baffled round bottom flask was charged with 25 ml of 2.0 molar PCl_3 in toluene. Under vigorous stirring a
- 25 mixture of 25 ml 2.0 molar triethylamine in toluene and 25 ml 2.0 molar o-cresol in toluene was added via a single syringe pump over a period of 200 min. During the addition period the reaction temperature was maintained at -5°C . The ^{31}P NMR analysis showed transformation to the corresponding dichloridite **2a** in only 14% selectivity. The distribution was
- 30 PCl_3 57 %; dichloridite 6 %; chloridite 10 %; and triarylphosphite 28 %.
- Another mixture of 25 ml 2.0 molar triethylamine in toluene and 25 ml 2.0 molar o-cresol in toluene was added under vigorous stirring via a single syringe pump over a period of 200 min. During the addition the reaction

temperature was maintained at -5 °C. The ^{31}P NMR analysis showed transformation to the corresponding chloridite **1a** in only 17 % overall selectivity. The distribution was PCl_3 18 %; dichloridite 9 %; chloridite 17 %; and triarylphosphite 56 %.

5

Comparative Example C: Synthesis of phosphorochloridite **1a** and phosphorodichloridite **2a** under conditions where two mol equivalents of the triorganoamine were added to a mixture of one equivalent of PCl_3 and two equivalents of alcohol.

10

A temperature controlled 300 ml baffled round bottom flask was charged with a mixture of 50 ml of 1.0 molar PCl_3 and 50 ml of 2.0 molar o-cresol both in toluene. A solution of 25 ml 2.0 molar triethylamine in toluene was added under vigorous stirring via a single syringe pump over a period of 100 min. During the addition period the reaction temperature

15

was maintained at -5°C. The ^{31}P NMR analysis showed transformation to the corresponding dichloridite **2a** in only 51% selectivity. The distribution was PCl_3 10 %; dichloridite 46 %; chloridite 29 %; triarylphosphite 15%. Another 25 ml of 2.0 molar triethylamine in toluene was added under vigorous stirring via a single syringe pump over a period of 100 min.

20

During the addition period the reaction temperature was maintained -5 °C. The ^{31}P NMR analysis showed transformation to the corresponding chloridite **1a** in only 68 % overall selectivity. The distribution was dichloridite 14 %, chloridite 68 %, and triarylphosphite 18 %.

Table 6: Comparison of yields for 1a and 2a for concurrent but separate addition procedure as given in example 2 with other procedures as given in Comparative Examples A-C.

Example	Temp (°C)	Mol equiv. ArOH and NEt ₃ added	% 1a	% 2a	% PCl ₃	% (o-tolyl-O) ₃ P
2	-5	1.0	3	97	0	0
		2.0	91	4	0	5
A	-5	1.0	9	7	56	28
		2.0	14	7	21	58
B	-5	1.0	10	6	57	27
		2.0	17	9	18	56
C	-5	1.0	29	46	10	15
		2.0	68	14	0	18

- 5 Comparative Examples D to G show the effect of the premix ratio of NEt₃ to ArOH in continuously but separately added components A and B on the selectivity of the conversion to phosphorochloridite **1a** and phosphorodichloridite **2a**. Distribution (Dis) represents the molar equivalent fraction of each of the components in the reaction mixture
- 10 phosphorochloridite **1a**, phosphorodichloridite **2a**, PCl₃ and triarylphosphite ((o-tolyl-O)₃P) given in percent. The selectivity to **2a** is calculated as $\text{Sel}_{(2a)} = \text{Dis}_{(2a)} / (\text{Dis}_{(2a)} + \text{Dis}_{(1a)} + \text{Dis}_{(\text{triarylphosphite})})$. The total selectivity to **1a** is calculated as $\text{Sel}_{(1a)} = \text{Dis}_{(1a)} / (\text{Dis}_{(1a)} + \text{Dis}_{(2a)} + \text{Dis}_{(\text{triarylphosphite})})$.

15

Comparative Example D

- A temperature controlled 500 ml baffled jacketed glass reactor with overhead stirrer was charged with 200 ml of 1.0 molar PCl₃ in toluene. A first solution (A) was prepared by mixing 0.2 mol of triethylamine and 0.2
- 20 mol of o-cresol and diluting that mixture with toluene to a total volume of 200 ml. A second solution (B) was prepared by mixing 0.2 mol of o-cresol and 0.2 mol of triethylamine and diluting that mixture with toluene to a total volume of 200 ml. Subsequently 100 ml of solution A and 100 ml of solution B were added separately and concurrently under vigorous stirring

via a peristaltic pump over a period of 45 min. During the addition period the reaction temperature was maintained at 5 ° C. The ^{31}P NMR analysis showed transformation to the corresponding dichloridite **2a** in 13% selectivity. The distribution was PCl_3 56 %; dichloridite **2a** 9 %; chloridite **1a** 10 %; triarylphosphite 20%. Subsequently a second 100 ml of solution A and 100 ml of solution B were added separately and concurrently under vigorous stirring via a peristaltic pump over a period of 45 min. The ^{31}P NMR analysis showed transformation to the corresponding chloridite **1a** in 19 % overall selectivity. The distribution was PCl_3 18 %; dichloridite **2a** 11 %; chloridite **1a** 16 %; triarylphosphite 55 %.

Comparative Example E

A temperature controlled 500 ml baffled jacketed glass reactor with overhead stirrer was charged with 200 ml of 1.0 molar PCl_3 in toluene. A first solution (A) was prepared by mixing 0.32 mol of triethylamine and 0.08 mol of o-cresol and diluting that mixture with toluene to a total volume of 200 ml. A second solution (B) was prepared by mixing 0.32 mol of o-cresol and 0.08 mol of triethylamine and diluting that mixture with toluene to a total volume of 200 ml. Subsequently 100 ml of solution A and 100 ml of solution B were added separately and concurrently under vigorous stirring via a peristaltic pump over a period of 45 min. During the addition period the reaction temperature was maintained at 5 ° C. The ^{31}P NMR analysis showed transformation to the corresponding dichloridite **2a** in 74% selectivity. The distribution was PCl_3 23 %; dichloridite **2a** 57 %; chloridite **1a** 10 %; triarylphosphite 10 %. Subsequently a second 100 ml of solution A and 100 ml of solution B were added separately and concurrently under vigorous stirring via a peristaltic pump over a period of 45 min. The ^{31}P NMR analysis showed transformation to the corresponding chloridite **1a** in 52 % overall selectivity. The distribution was dichloridite **2a** 21 %; chloridite **1a** 52 %; triarylphosphite 27 %.

Comparative Example F

A temperature controlled 500 ml baffled jacketed glass reactor with overhead stirrer was charged with 200 ml of 1.0 molar PCl_3 in toluene. A

first solution (A) was prepared by mixing 0.36 mol of triethylamine and 0.04 mol of o-cresol and diluting that mixture with toluene to a total volume of 200 ml. A second solution (B) was prepared by mixing 0.36 mol of o-cresol and 0.04 mol of triethylamine and diluting that mixture with toluene to a total volume of 200 ml. Subsequently 100 ml of solution A and 100 ml of solution B were added separately and concurrently under vigorous stirring via a peristaltic pump over a period of 45 min. During the addition period the reaction temperature was maintained at 5 ° C. The ^{31}P NMR analysis showed transformation to the corresponding dichloridite **2a** in 88% selectivity. The distribution was PCl_3 12 %; dichloridite **2a** 77 %; chloridite **1a** 8 %; triarylphosphite 3 %. Subsequently a second 100 ml of solution A and 100 ml of solution B were added separately and concurrently under vigorous stirring via a peristaltic pump over a period of 45 min. The ^{31}P NMR analysis showed transformation to the corresponding chloridite **1a** in 79 % overall selectivity. The distribution was dichloridite **2a** 9 %; chloridite **1a** 79 %; triarylphosphite 13 %.

Comparative Example G

A temperature controlled 500 ml baffled jacketed glass reactor with overhead stirrer was charged with 200 ml of 1.0 molar PCl_3 in toluene. A first solution (A) was prepared by mixing 0.4 mol of triethylamine with toluene to a total volume of 200 ml. A second solution (B) was prepared by mixing 0.4 mol of o-cresol with toluene to a total volume of 200 ml. Subsequently 100 ml of solution A and 100 ml of solution B were added separately and concurrently under vigorous stirring via a peristaltic pump over a period of 45 min. During the addition period the reaction temperature was maintained at 5 ° C. The ^{31}P NMR analysis showed transformation to the corresponding dichloridite **2a** in 97% selectivity. The distribution was PCl_3 4 %; dichloridite **2a** 93 %; chloridite **1a** 3 %; triarylphosphite 0 %. Subsequently a second 100 ml of solution A and 100 ml of solution B were added separately and concurrently under vigorous stirring via a peristaltic pump over a period of 45 min. The ^{31}P NMR analysis showed transformation to the corresponding chloridite **1a** in 92 %

overall selectivity. The distribution was dichloridite **2a** 4 %; chloridite **1a** 92 %; triarylphosphite 4 %.

Table 7: Comparison of Selectivity (Sel) and yields for 1a and 2a for the concurrent but separate addition procedure depending on the premix ratio of NEt₃ to ArOH in continuously but separately added components A and B as given in examples D-G.

Example	T (°C)	Premix ratio of NEt ₃ to ArOH in components A and B	Mol equiv. ArOH and NEt ₃ added	% Sel	% 1a	% 2a	% PCl ₃	% (o-tolyl-O) ₃ P
D	5	1:1(A); 1:1(B)	1.0	13	10	9	56	20
			2.0	19	16	11	18	55
E	5	4:1(A); 1:4(B)	1.0	74	10	57	23	10
			2.0	52	52	21	0	27
F	5	9:1(A); 1:9(B)	1.0	88	8	77	12	3
			2.0	79	79	9	0	13
G	5	Pure components A (NEt ₃) and B (ArOH)	1.0	97	3	93	4	0
			2.0	92	92	4	0	4

- 10 Comparative Example H: Synthesis of phosphorochloridite **1e** and phosphorodichloridite **2e** under conditions where two mol equivalents of the triorganoamine were added to a mixture of one mol equivalent of PCl₃ and two mol equivalents of ethyl alcohol.

A temperature controlled 300 ml baffled round bottom flask was charged with a solution of 25 ml 2.0 molar PCl₃ in toluene and mixed with a -20 °C cold solution of 50 ml 2.0 molar ethyl alcohol in toluene. Under vigorous stirring a solution of 25 ml 2.0 molar triethylamine in toluene was added via a single syringe pump over a period of 100 min. During the addition period the reaction temperature was maintained at -10 °C. The ³¹P NMR analysis exhibited transformation to the corresponding dichloridite **2e** in only 48% selectivity. The distribution was dichloridite 48%, chloridite 24%, and 28% (EtO)₂PO(H) (δ 4.1) as a byproduct of ethyl

chloride formation. Another solution of 25 ml 2.0 molar triethylamine in toluene was added via a single syringe pump over a period of 100 min. During the addition period the reaction temperature was maintained at -10°C. The ^{31}P NMR analysis exhibited a transformation to the
5 corresponding chloridite **1e** in 25 % overall selectivity. The distribution was dichloridite 46%, chloridite 25 %, and 29 % $(\text{EtO})_2\text{PO}(\text{H})$ as a byproduct of ethyl chloride formation.

Comparative Example I: Synthesis of phosphorochloridite **1e** and
10 phosphorodichloridite **2e** under conditions where a mixture of two mol equivalents each of triorganoamine and alcohol were added to one equivalent of PCl_3

A temperature controlled 300 ml baffled round bottom flask was charged with 25 ml of 2.0 molar PCl_3 in toluene. Under vigorous stirring a
15 mixture of 25 ml 2.0 molar triethylamine in toluene and 25 ml 2.0 molar ethyl alcohol in toluene was added via a single syringe pump over a period of 200 min. During the addition period the reaction temperature was maintained at -10 °C. The ^{31}P NMR analysis exhibited transformation to the corresponding dichloridite **2e** in 26 % selectivity. The distribution was
20 PCl_3 61 %, dichloridite 10%, chloridite 13 % and triethylphosphite 16%. A second mixture of 25 ml both 2.0 molar triethylamine in toluene and 2.0 molar ethyl alcohol in toluene were added under vigorous stirring via a single syringe pump over a period of 200 min. During the addition period the reaction temperature was maintained at -10°C. The ^{31}P NMR analysis
25 exhibited transformation to the corresponding chloridite **1e** in 31% overall selectivity. The distribution was PCl_3 18%, dichloridite 15%, chloridite 31% and triethylphosphite 35%.

TABLE 8: Comparison of yields for 1e and 2e through a concurrent but separate addition procedure as given in Example 23 with other procedures as given in Comparative Examples H and I.

Example	Temp (°C)	Equivalents ArOH and NEt ₃ added	%1a	% 2a	% PCl ₃	% (EtO) ₂ PO(H)	% (EtO) ₃ P
23	-10	1.0	4	79	14	0	3
		2.0	70	19	0	0	11
		2.18	82	0	0	0	18
H	-10	1.0	24	48	0	28	0
		2.0	25	46	0	29	0
I	-10	1.0	13	10	61	0	16
		2.0	31	15	18	0	35

CLAIMS

What is claimed is:

1. A method for making a composition comprising a compound of the formula $(R^1O)PX_2$, wherein X is selected from the group consisting of Cl, Br, and I, R^1 is a C_1 to C_{18} alkyl, a C_6 to C_{18} aryl radical, or a C_3 to C_{18} cycloalkyl radical, wherein said method comprises: contacting a first solution comprising a predetermined amount of PX_3 dissolved in an aprotic solvent with (i) a second solution comprising a predetermined amount of an alcohol R^1OH , and a predetermined amount of a triorganoamine $(R')(R'')(R''')N$, wherein R' , R'' and R''' are independently selected from the group consisting of C_1 to C_{18} alkyl, C_6 to C_{18} aryl and C_4 to C_{18} heteroaryl radicals, and wherein the molar ratio of the alcohol to the triorganoamine is greater than 5, and (ii) a third solution comprising a predetermined amount of the triorganoamine and a predetermined amount of the alcohol, wherein the molar ratio of the triorganoamine to the alcohol is greater than 5, and wherein in said method the second and third solutions are added to the first solution separately by either
 - (a) adding each of the second and third solutions concurrently and continuously into the first solution at a rate of no greater than 4 molar equivalents of each of the alcohol and triorganoamine, relative to the PX_3 , per hour until the predetermined amounts of each of the alcohol and triorganoamine have been added to the first solution, provided that at any given time, the total molar amount of alcohol added does not exceed the total molar amount of triorganoamine added by more than 25% of the total molar amount of the triorganoamine added; or
 - (b) adding each of the second and third solutions concurrently and discontinuously into the first solution at a rate of no greater than 4 molar equivalents of each of the alcohol and triorganoamine, relative to the PX_3 , per hour in aliquots of the second solution containing no more than 0.5 molar equivalents of alcohol and in aliquots of the third solution containing no more than 0.5 equivalents of triorganoamine, until the predetermined amounts of each of the alcohol and triorganoamine have been added to the first solution; or

(c) adding each of the second and third solutions discontinuously into the first solution at a rate of no greater than 4 molar equivalents of each of the alcohol and triorganoamine, relative to the PX_3 , per hour in aliquots of the second solution containing no more than 0.5 molar equivalents of alcohol and in aliquots of the third solution containing no more than 0.5 equivalents of triorganoamine, until the predetermined amounts of each of the alcohol and triorganoamine have been added to the first solution by repetitively adding an aliquot of either the triorganoamine followed sequentially by an aliquot of the alcohol, or an aliquot of the alcohol followed by an aliquot of the triorganoamine, until the predetermined amounts of each of the alcohol and triorganoamine have been added to the first solution;

to produce the composition comprising the compound of the formula R^1OPX_2 , provided that in either of the alternatives (b) or (c), for any given additions, whether concurrent or sequential, within a series of discontinuous additions, the molar difference between the triorganoamine added and the alcohol added does not exceed 0.5 equivalent, relative to the PX_3 .

2. The method of Claim 1 wherein the molar ratio of alcohol to triorganoamine in the second solution is infinite.

3. The method of Claim 1 wherein the molar ratio of triorganoamine to alcohol in the third solution is infinite.

4. The method of Claim 1 wherein the molar ratio of alcohol to triorganoamine in the second solution is infinite and the molar ratio of triorganoamine to alcohol in the third solution is infinite.

5. The method of Claim 4 wherein the molar ratio of the total triorganoamine added to the total alcohol added from the inception of the method until the end of the additions is between 1 and 1.1, and the molar ratio of the predetermined amount of PX_3 to the total amount of alcohol added is between 0.8 and 1.2.

6. The method of Claim 5 wherein in alternatives (a) and (b) the molar amount of alcohol added at any given time does not exceed the molar amount of triorganoamine added at that time, thereby providing to the reaction a non-acidic environment at all times.

7. The method of Claim 5 wherein in alternative (c) an aliquot of the triorganoamine is added first, followed by an aliquot of the alcohol.

8. The method of Claim 5 wherein the triorganoamine is a trialkylamine or a substituted or unsubstituted heteroaromatic amine.

5 9. The method of Claim 8 wherein the trialkylamine is selected from the group consisting of trimethylamine, dimethylethylamine, diethylmethylamine, triethylamine, dimethylpropylamine, and dimethylisopropylamine.

10 10. The method of Claim 9 wherein the trialkylamine is triethylamine.

11. A method for making a composition comprising a compound of the formula $(R^1O)(R^2O)PX$, wherein X is selected from the group consisting of Cl, Br, and I, R^1 and R^2 are independently selected from the group consisting of C_1 to C_{18} alkyl, C_6 to C_{18} aryl, and C_3 to C_{18} cycloalkyl
15 radicals, wherein said method comprises: contacting a first solution comprising a predetermined amount of R^1OPX_2 dissolved in an aprotic solvent with (i) a second solution comprising a predetermined amount of an alcohol R^2OH , and a predetermined amount of a triorganoamine $(R')(R'')(R''')N$, wherein R' , R'' and R''' are independently selected from the
20 group consisting of C_1 to C_{18} alkyl, C_6 to C_{18} aryl and C_4 to C_{18} heteroaryl radical, and wherein the molar ratio of the alcohol to the triorganoamine is greater than 5, and (ii) a third solution comprising a predetermined amount of the triorganoamine and a predetermined amount of the alcohol, wherein the molar ratio of the triorganoamine to the alcohol is greater than 5, and
25 wherein in said method the second and third solutions are added to the first solution separately by either

(a) adding each of the second and third solutions concurrently and continuously into the first solution at a rate of no greater than 4 molar equivalents of each of the alcohol and triorganoamine relative to the
30 $(R^1O)PX_2$, per hour until the predetermined amounts of each of the alcohol and triorganoamine have been added to the first solution, provided that at any given time, the total molar amount of alcohol added does not exceed the total molar amount of triorganoamine added by more than 25% of the total molar amount of the triorganoamine added; or

(b) adding each of the second and third solutions concurrently and discontinuously into the first solution at a rate of no greater than 4 molar equivalents of each of the alcohol and triorganoamine, relative to the $(R^1O)PX_2$, per hour in aliquots of the second solution containing no more than 0.5 molar equivalents of alcohol and in aliquots of the third solution containing no more than 0.5 equivalents of triorganoamine, until the predetermined amounts of each of the alcohol and triorganoamine have been added to the first solution; or

(c) adding each of the second and third solutions discontinuously into the first solution at a rate of no greater than 4 molar equivalents of each of the alcohol and triorganoamine, relative to the $(R^1O)PX_2$, per hour in aliquots of the second solution containing no more than 0.5 molar equivalents of alcohol and in aliquots of the third solution containing no more than 0.5 equivalents of triorganoamine, until the predetermined amounts of each of the alcohol and triorganoamine have been added to the first solution by repetitively adding an aliquot of either the triorganoamine followed sequentially by an aliquot of the alcohol, or an aliquot of the alcohol followed by an aliquot of the triorganoamine, until the predetermined amounts of each of the alcohol and triorganoamine have been added to the first solution;

to produce the composition comprising the compound of the formula $(R^1O)(R^2O)PX$, provided that in either of the alternatives (b) or (c), for any given additions, whether concurrent or sequential, within a series of discontinuous additions, the molar difference between the triorganoamine added and the alcohol added does not exceed 0.5 equivalent, relative to the R^1OPX_2 .

12. The method of Claim 11 wherein the molar ratio of alcohol to triorganoamine in the second solution is infinite.

13. The method of Claim 11 wherein the molar ratio of triorganoamine to alcohol in the third solution is infinite.

14. The method of Claim 11 wherein the molar ratio of alcohol to triorganoamine in the second solution is infinite and the molar ratio of triorganoamine to alcohol in the third solution is infinite.

15. The method of Claim 14 wherein the molar ratio of the total triorganoamine added to the total alcohol added from the inception of the method until the end of the additions is between 1 and 1.1, and the molar ratio of the predetermined amount of R^1OPX_2 to the total amount of alcohol added is between 0.8 and 1.2.

16. The method of Claim 15 wherein in alternatives (a) and (b) the molar amount of alcohol added at any given time does not exceed the molar amount of triorganoamine added at that time, thereby providing to the reaction a non-acidic environment at all times.

17. The method of Claim 15 wherein in alternative (c) an aliquot of the triorganoamine is added first, followed by an aliquot of the alcohol.

18. The method of Claim 15 wherein the triorganoamine is a trialkylamine or a substituted or unsubstituted heteroaromatic amine.

19. The method of Claim 18 wherein the trialkylamine is selected from the group consisting of trimethylamine, dimethylethylamine, diethylmethylamine, triethylamine, dimethylpropylamine, and dimethylisopropylamine.

20. The method of Claim 19 wherein the trialkylamine is triethylamine.

21. The method of Claim 11 further comprising contacting a predetermined amount of the composition comprising the compound of the formula $(R^1O)(R^2O)PX$ with (i) a fourth solution comprising a predetermined amount of an alcohol R^3OH , wherein R^1 , R^2 and R^3 are selected from the group consisting of C_1 to C_{18} alkyl, C_6 to C_{18} aryl, and C_3 to C_{18} cycloalkyl radicals, and (ii) a fifth solution comprising a predetermined amount of the triorganoamine, to produce a composition comprising the compound of the formula $(R^1O)(R^2O)P(OR^3)$.

22. The method of Claim 21 wherein R^3 is the same as R^2 .

23. The method of Claim 22 wherein R^2 is the same as R^1 .