Lewis Acid or Alkyl Halide Promoted Rearrangements of Phosphor- and Phosphinimidates to N,N-Disubstituted Phosphor- and Phosphinamidates

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Abstract: In this paper, we describe the synthesis of N,N-disubstituted phosphor- and phosphinamidates via alkyl halide or Lewis acid catalyzed rearrangements of phosphor- or phosphinimidates. Furthermore, we introduce a novel one-pot procedure for the synthesis of N,N-disubstituted phosphoramidates which prevents the isolation of potentially explosive alkyl azide derivatives. In this reaction sequence, several alkyl halides are converted in situ into the corresponding azides and reacted with phosphites to generate phosphorimidates. Final addition of a catalytic amount of Lewis acid to the mixture affords the N,N-disubstituted phosphoramidates in good to excellent overall yields.

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Key words: Staudinger reaction, phosphorimidate rearrangement, phosphoramidates, phosphinamidate, one-pot procedure, Lewis acid catalysis

1 Introduction

Organic molecules containing a P(=O)–N bond are attractive targets in organic chemistry since they have found widespread use in several areas of modern organic chemistry, including applications in catalytic transformations as well as chemical biology. Phosphoric acid derivatives, in particular, have been used in the area of asymmetric catalysis and they are attracting increasing interest as Brønsted acid or base catalysts and substantial progress has been made concerning their catalytic ability.[1] In the domain of medicinal chemistry, phosphonamidates have been used as surrogates for amide bonds in the synthesis of pharmaceutically active peptide-based protease inhibitors, since the P(=O)–NH moiety mimics the tetrahedral transition state during amide bond hydrolysis.[2] Similarly, phosphoramidates have been used as analogues of phosphate esters in nucleotides[3] or even in post-translationally modified proteins.[4]

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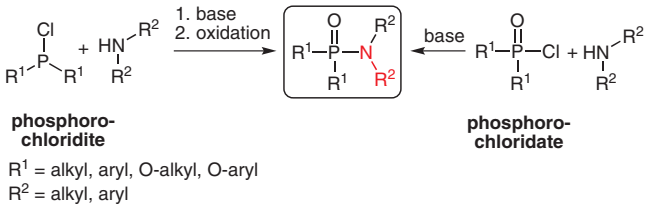
Traditionally, the synthesis of P(=O)–N containing phosphonamidates or phosphoramidates has found inspiration in the classical strategies for the formation of amide bonds, in which carboxylic acid derivatives are converted into activated esters before substitution with an amine nucleophile occurs. Similarly, electrophilic phosphorus or phosphonic acid derivatives, in particular in the form of the P(III) phosphorochloridites or P(V) phosphorochloridates, can react in a nucleophilic substitution reaction with amines, leading to the formation of a P–N bond.[5] In order to obtain phosphorus(V) phosphoramidates or phosphonamidates, the phosphorus(III) has to be oxidized afterwards (Scheme 1).[6]



Scheme 1 Traditional access to N,N-disubstituted phosphin-, phosphon-, and phosphoramidates

An alternative route for the formation of P–N compounds is offered by the Staudinger reaction between trivalent phosphorus species and azides.[7] Depending on the nature of the phosphorus counterpart, different phosphorus compounds became accessible (Scheme 2).[8] In a widely applied synthetic transformation, the so called Staudinger reduction, primary amines can be derived from azides via hydrolysis of iminophosphoranes, which are formed by Staudinger reaction of azides with phosphines.[7] During the hydrolysis, P–N bond cleavage occurs to form an amine and a phosphine oxide. The replacement of at least one of the alkyl or aryl substituents at the phosphorus by an alkoxy group, can result in a different reaction pathway causing formation of a P=O bond without corresponding cleavage of the P–N bond. Thereby, phosphin-, phosphon- or phosphoramidates become accessible and only acidic conditions result in P–N bond cleavage.[8]

To date the Staudinger reaction has been the subject of several hundreds of articles.[8,9] The interest in this reaction was additionally bolstered by the pioneering work of Bertozzi and co-workers, who have identified the chemoselective potential of the Staudinger reaction. Hence, they have engineered a bioorthogonal Staudinger ligation for the transformation of azides under physiolog-

ical conditions in complex biomolecules.[10] Recently, our group has used the Staudinger reaction of azides with phosphites[4] or silylated phosphinic acid esters or acids[2] for chemoselective transformations. In the latter protocols, phosphorimidates react with water and the nitrogen of the P=N bond is protonated to form a P(=O)–NH bond (Scheme 2).

In another synthetically useful reaction, phosphorimidates can be N-alkylated by reaction with electrophiles to give N,N-disubstituted phosphoramidates. These compounds can be regarded as protected secondary amines, which are valuable building blocks in organic synthesis and in some cases difficult to access.[11–14] In order to avoid the aforementioned hydrolytic formation of N-monosubstituted

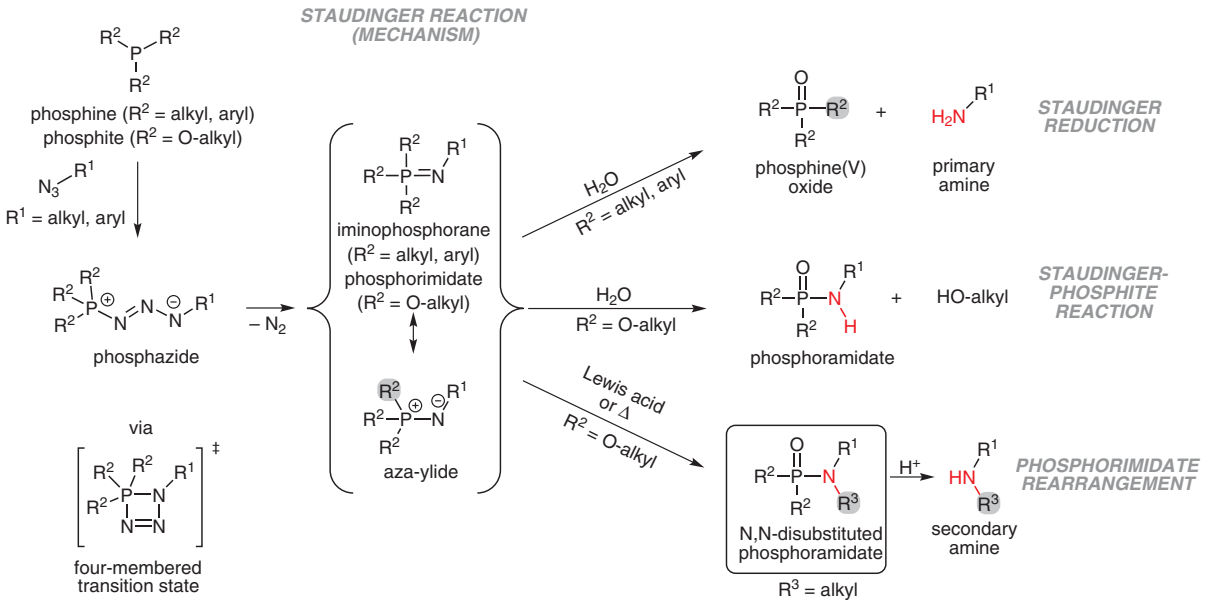
Biographical Sketches

Ina Wilkening studied chemistry at the Friedrich-Wilhelms Universität Bonn and received her diploma in 2006. After her diploma work in the group of Prof. Konrad Sandhoff under the supervision of Dr. Ute Schepers she moved to Berlin in 2007 to start her Ph.D. under the direction of Prof. Christian Hackenberger on the synthesis of P–N compounds by Staudinger reactions and their applications in peptide modifications at the Freie Universität Berlin.

Dr. Giuseppe Del Signore was born in Rome. He received his M.Sc. in 1999 from La Sapienza University of Rome and his Ph.D. in 2003 at the RWTH Aachen. Currently, he is a senior scientist in the organic and medicinal chemistry department at Mercachem S.V.

Dr. Wiebke Ahlbrecht obtained her diploma in chemistry from the Freie Universität Berlin in 2006. During her diploma thesis under the supervision of Prof. Christian Hackenberger she was involved in synthetic development of imide-amide rearrangement to yield phosphoramides. In 2010 she received her Ph.D. with Professor Dirk Menche at the University of Heidelberg on the total synthesis of natural products.

Prof. Dr. Christian P. R. Hackenberger studied chemistry in Freiburg and in Madison/Wisconsin (M.Sc. in 1999 with Samuel H. Gellman). In 2003 he completed his Ph.D. with Carsten Bolm at RWTH Aachen. After postdoctoral research with Barbara Imperiali (2003–2005) at MIT he moved to the Freie Universität Berlin, where he first led an Emmy Noether junior group from 2006–2010. In 2011 he was appointed as associate professor for bioorganic chemistry. He has received several research awards, most recently the Heinz Maier-Leibnitz Prize of the DFG, the ADUC prize of the GDCh, and the Karl Winnacker Dozentenstipendium of the FCI. The scientific research interests of the Hackenberger group focus on various areas in organic chemistry and chemical biology, including the methodological development of reactions, in particular chemoselective transformations, protein semi-synthesis, design of multivalent scaffolds, cyclic proteins, biosynthesis of sialic acids as well as the structural and functional analysis of protein modifications including signal transduction and protein aggregation.



Scheme 2 Mechanism of the Staudinger reaction and possible reaction pathways, including Staudinger reduction, Staudinger–phosphite reaction and rearrangements of phosphorimidates

phosphoramidates during the alkylation, strictly anhydrous conditions have to be ensured.[11] Challis and coworkers have pioneered a thermal rearrangement of phosphorimidates to phosphoramidates.[12] The rearrangement proceeds via an intermolecular mechanism, in which one imidate undergoes nucleophilic attack by the nitrogen of a second imidate molecule. Additionally, the groups of Mapp[13] and Batey[1i] have reported an intramolecular [3,3]-sigmatropic rearrangement of allylic phosphorimidates as a powerful tool for the synthesis of protected allylamines. Another possibility to enhance the formation of N,N-disubstituted phosphoramidates is the use of catalysts, which accelerate the phosphorimidate rearrangement, e.g. by addition of alkyl halides[14] or Lewis acids.[11,15]

In this article, we focus on the scope of alkyl halide and Lewis acid catalyzed rearrangements of different P=N-containing compounds, in particular phosphinimidates, which can be obtained by reaction of azides with phosphinites. Additionally, we report our efforts to establish a one-pot procedure for the formation of N,N-disubstituted phosphoramidates from simple alkyl halides, thereby avoiding the isolation of potentially explosive azides.

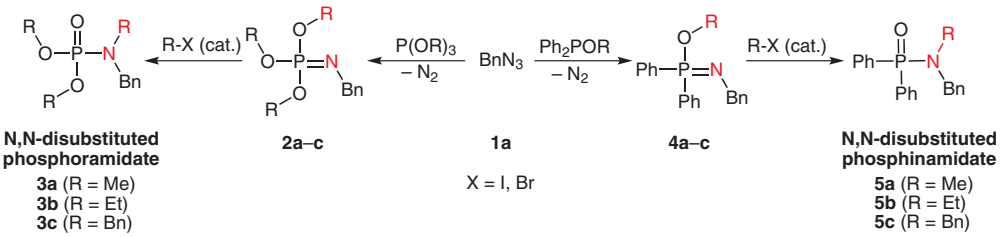
2 Synthesis of N,N-Disubstituted Phosphor- and Phosphinamidates

2.1 Alkyl Halide Catalyzed Rearrangement of Phosphin- and Phosphorimidates

Alkyl halide promoted rearrangements of phosphorimidates derived from the Staudinger reaction of azides with phosphites, are already known in the literature (Scheme 3).[14,16] In these transformations, phosphorimidates **2** require only low amounts of the alkyl halide species to deliver the N,N-disubstituted phosphoramidates **3** in high yields, as also verified by our own experience for the reaction of benzyl azide (**1a**) with different phosphites (Table 1, entries 1–3). Due to the efficiency of this transformation, we decided to extend this methodology to diaryl phosphinimidates **5a–c** obtained from Staudinger reaction of benzyl azide (**1a**) with phosphinites (Scheme 3, Table 1, entries 4–6). To the best of our knowledge, the rearrangement of phosphinimidates **4** using alkyl halide as catalysts has not been previously reported. Furthermore, phosphinites are rarely used in Staudinger reactions because they are very prone to oxidation or hydrolysis and have to be kept under an argon atmosphere. Three different diphenylphosphinites were selected as model compounds to study the rearrangement of phosphinimidates **4**. Whereas methyl and ethyl diphenylphosphinite are commercially available, benzyl diphenylphosphinite was prepared from chlorodiphenylphosphine and benzyl alcohol.[17] As shown in Table 1, in all cases the desired phosphinamidates **5a–c** were accessible in high yields under reaction conditions similar to the ones we used previously for the rearrangement of phosphorimidates **2a–c**. However, a higher amount of alkyl halides was required, in particular when less reactive benzyl diphenylphosphinite and ethyl diphenylphosphinite were used.

2.2 Lewis Acid Catalyzed Rearrangement of Phosphin- and Phosphorimidates

In a previous study, we used Lewis acids to induce the rearrangement of phosphorimidates **2** to obtain N,N-disubstituted phosphoramidates **3**.[11] We showed that the reaction proceeded well with a variety of azides, in particular when the reaction was performed with boron trifluoride–diethyl ether complex or trimethylsilyl triflate as the Lewis acid catalyst. Now, we have further tested the scope



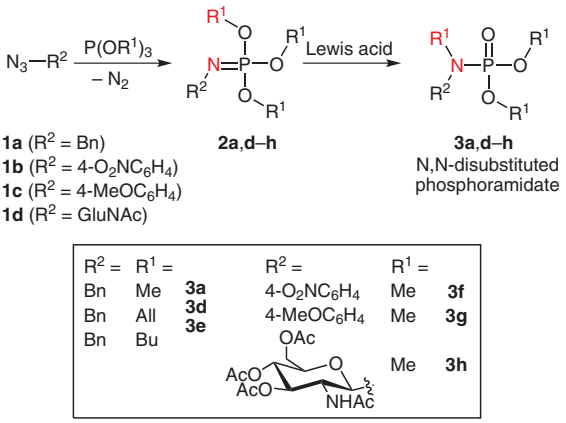
Scheme 3 Alkyl halide catalyzed rearrangement of phosphorimidates **2a–c** and phosphinimidates **4a–c**

Table 1 Staudinger Reaction and Alkyl Halide Catalyzed Rearrangement between Benzyl Azide and Different Phosphites and Phosphinites

Entry	Phosphite or phosphinite	Alkyl halide (mol%)	Conditions[a]	Solvent	Product	Yield (%)
1[b]	$P(OMe)_3$	MeI (5)	1. 80 °C, 2 h 2. 80 °C, 4 h	benzene	**3a**	90
2[b]	$P(OEt)_3$	EtI (20)	1. 110 °C, 2 h 2. 110 °C, 4 h	toluene	**3b**	70
3[b]	$P(OBn)_3$	BnBr (25)	1. 80 °C, 2 h 2. 80 °C, 8 h	benzene	**3c**	71
4[c]	Ph_2POMe	MeI (25)	1. r.t., 20 min 2. 80 °C, 4 h	benzene	**5a**	83
5[c]	Ph_2POEt	EtI (20)	1. r.t., 20 min 2. 110 °C, 8 h	toluene	**5b**	60
6[c]	Ph_2POBn	BnBr (25)	1. 80 °C, 2 h 2. 80 °C, 4 h	benzene	**5c**	76

[a] 1. Imidate formation. 2. Rearrangement by addition of catalytic amounts of alkyl halides.
[b] General procedure I.
[c] General procedure II.

and also possible limitations of this transformation (Scheme 4). Originally, the rearrangement was performed after formation of the phosphorimidate upon the addition of the Lewis acid at 80 °C. Here, we found that the product **3a** was also formed at room temperature with 1 mol% of catalyst added; however, longer reaction times were required (Table 2, entry 1). In addition to trimethyl and triethyl phosphite also tributyl or triallyl phosphite could be used in good overall yields to produce **3d** and **3e** with both Lewis acid catalysts (entries 2–4). We were also pleased to find that different functional groups on the azide were



Scheme 4 Lewis acid catalyzed rearrangement of phosphorimidates

well tolerated under the reaction conditions (entries 5–7), including esters in the synthesis of the GlcNAc-phosphoramidate **3h**. On the other hand, when longer alkyl chains were tested, as for the reaction of benzyl azide (**1a**) with trioleyl phosphite, the rearrangement turned out to be less efficient; an inseparable mixture of N,N-disubstituted and hydrolyzed compounds was obtained (data not shown).

Next, we probed the Lewis acid catalyzed rearrangement of phosphinimidates **4** (Scheme 5), which were obtained by Staudinger reaction of methyl diphenylphosphinite with benzyl azide (**1a**) or phenyl azide (**1e**). For both phosphinimidates **4a** and **4d**, the transfer of the methyl group proceeded very well and delivered phosphinamidates **5a** and **5d** in 87% and 75% yields, respectively (Table 3, entries 1 and 2). In contrast, the phosphinimidate **4b** and **4e**, derived from ethyl diphenylphosphinite and azides **1a** and **1e**, reacted very slowly and even higher amounts of catalysts delivered only moderate amounts of phosphinamidates **5b** and **5e** (entries 3 and 4).

Similarly, the rearrangement of phosphinimidates **4c** and **4f**, derived from Staudinger reaction with benzyl diphenylphosphinite turned out to be rather inefficient under the standard protocol (Table 3, entries 5–10). Screening of different aluminum- and boron-based Lewis acids did not afford any improvement (data not shown). Apolar solvents like toluene or xylene gave the highest but still mod-

Table 2 Lewis Acid Catalyzed Rearrangement of Phosphorimidates **2**[a]

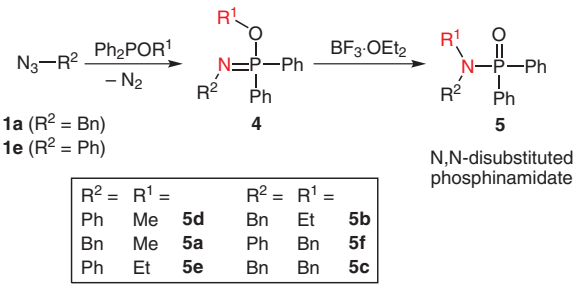
Entry	Azide	Phosphite[b]	$BF_3{\cdot}OEt_2$ (mol%)	Conditions[c]	Product	Yield (%)
1	BnN_3 **1a**	$P(OMe)_3$	1	1. 80 °C, 2 h 2. r.t., 16 h	**3a**	95
2	BnN_3 **1a**	$P(OAll)_3$	1	1. 80 °C, 2 h 2. 80 °C, 2 h	**3d**	71
3	BnN_3 **1a**	$P(OBu)_3$	1	1. 80 °C, 5 h 2. 80 °C, 5 h	**3e**	72
4	BnN_3 **1a**	$P(OBu)_3$	1[d]	1. 80 °C, 5 h 2. 80 °C, 5 h	**3e**	65
5	4-$O_2NC_6H_4N_3$ **1b**	$P(OMe)_3$	1	1. 80 °C, 2 h 2. 80 °C, 2 h	**3f**	85
6	4-$MeOC_6H_4N_3$ **1c**	$P(OMe)_3$	1	1. 80 °C, 2 h 2. 80 °C, 2 h	**3g**	88
7	$GlcNAcN_3$ **1d**	$P(OMe)_3$	1	1. r.t., 16 h 2. r.t., 24 h	**3h**	67

[a] General procedure III.
[b] All = allyl.
[c] All reactions were performed in benzene as solvent.
[d] TMSOTf.

Table 3 Induced Rearrangement of Phosphinimidates[a]

Entry	Azide	Phosphinite	$BF_3{\cdot}OEt_2$ (mol%)	Conditions[a]	Solvent	Product	Yield (%)
1	PhN_3 **1e**	Ph_2POMe	1	1. 80 °C, 2 h 2. 80 °C, 2 h	benzene	**5d**	75
2	BnN_3 **1a**	Ph_2POMe	1	1. 80 °C, 2 h 2. 80 °C, 2 h	benzene	**5a**	87
3	PhN_3 **1e**	Ph_2POEt	5	1. 80 °C, 2 h 2. 80 °C, 16 h	benzene	**5e**	36
4	BnN_3 **1a**	Ph_2POEt	10	1. 80 °C, 2 h 2. 80 °C, 24 h	benzene	**5b**	51
5	PhN_3 **1e**	Ph_2POBn	10	1. 80 °C, 2 h 2. 80 °C, 2 h	benzene	**5f**	25
6	PhN_3 **1e**	Ph_2POBn	20	1. 0 °C to r.t. 2. 80 °C, 5 h	toluene	**5f**	20
7	BnN_3 **1a**	Ph_2POBn	40	1. 0 °C to r.t. 2. 80 °C, 5 h	xylene	**5c**	13
8	BnN_3 **1a**	Ph_2POBn	20	1. 0 °C to r.t. 2. 80 °C, 5 h	xylene	**5c**	30
9	BnN_3 **1a**	Ph_2POBn	20	1. 0 °C to r.t. 2. 80 °C, 17 h	xylene	**5c**	30
10	BnN_3 **1a**	Ph_2POBn	20	1. 0 °C to r.t. 2. 80 °C, 5 h	toluene	**5c**	40

[a] General procedure IV.
[b] 1. Imidate formation. 2. Rearrangement under addition of catalytic amounts of Lewis acid.



Scheme 5 Lewis acid induced rearrangement

erate yields (30–40%), and in all cases, significant amounts of hydrolysis byproducts were observed.

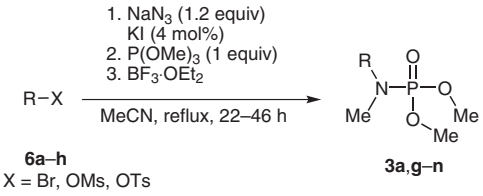
2.3 One-Pot Procedure for the Formation of N,N-Disubstituted Phosphoramidates from Alkyl Halides

Azides are regarded as important compounds in organic synthesis, in particular because of their high intrinsic reactivity. Various methodologies for their synthesis exist among which the nucleophilic substitution of a good leaving group at sp^3-hybridized carbons with inorganic azides is probably the mostly widely applied method.[18] Nevertheless, the isolation of azides, especially for derivatives of low molecular weight, is not desirable due to their potential explosive nature.[18] Consequently, we aimed to develop a procedure, in which isolation could be avoided by performing the reaction as a one-pot process starting from simple azide precursors. In the desired protocol (Scheme 6), an alkyl or benzyl derivative with an appropriate leaving group should give a nucleophilic substitution with sodium azide, followed by Staudinger reaction with the appropriate phosphite and final rearrangement after addition of the Lewis acid. Noteworthy, all the steps should be carried out in one flask without isolation of any intermediate species. It is important to note that for the success of this one-pot protocol, full conversion of the bromide to the corresponding azide is essential to avoid side reactions: (1) the alkyl bromide may lead to formation of a phosphonate from the phosphite in an Arbuzov reaction; and (2) alkylation of the intermediate phosphorimidate should be prevented. Also the addition of the Lewis acid is a crucial factor, since incomplete consumption of the phosphite would again lead to the formation of a phosphonate, which cannot undergo the Staudinger reaction.

The one-pot reaction sequence was first tested with benzyl bromide (**6a**) (Table 4, entry 1) as starting material, which was reacted in acetonitrile with 1.2 equivalents of sodium azide and a catalytic amount of potassium iodide. Usually, nucleophilic substitution of benzyl bromides is performed at room temperature in solvents like *N*,*N*-dimethylformamide or dimethyl sulfoxide, which are, however, not well suited for the subsequent rearrangement, due to their hydroscopic nature and subsequent formation of the hydrolysis byproduct.[19] Consequently, we chose acetonitrile as the solvent, which demands higher temperatures mainly due to the low solubility of sodium azide. After refluxing the reaction mixture for 24 hours, complete formation of benzyl azide (**1a**) was observed by NMR. After refluxing the reaction mixture for five hours with trimethyl phosphite and an additional three hours after addition of the Lewis acid (10 mol%), the desired phosphoramidate **3a** was obtained in an excellent overall yield of 92%.

In the case of activated bromides, like benzyl bromide (**6a**) or cinnamyl bromide (**6b**) (entries 2 and 4), the reaction proceeded in very high yields also without the addition of potassium iodide. Decreasing the amount of Lewis acid catalyst from 10 mol% to 1 mol% led only to a yield of 45% after three hours of rearrangement (entry 3). By refluxing the reaction mixture for a further two days with additional amounts of catalyst the reaction could be run to completion (83%) with 17% hydrolyzed phosphoramidate as a side product.

Besides benzyl bromide (**6a**) also normal primary bromides could be used in the reaction sequence (entries 6–10). Furthermore, alkyl mesylates and tosylates were tolerated, although with lower yields. Tertiary azides obtained from the corresponding bromide like the malonic acid derivative **6h** could only be converted into the desired phosphoramidates **3n** to a very low extend, although the formation of the azide and the phosphorimidate **2n** was quantitative. Nevertheless, the successive addition of the Lewis acid did not lead to a satisfying rearrangement and even after four days only 32% of the rearranged product **3n** was obtained with 35% of unreacted phosphorimidate **2n** and 22% of hydrolyzed product being present. This result may probably be attributed to the steric hindrance and to the strong electron-withdrawing effect of the two ester groups which decrease the nucleophilicity of the phosphorimidate nitrogen.

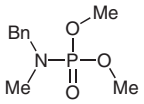
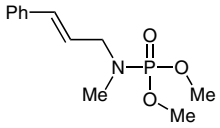
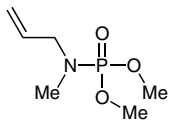
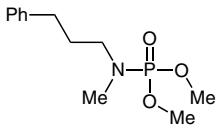
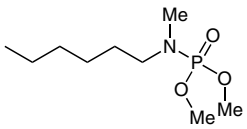
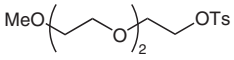
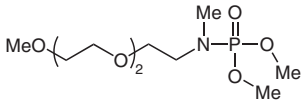
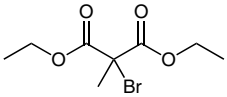
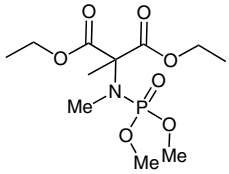


Scheme 6 One-pot procedure towards N,N-disubstituted phosphoramidites

3 Conclusion

In summary, we have used the alkyl halide or Lewis acid catalyzed rearrangement of phosphor- and phosphinimidates for the formation of N,N-disubstituted phosphoramidates and phosphinamidates. In these protocols different alkyl substituents can be introduced at the nitrogen of the P(=O)–N bond in good to high yields. In addition, we have successfully introduced a one-pot procedure for the formation of N,N-disubstituted phosphoramidates without the intermediate isolation of alkyl azide deriva-

Table 4 Reaction Scope of the One-Pot Process[a]

Entry	Bromide	Conditions	Phosphoramidate	Yield (%)
1	BnBr **6a**	NaN_3, KI (4 mol%), MeCN, 80 °C, 24 h $P(OMe)_3$, MeCN, 80 °C, 5 h $BF_3{\cdot}OEt_2$ (10 mol%), MeCN, 80 °C, 3 h	 **3a**	92
2	BnBr **6a**	NaN_3, MeCN, 80 °C, 24 h $P(OMe)_3$, MeCN, 80 °C, 5 h $BF_3{\cdot}OEt_2$ (10 mol%), MeCN, 80 °C, 5 h	**3a**	90
3	BnBr **6a**	NaN_3, KI, MeCN, 80 °C, 24 h $P(OMe)_3$, MeCN, 80 °C, 5 h $BF_3{\cdot}OEt_2$ (1 mol%), MeCN, 80 °C, 3 h $BF_3{\cdot}OEt_2$ (2 mol%), MeCN, 80 °C, 24 h $BF_3{\cdot}OEt_2$ (2 mol%), MeCN, 80 °C, 24 h	**3a**	45[b] (3 h) 78[b] (27 h) 83 (51 h)
4	(*E*)-PhCH=CHCH$_2$Br **6b**	1. NaN_3, MeCN, 80 °C, 24 h 2. $P(OMe)_3$, MeCN, 80 °C, 5 h 3. $BF_3{\cdot}OEt_2$ (10 mol%), MeCN, 80 °C, 5 h	 **3i**	80
5	H$_2$C=CHCH$_2$Br **6c**	1. NaN_3, KI (4 mol%), MeCN, 80 °C, 24 h 2. $P(OMe)_3$, MeCN, 80 °C, 5 h 3. $BF_3{\cdot}OEt_2$ (10 mol%), MeCN, 80 °C, 3 h	 **3j**	51
6	Ph(CH$_2$)$_3$Br **6d**	1. NaN_3, MeCN, 80 °C, 16 h 2. $P(OMe)_3$, MeCN, 80 °C, 2 h 3. $BF_3{\cdot}OEt_2$ (10 mol%), MeCN, 80 °C, 2 h	 **3k**	£20[b]
7	Ph(CH$_2$)$_3$OMs **6e**	1. NaN_3, MeCN, 80 °C, 24 h 2. $P(OMe)_3$, MeCN, 80 °C, 5 h 3. $BF_3{\cdot}OEt_2$ (10 mol%), MeCN, 80 °C, 5 h	**3k**	50[b]
8	Ph(CH$_2$)$_3$Br **6d**	1. NaN_3, KI (4 mol%), MeCN, 80 °C, 24 h 2. $P(OMe)_3$, MeCN, 80 °C, 5 h 3. $BF_3{\cdot}OEt_2$ (10 mol%), MeCN, 80 °C, 3 h	**3k**	81
9	Me(CH$_2$)$_5$Br **6f**	1. NaN_3, DMF, 60 °C, 16 h 2. $P(OMe)_3$, DMF, 80 °C, 3 h 3. $BF_3{\cdot}OEt_2$ (10 mol%), DMF, 80 °C, 12 h	 **3l**	40
10	 **6g**	NaN_3, KI (4 mol%), MeCN, 80 °C, 24 h $P(OMe)_3$, MeCN, 80 °C, 5 h $BF_3{\cdot}OEt_2$ (1 mol%), MeCN, 80 °C, 3 h	 **3m**	61
11	 **6h**	1. NaN_3, KI (4 mol%), MeCN, 80 °C, 24 h 2. $P(OMe)_3$, MeCN, 80 °C, 5 h 3. $BF_3{\cdot}OEt_2$ (10 mol%), MeCN, 80 °C, 3 h 4. $BF_3{\cdot}OEt_2$ (10 mol%), MeCN, 80 °C, 24 h 5. $BF_3{\cdot}OEt_2$ (10 mol%), MeCN, 80 °C, 49 h	 **3n**	3[b] (3 h) 12[b] (27 h) 21[b] (51 h) 32[b] (100 h)

[a] General procedure V.
[b] Yield determined by ^{31}P NMR.

tives. Our future efforts are devoted to applying this methodology to the synthesis of new derivatives in which the biological potential of the phosphoramidate moiety is fully addressed.

All reagents, starting materials and solvents were purchased from commercial suppliers and used without further purification if not further mentioned. Methyl diphenylphosphinite and ethyl diphenylphosphinite as well as dry solvents (MeCN, toluene, DMF) were purchased from Acros Organics. Anhyd benzene and 3,4,6-tri-*O*-acetyl-2-acetamido-2-deoxy-β-D-glucopyranosyl azide (**1d**) were purchased from Sigma Aldrich. Flash chromatography was performed on silica gel (Acros Silica gel 60 A, 0.035–0.070 mm). TLC was performed on aluminum-backed silica plates (60 F254, 0.2 mm) which were developed using $KMnO_4$ as visualizing agent. ^1H, ^{13}C, and ^{31}P NMR spectra were recorded on a Jeol ECX/400, Bruker AC 250 or AMX 500.

Benzyl Diphenylphosphinite

BnOH (0.518 mL, 541 mg, 5.00 mmol) was dissolved in Et_2O (25 mL) under an argon atmosphere. The soln was cooled to 0 °C and Et_3N (1.40 mL, 1.01 g, 10.0 mmol) and DMAP (61.0 mg, 0.599 mmol) in Et_2O (5 mL) were added, followed by Ph_2PCl (0.895 mL, 1.10 g, 5.00 mmol). The mixture was allowed to warm up to r.t. and after 90 min the precipitated salt was filtered off. The solvent was removed under reduced pressure and benzyl diphenylphosphinite was obtained as a colorless solid; yield; 1.30 g (90%).[17]

^1H NMR (250 MHz, CD_3Cl): δ = 4.93 (d, *J* = 9.10 Hz, 2 H, CH_2), 7.30–7.58 (m, 15 H, Ph).

^{31}P NMR (202 MHz, CD_3Cl): δ = 114.48.

Tribenzyl Phosphite

PCl_3 (0.437 mL, 687 mg, 5.00 mmol) was slowly added to a soln of Et_3N (2.09 mL, 1.52 mg, 15.0 mmol) in Et_2O (120 mL). The mixture was cooled to 0 °C and BnOH (1.55 mL, 1.62 mg, 15.0 mmol) was added. The mixture was stirred at 0 °C for 1 h and left at r.t. overnight. The precipitate was filtered and the solvent removed under reduced pressure. The product was obtained as a colorless oil and used without further purification; yield: 1.71 g (97%).[19]

^1H NMR (400 MHz, $CDCl_3$): δ = 4.88 (d, *J* = 5.0 Hz, 6 H, CH_2), 7.40–7.25 (m, 15 H, Ph).

Alkyl Halide Catalyzed Rearrangement of Phosphorimidates; General Procedure I

In a 2-necked round-bottom flask the azide derivative was dissolved in anhyd benzene or toluene (see Table 1) (0.3 mmol/mL) and phosphite (1.0 equiv) was added. The mixture was refluxed for 2 h. After cooling to r.t. the alkyl halide was added to the formed phosphorimidate and the rearrangement was allowed to proceed at 80 °C or 110 °C for 4–8 h. The solvent was removed under reduced pressure to give the crude product. Final purification by flash column chromatography (EtOAc–hexane, 3:1) afforded the pure product in 70–90% yields.

Alkyl Halide Catalyzed Rearrangement of Phosphinimidates; General Procedure II

In a 2-necked round-bottom flask the azide derivative was dissolved in anhyd benzene or toluene (see Table 1) (0.3 mmol/mL) and phosphinite (1 equiv) was added slowly. The mixture was stirred at r.t. for 20 min and only in case of benzyl diphenylphosphinite refluxed for 2 h to form the phosphinimidate. The alkyl halide was added to the formed phosphinimidate and the rearrangement was allowed to proceed at 80 °C or 110 °C for 4–8 h. The solvent was removed under reduced pressure to give the crude product. Final purification by flash column chromatography (EtOAc–hexane, 1:1) afforded the pure product in 60–83% yield.

Lewis Acid Induced Rearrangement of Phosphorimidates; General Procedure III

In a 2-necked round-bottom flask the azide derivative was dissolved in anhyd benzene (0.6 mmol/mL) and phosphite (1 equiv) was added. The mixture was refluxed at 80 °C for 2–5 h or stirred at r.t. for 24 h (see Table 2). After cooling to r.t. $BF_3{\cdot}OEt_2$ (1 mol%) dissolved in anhyd benzene (50 μL) was added to the formed phosphorimidate and the rearrangement was allowed to proceed at 80 °C for 2–5 h or at r.t. for 16–24 h. The solvent was removed under reduced pressure to give the crude product. Final purification by flash column chromatography [EtOAc–hexane, 3:1; for the sugar derivative EtOAc–MeOH (0 to 5%)] afforded the pure product in 65–90% yield.

Lewis Acid Catalyzed Rearrangement of Phosphinimidates; General Procedure IV

In a 2-necked round-bottom flask the azide derivative was dissolved in anhyd benzene or toluene (0.6 mmol/mL) and phosphinite (1 equiv) was added slowly at r.t. or 0 °C (see Table 3). The mixture was stirred at r.t. for 1–2 h or refluxed for 2 h and then $BF_3{\cdot}OEt_2$ was added to the formed phosphinimidate. The rearrangement was allowed to proceed at 80 °C for 2–24 h. The solvent was removed under reduced pressure to give the crude product. Final purification by flash column chromatography (EtOAc–hexane, 3:1) afforded the pure product in 13–87% yield.

One-Pot Procedure to N,N-Disubstituted Phosphoramidates; General Procedure V

To a suspension of NaN_3 (358 mg, 5.50 mmol), KI (33.0 mg, 0.199 mmol, 4 mol%), and MeCN (10 mL), the bromide (5.00 mmol) was added. The mixture was refluxed for 16–30 h until formation of the azide was complete. Afterwards $P(OMe)_3$ (590 μL, 620 mg, 5.00 mmol) was added and the mixture was refluxed for an additional 5 h and then $BF_3{\cdot}OEt_2$ (10 mol%) in MeCN (500 μL) was added. The rearrangement was complete after a further 3–51 h at 80 °C and the solvent was removed under reduced pressure. Final purification by flash column chromatography (EtOAc–cyclohexane, 2:1) afforded the pure product in 51–92% yield.

Dimethyl *N*-Benzyl-*N*-methylphosphoramidate (3a)

Prepared according to general procedure I or III from BnN_3 (399 mg, 3.00 mmol) and $P(OMe)_3$ (354 μL, 372 mg, 3.00 mmol); yield: 619 mg (90%) (GPI) and 653 mg (95%) (GPIII). Alternative according to general procedure V from BnBr (595 μL, 855 mg, 5.00 mmol) and $P(OMe)_3$ (590 μL, 620 mg, 5.00 mmol) as a colorless oil; yield: 1.05 g (92%).

^1H NMR (400 MHz, $CDCl_3$): δ = 2.51 (d, *J* = 9.7 Hz, 3 H, NCH_3), 3.68 (d, *J* = 11.0 Hz, 6 H, OCH_3), 4.16 (d, *J* = 8.9 Hz, 2 H, CH_2), 7.24–7.22 (m, 5 H, Ph).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 33.1 (d, *J* = 3.8 Hz, NCH_3), 53.0 (d, *J* = 5.0 Hz, CH_2), 53.1 (d, *J* = 5.8 Hz, OCH_3), 127.4, 128.2, 128.5, 137.8 (d, *J* = 4.6 Hz) (Ph).

^{31}P NMR (162 MHz, $CDCl_3$): δ = 13.59.

HRMS (ESI-TOF): *m*/*z* $[M + H]^+$ calcd for $C_{10}H_{17}NO_3P$: 230.0946; found: 230.0949.

Diethyl *N*-Benzyl-*N*-ethylphosphoramidate (3b)

Prepared according to general procedure I from BnN_3 (399 mg, 3.00 mmol) and $P(OEt)_3$ (514 μL, 487 mg, 3.00 mmol) as a colorless oil; yield: 570 mg (70%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.02–1.06 (m, 3 H, NCH_3), 1.28–1.32 (m, 6 H, OCH_3), 2.99–3.00 (m, 2 H, NCH_2), 3.97–4.11 (m, 4 H, OCH_2), 4.21 (d, *J* = 9.6 Hz, 2 H, CH_2), 7.23–7.24 (m, 5 H, Ph).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 13.3 (d, *J* = 1.5 Hz, NCH_3), 16.3 (d, *J* = 7.3 Hz, OCH_3), 39.5 (d, *J* = 3.8 Hz, NCH_2), 48.7 (d, *J* = 5.0 Hz, CH_2), 62.3 (d, *J* = 5.8 Hz, OCH_2), 127.3, 128.3, 128.5, 138.3 (d, *J* = 3.8 Hz) (Ph).

^{31}P NMR (162 MHz, $CDCl_3$): δ = 10.79.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{23}NO_3P$: 272.1416; found: 272.1413.

Dibenzyl *N*,*N*-Dibenzylphosphoramidate (3c)

Prepared according to general procedure I from BnN_3 (399, 3.00 mmol) and $P(OBn)_3$ (1.06 g, 3.00 mmol). A second column chromatography (CH_2Cl_2) gave the product; yield: 975 mg (71%).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 4.17 (d, *J* = 10.3 Hz, 4 H, NCH_2), 5.09 (d, *J* = 11.8, 7.4 Hz, 2 H, OCH_2), 5.18 (d, *J* = 11.8, 7.4 Hz, 2 H, OCH_2), 7.25–7.39 (m, 20 H, Ph).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 48.4 (d, *J* = 7.8 Hz, NCH_2), 68.1 (d, *J* = 9.8 Hz, OCH_2), 127.4, 127.7, 128.2, 128.4, 128.5, 128.7, 136.5 (d, *J* = 5.9 Hz), 137.3 (d, *J* = 13.7 Hz) (Ph).

^{31}P NMR (162 MHz, $CDCl_3$): δ = 10.91.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{28}H_{29}NO_3P$: 458.1880; found: 458.1901.

***N*-Benzyl-*N*-methyl-*P*,*P*-diphenylphosphinic Amide (5a)**

Prepared according to general procedure II or IV from BnN_3 (399 mg, 3.00 mmol) and Ph_2POMe (602 μL, 648 mg, 3.00 mmol); yield: 800 mg (83%) (GPII) and 838 mg (87%) (GPIV). If necessary, the compound was recrystallized (toluene–hexane) to obtain the pure product as a colorless solid.

^{1}H NMR (400 MHz, CD_3CN): δ = 2.46 (d, *J* = 10.7 Hz, 3 H, NCH_3), 4.09 (d, *J* = 8.5 Hz, 2 H, NCH_2), 7.25–7.31 (m, 1 H, Ph), 7.33–7.43 (m, 4 H, Ph), 7.47–7.59 (m, 6 H, Ph), 7.84–7.92 (m, 4 H, Ph).

^{13}C NMR (101 MHz, CD_3CN): δ = 34.1 (d, *J* = 3.0 Hz, NCH_3), 53.3 (d, *J* = 3.1 Hz, NCH_2), 128.2, 129.0, 129.4, 129.7 (d, *J* = 12.3 Hz), 132.9 (d, *J* = 2.5 Hz), 133.1, 134.1 (d, *J* = 9.1 Hz), 139.0 (d, *J* = 5.9 Hz) (Ph).

^{31}P NMR (162 MHz, CD_3CN): δ = 30.38.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{21}NOP$: 322.1355; found: 322.1381.

Anal. Calcd for $C_{20}H_{20}NOP$: C, 74.75; H, 6.27; N, 4.36. Found: C, 74.87; H, 6.316; N, 4.366.

***N*-Benzyl-*N*-ethyl-*P*,*P*-diphenylphosphinic Amide (5b)**

Prepared according to general procedure II or IV from BnN_3 (399 mg, 3.00 mmol) and Ph_2POEt (648 μL, 691 mg, 3.00 mmol) as a colorless oil; yield: 604 mg (60%) (GPII) and 513 mg (51%) (GPIV).

^{1}H NMR (400 MHz, CD_3CN): δ = 0.97 (t, *J* = 7.1 Hz, 3 H, CH_3), 2.86 (dq, *J* = 10.7, 7.1 Hz, 2 H, NCH_2), 4.18 (d, *J* = 10.3 Hz, 2 H, CH_2Ph), 7.23–7.28 (m, 1 H, Ph), 7.31–7.36 (m, 2 H, Ph), 7.42–7.46 (m, 2 H, Ph), 7.46–7.55 (m, 6 H, Ph), 7.85–7.95 (m, 4 H, Ph).

^{13}C NMR (101 MHz, CD_3CN): δ = 13.5 (d, *J* = 3.7 Hz, CH_3), 40.5 (d, *J* = 3.5 Hz, NCH_2), 49.1 (d, *J* = 3.6 Hz, CH_2Ph), 128.1, 129.2, 129.3, 129.6, 129.7, 132.8 (d, *J* = 2.7 Hz), 133.2 (d, *J* = 9.1 Hz), 133.8 (d, *J* = 127.9 Hz), 139.1 (d, *J* = 4.5 Hz) (Ph).

^{31}P NMR (162 MHz, CD_3CN): δ = 29.81.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{23}NOP$: 336.1512; found: 336.1543.

***N*,*N*-Dibenzyl-*P*,*P*-diphenylphosphinic Amide (5c)**

Prepared according to general procedure II or IV from BnN_3 (266 mg, 2.00 mmol) and Ph_2POBn (557 mg, 2.00 mmol) as a colorless solid; yield: 103–604 mg (13–76%).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 4.04 (d, *J* = 10.0 Hz, 4 H, CH_2Ph), 7.24–8.02 (m, 20 H, Ph).

^{13}C NMR (500 MHz, $CDCl_3$): δ = 48.6 (d, *J* = 3.6 Hz, CH_2Ph, 127.2, 127.8, 128.4, 128.7 (d, *J* = 12.5 Hz), 128.9, 131.4, 131.6, 131.6, 131.9 (d, *J* = 2.6 Hz), 132.7 (d, *J* = 9.3 Hz), 136.6 (d, *J* = 3.6 Hz) (Ph).

^{31}P NMR (162 MHz, CD_3CN): δ = 31.69.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{26}H_{25}NOP$: 398.1668; found: 398.1350.

Diallyl *N*-Allyl-*N*-benzylphosphoramidate (3d)

Prepared according to general procedure III from BnN_3 (399 mg, 3.00 mmol) and triallyl phosphite (607 mg, 3.00 mmol) as a colorless oil; yield: 655 mg (71%).

^{1}H NMR (400 MHz, CD_3CN): δ = 3.45 (dd, *J* = 11.6, 6.4 Hz, 2 H, NCH_2), 4.17 (d, *J* = 10.2 Hz, 2 H, CH_2Ph), 4.41–4.56 (m, 4 H, OCH_2), 5.11 (ddd, *J* = 17.1, 1.4 Hz, 1 H, CH_2), 5.17 (ddd, *J* = 10.2, 1.6, 0.5 Hz, 1 H, CH_2), 5.21 (ddd, *J* = 10.5, 2.8, 1.4 Hz, 2 H, CH_2), 5.33 (ddd, *J* = 17.2, 1.6 Hz, 2 H, CH_2), 5.74 (ddt, *J* = 16.6, 10.2, 6.4 Hz, 1 H, CH), 5.88–6.01 (m, 2 H, CH), 7.26–7.37 (m, 5 H, Ph).

^{13}C NMR (101 MHz, CD_3CN): δ = 48.3 (d, *J* = 4.6 Hz, NCH_2), 49.3 (d, *J* = 5.0 Hz, CH_2Ph), 68.0 (d, *J* = 5.3 Hz, OCH_2), 118.2 (pt, *J* = 2.8 Hz, CH_2), 119.1 (pt, *J* = 4.3 Hz, CH_2), 128.4, 129.4, 129.5 (Ph), 134.12 (m, CH), 134.91 (m, CH), 138.54 (d, *J* = 3.3 Hz, Ph).

^{31}P NMR (162 MHz, CD_3CN): δ = 9.03.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{23}NO_3P$: 308.1410; found: 308.1424.

Dibutyl *N*-Benzyl-*N*-butylphosphoramidate (3e)

Prepared according to general procedure III from BnN_3 (399 mg, 3.00 mmol) and $P(OBu)_3$ (812 μL, 751 mg, 3.00 mmol) as a colorless oil; yield: 693 mg (65%) and 768 mg (72%).

^{1}H NMR (400 MHz, CD_3CN): δ = 0.83 (t, *J* = 7.4 Hz, 3 H, CH_3), 0.90 (t, *J* = 7.4 Hz, 6 H, CH_3), 1.19 (tq, *J* = 15.0, 7.6 Hz, 2 H, CH_2), 1.40 (m, 6 H, CH_2), 1.55–1.64 (m, 4 H, CH_2), 2.76–2.84 (m, 2 H, NCH_2), 3.83–3.99 (m, 4 H, OCH_2), 4.17 (d, *J* = 10.4 Hz, 2 H, CH_2Ph), 7.22–7.36 (m, 5 H, Ph).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 13.8 (CH_3), 14.0 (CH_3), 19.0 (CH_2), 20.1 (CH_2), 30.1 (CH_2), 32.5 (d, *J* = 7.0 Hz, CH_2), 44.9 (d, *J* = 3.9 Hz, NCH_2), 49.2 (d, *J* = 4.9 Hz, CH_2Ph), 66.1 (d, *J* = 5.8 Hz, OCH_2), 127.3, 128.4, 128.5, 138.4 (d, *J* = 3.1 Hz) (Ph).

^{31}P NMR (162 MHz, CD_3CN): δ = 10.85.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{35}NO_3P$: 356.2349; found: 356.2356.

Dimethyl *N*-Methyl-*N*-(4-nitrophenyl)phosphoramidate (3f)

Prepared according to general procedure III from 4-nitrophenyl azide (492 mg, 3.00 mmol) and $P(OMe)_3$ (354 μL, 372 mg, 3.00 mmol) as a colorless solid; yield: 663 mg (85%).

^{1}H NMR (400 MHz, CD_3CN): δ = 3.23 (d, *J* = 8.2 Hz, 3 H, NCH_3), 3.69 (d, *J* = 11.5 Hz, 6 H, OCH_3), 7.43 (d, *J* = 9.2 Hz, 2 H, Ph), 8.12 (d, *J* = 8.9 Hz, 2 H, Ph).

^{13}C NMR (101 MHz, CD_3CN): δ = 36.5 (d, *J* = 3.7 Hz, NCH_3), 54.1 (d, *J* = 5.3 Hz, OCH_3), 120.0 (d, *J* = 4.6 Hz), 125.4, 143.1, 151.4 (d, *J* = 6.0 Hz) (Ph).

^{31}P NMR (162 MHz, CD_3CN): δ = 7.59.

HRMS (ESI-TOF): *m/z* [M + H]$^+$ calcd for $C_9H_{14}N_2O_5P$: 261.0635; found: 261.0657.

Dimethyl *N*-(4-Methoxyphenyl)-*N*-methylphosphoramidate (3g)

Prepared according to general procedure III from 4-methoxyphenyl azide (447 mg, 3.00 mmol) and $P(OMe)_3$ (354 μL, 372 mg, 3.00 mmol) as a colorless oil; yield: 647 mg (88%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.10 (d, *J* = 9.0 Hz, 3 H, NCH_3), 3.69 (d, *J* = 11.2 Hz, 6 H, $POCH_3$), 3.76 (s, 3 H, OCH_3), 6.79–6.85 (m, 2 H, Ph), 7.15–7.20 (m, 2 H, Ph).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 38.2 (d, *J* = 5.2 Hz, NCH_3), 53.3 (d, *J* = 5.7 Hz, $POCH_3$), 55.5 (OCH_3), 114.4 (Ph), 125.6 (d, *J* = 3.7 Hz), 137, 156.96 (d, *J* = 4.2 Hz).

^{31}P NMR (162 MHz, $CDCl_3$): δ = 9.83.

HRMS (ESI-TOF): *m/z* [M + H]$^+$ calcd for $C_{10}H_{17}NO_4P$: 246.0890; found: 246.0868.

(2*R*,3*S*,4*R*,5*R*,6*R*)-5-Acetamido-3,4-diacetoxy-2-(acetoxymethyl)-6-[(dimethoxyphosphoryl)(methyl)amino]tetrahydro-2*H*-pyran (3h)

Prepared according to general procedure III from 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl azide (50.0 mg, 0.134 mmol) and $P(OMe)_3$ (15.0 μL, 16.0 mg, 0.134 mmol); for solubility reasons benzene (1.5 mL) was used as solvent with additional MeCN (200 μL) to give the product as a white solid; yield: 37.1 mg (67%).

^{1}H NMR (400 MHz, CD_3CN): δ = 1.90 (s, 3 H, CH_3), 2.01 (s, 3 H, CH_3), 2.05 (s, 6 H, CH_3), 2.63 (d, *J* = 9.2 Hz, 3 H, NCH_3), 3.67 (d, *J* = 11.3 Hz, 3 H, OCH_3), 3.71 (d, *J* = 11.5 Hz, 3 H, OCH_3), 3.87 (ddd, *J* = 10.1, 4.5, 3.6 Hz, 1 H, CH), 4.18 (m, 1 H, CH), 4.19 (d, *J* = 1.1 Hz, 1 H, CH), 4.34 (dd, *J* = 10.0 Hz, 1 H, CH), 4.86 (dd, *J* = 9.7, 8.9 Hz, 1 H, CH), 5.01 (dd, *J* = 9.8 Hz, 1 H, CH), 5.21 (dd, *J* = 9.9 Hz, 1 H, CH).

^{13}C NMR (101 MHz, CD_3CN): δ = 19.7 (CH_3), 19.7 (CH_3), 19.8 (CH_3), 21.8 (CH_3), 26.6 (d, *J* = 2.7 Hz, NCH_3), 49.8 (d, *J* = 7.4 Hz, C2), 52.5 (d, *J* = 4.8 Hz, OCH_3), 52.7 (d, *J* = 4.9 Hz, OCH_3), 62.3 (C6), 68.7 (C4), 73.2 (C3), 73.5 (C5), 85.1 (d, *J* = 6.8 Hz, C1), 169.9 (C=O), 170.4 (C=O), 170.7 (C=O), 171.1 (C=O).

^{31}P NMR (162 MHz, CD_3CN): δ = 12.94.

HRMS (ESI-TOF): *m/z* [M + H]$^+$ calcd for $C_{17}H_{30}N_2O_{11}P$: 469.1582; found: 469.1598.

***N*-Methyl-*N*,*P*,*P*-triphenylphosphinic Amide (5d)**

Prepared according to general procedure IV from PhN_3 (357 mg, 3.00 mmol) and Ph_2POMe (602 mL, 649 mg, 3.00 mmol) as a colorless oil; yield: 691 mg (75%). The product contained small amounts (~6%) of Ph_2POMe and analytical amount can be further purified by HPLC (0–5 min 100% H_2O, 5–45 min 0% MeCN to 100% MeCN).

^{1}H NMR (400 MHz, CD_3CN): δ = 3.02 (d, *J* = 9.9 Hz, 3 H, CH_3), 6.97–7.03 (m, 1 H, Ph), 7.15–7.22 (m, 2 H, Ph), 7.33–7.39 (m, 2 H, Ph), 7.38–7.49 (m, 6 H, Ph), 7.83–7.90 (m, 4 H, Ph).

^{13}C NMR (101 MHz, CD_3CN): δ = 39.5 (d, *J* = 4.3 Hz, CH_3), 125.4, 126.2 (d, *J* = 5.1 Hz), 129.5 (d, *J* = 12.5 Hz), 129.8, 132.7 (d, *J* = 2.7 Hz), 133.3 (d, *J* = 9.1 Hz), 133.7 (d, *J* = 129.0 Hz), 147.2 (d, *J* = 2.5 Hz) (Ph).

^{31}P NMR (162 MHz, CD_3CN): δ = 25.45.

HRMS (ESI-TOF): *m/z* [M + H]$^+$ calcd for $C_{19}H_{19}NOP$: 308.1199; found: 308.1223.

***N*-Ethyl-*N*,*P*,*P*-triphenylphosphinic Amide (5e)**

Prepared according to general procedure IV from PhN_3 (357 mg, 3.00 mmol) and Ph_2POEt (648 μL, 691 mg, 3.00 mmol) as a colorless oil; yield: 347 mg (36%). In case of small amounts of Ph_2POEt in the product, analytical amounts phosphinamidate can be further purified by HPLC as described above.

^{1}H NMR (400 MHz, CD_3CN): δ = 1.01 (t, *J* = 7.1 Hz, 3 H, CH_3), 3.43 (dq, *J* = 10.7, 7.1 Hz, 2 H, CH_2), 7.01–7.08 (m, 1 H, Ph), 7.16–7.24 (m, 2 H, Ph), 7.36–7.45 (m, 8 H, Ph), 7.87–7.95 (m, 4 H, Ph).

^{13}C NMR (101 MHz, CD_3CN): δ = 15.1 (d, *J* = 3.0 Hz, CH_3), 46.8 (d, *J* = 3.6 Hz, CH_2), 126.4, 129.3 (d, *J* = 7.1 Hz), 129.4, 129.8, 132.5, 133.3 (d, *J* = 8.9 Hz), 133.7 (d, *J* = 129.3 Hz), 144.1 (d, *J* = 1.3 Hz) (Ph).

^{31}P NMR (162 MHz, CD_3CN): δ = 25.07.

HRMS (ESI-TOF): *m/z* [M + H]$^+$ calcd for $C_{20}H_{21}NOP$: 322.1355; found: 322.1375.

***N*-Benzyl-*N*,*P*,*P*-triphenylphosphinic Amide (5f)**

Prepared according to general procedure IV from PhN_3 (357 mg, 3.00 mmol) and Ph_2POBn (877 mg, 3.00 mmol) as a colorless solid; maximum yield: 288 mg (25%).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 4.59 (d, *J* = 9.1 Hz, 2 H, CH_2), 6.86–7.39 (m, 15 H, Ph), 7.86–7.94 (m, 5 H, Ph).[20]

^{13}C NMR (101 MHz, $CDCl_3$): δ = 54.8 (d, *J* = 3.1 Hz, CH_2), 125.2, 127.1, 127.9, 128.1 (d, *J* = 4.6 Hz), 128.3, 128.4, 128.5, 128.7, 128.9, 131.5, 131.6 (d, *J* = 3.1 Hz), 132.6, 132.7 (d, *J* = 9.2 Hz), 137.5 (d, *J* = 4.6 Hz), 142.8 (Ph).

^{31}P NMR (162 MHz, $CDCl_3$): δ = 27.38.

Dimethyl *N*-Cinnamyl-*N*-methylphosphoramidate (3i)

Prepared according to general procedure V from cinnamyl bromide (985 mg, 5.00 mmol) as a pale-yellow oil; yield 1.02 g (80%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.58 (d, *J* = 9.7 Hz, 3 H, NCH_3), 3.63 (d, *J* = 11.1 Hz, 6 H, OCH_3), 3.69 (ddd, *J* = 10.0, 6.5, 0.9 Hz, 2 H, NCH_2), 6.07 (dt, *J* = 15.8, 6.6 Hz, 1 H, CH), 6.46 (d, *J* = 15.9 Hz, 1 H, CH), 7.14–7.31 (m, 5 H, Ph).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 33.0 (d, *J* = 3.9 Hz, NCH_3), 51.1 (d, *J* = 4.5 Hz, NCH_2), 52.8 (d, *J* = 5.8 Hz, OCH_3), 125.6 (d, *J* = 3.6 Hz, CH), 126.2, 127.5, 128.4, (Ph), 132.7 (CH), 136.4 (Ph).

^{31}P NMR (162 MHz, CD_3CN): δ = 13.45.

HRMS (ESI-TOF): *m/z* [M + H]$^+$ calcd for $C_{12}H_{19}NO_3P$: 256.1097; found: 256.1112.

Dimethyl *N*-Allyl-*N*-methylphosphoramidate (3j)

Prepared according to general procedure V from allyl bromide (434 μL, 605 mg, 5.00 mmol) as a colorless oil; yield: 457 mg (51%).

^{1}H NMR (400 MHz, CD_3CN): δ = 2.56 (d, *J* = 9.6 Hz, 3 H, NCH_3), 3.54–3.60 (m, 2 H, CH_2), 3.59 (d, *J* = 11.1 Hz, 6 H, OCH_3), 5.17 (ddtd, *J* = 10.2, 1.8, 1.3, 0.6 Hz, 1 H, CH_2), 5.22 (ddd, *J* = 17.2, 3.2, 1.6 Hz, 1 H, CH_2), 5.79 (ddt, *J* = 17.1, 10.2, 6.1 Hz, 1 H, CH).

^{13}C NMR (101 MHz, CD_3CN): δ = 33.4 (d, *J* = 3.9 Hz, NCH_3), 52.3 (d, *J* = 4.6 Hz, NCH_2), 53.3 (d, *J* = 5.5 Hz, OCH_3), 117.7–117.8 (m, CH_2), 135.8–135.9 (m, CH).

^{31}P NMR (162 MHz, CD_3CN): δ = 13.44.

HRMS (ESI-TOF): *m/z* [M + H]$^+$ calcd for $C_6H_{15}NO_3P$: 180.0784; found: 180.0782.

Dimethyl *N*-Methyl-*N*-(3-phenylpropyl)phosphoramidate (3k)

Prepared according to general procedure V from 3-phenylpropyl bromide (754 μL, 995 mg, 5.00 mmol) as a colorless oil; yield: 104 mg (81%).

^{1}H NMR (400 MHz, CD_3CN): δ = 1.72–1.85 (m, 2 H, CH_2), 2.58 (t, J = 7.9 Hz, 2 H, CH_2), 2.59 (d, J = 9.7 Hz, 3 H, NCH_3), 2.94–3.04 (m, 2 H, CH_2), 3.56 (d, J = 11.1 Hz, 6 H, OCH_3), 7.12–7.31 (m, 5 H, Ph).

^{13}C NMR (400 MHz, CD_3CN): δ = 30.8 (d, J = 2.6 Hz, CH_2), 33.6 (CH_2), 33.7 (d, J = 3.8 Hz, NCH_3), 49.5 (d, J = 4.1 Hz, NCH_2), 52.3 (d, J = 5.4 Hz, OCH_3), 126.8, 129.3, 129.3, 143.2 (Ph).

^{31}P NMR (162 MHz, CD_3CN): δ = 13.78.

HRMS (ESI-TOF): m/z $[M + H]^+$ calcd for $C_{12}H_{21}NO_3P$: 258.1254; found: 258.1283.

Dimethyl *N*-Hexyl-*N*-methylphosphoramidate (3l)

Prepared according to general procedure V from 1-bromohexane (702 μL, 820 mg, 5.00 mmol) in DMF (10 mL) as a colorless oil; yield: 447 mg (40%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.83 (t, J = 6.7 Hz, 3 H, CH_3), 1.24 (m, 6 H, CH_2), 1.39–1.52 (m, 2 H, CH_2), 2.59 (d, J = 9.9 Hz, 3 H, NCH_3), 2.88–2.98 (m, 2 H, NCH_2), 3.61 (d, J = 11.0 Hz, 6 H, OCH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 14.1 (CH_3), 22.7 (CH_2), 26.3 (CH_2), 28.1 (d, J = 2.6 Hz, CH_2), 31.6 (CH_2), 33.3 (d, J = 4.0 Hz, NCH_3), 49.2 (d, J = 3.8 Hz, NCH_2), 52.9 (d, J = 5.7 Hz, OCH_3).

^{31}P NMR (162 MHz, $CDCl_3$): δ = 13.91.

HRMS (ESI-TOF): m/z $[M + H]^+$ calcd for $C_9H_{23}NO_3P$: 224.1410; found: 224.1455.

Dimethyl *N*-{2-[2-(2-Methoxyethoxy)ethoxy]ethyl}-*N*-methylphosphoramidate (3m)

Prepared according to general procedure V from 2-[2-(2-methoxyethoxy)ethoxy]ethyl 4-toluenesulfonate (318 mg, 1.00 mmol), $P(OMe)_3$ (118 μL, 124 mg, 1.00 mmol), NaN_3 (72.0 mg, 1.10 mmol), and KI (6.60 mg, 39.7 μmol, 4 mol%) in MeCN (3 mL) with $BF_3{\cdot}OEt_2$ (10 mol%) in MeCN (50 μL). Purification by column chromatography (EtOAc to EtOAc–10% MeOH) gave the product as a colorless oil; yield: 174 mg (61%).

^{1}H NMR (400 MHz, CD_3CN): δ = 2.64 (d, J = 9.5 Hz, 3 H, NCH_3), 3.14 (dt, J = 10.5, 5.7 Hz, 2 H, NCH_2), 3.28 (s, 3 H, OCH_3), 3.43–3.46 (m, 2 H, CH_2), 3.50–3.55 (m, 8 H, CH_2), 3.59 (d, J = 11.1 Hz, 6 H, $POCH_3$).

^{13}C NMR (101 MHz, C_6D_6): δ = 34.3 (d, J = 3.6 Hz, NCH_3), 49.0 (d, J = 4.6 Hz, NCH_2), 52.5 (d, J = 5.4 Hz, OCH_3P), 58.7 (OCH_3), 70.2 (d, J = 2.5 Hz, CH_2), 70.6 (d, J = 1.3 Hz, CH_2), 70.8 (CH_2), 71.0 (CH_2), 72.4 (CH_2).

^{31}P NMR (162 MHz, CD_3CN): δ = 13.66.

HRMS (ESI-TOF): m/z $[M + Na]^+$ calcd for $C_{10}H_{24}NNaO_6P$: 308.1233; found: 308.1240.

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