Synthesis of *N*,*N*-disubstituted phosphoramidates *via* a Lewis acid-catalyzed phosphorimidate rearrangement†‡

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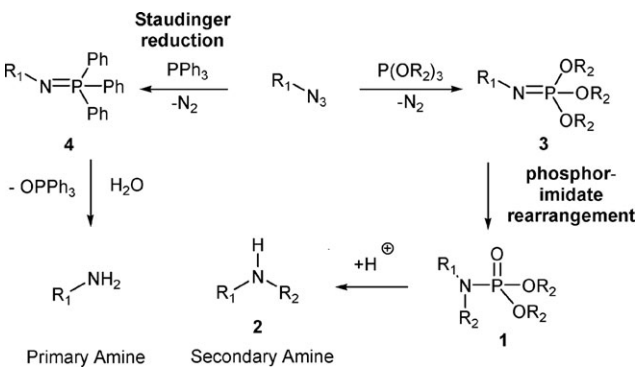
A Lewis acid-catalyzed rearrangement of phosphorimidates allows a direct, high-yielding transformation of azides with commercially available phosphites into secondary phosphoramidates.

P–N bond-containing molecules have emerged as an important class of compounds in modern organic chemistry, with numerous applications as ligands in catalytic synthetic transformations.[1] Amongst these, phosphoramides have attracted considerable interest, as they have been applied in high-yielding, enantioselective Lewis base-activated catalytic processes,[2] including aldol additions[3] and allylation reactions.[4] The phosphoramide skeleton offers the possibility of creating a great variety of different structural motifs by introducing substituents containing chiral information, thus allowing the design of catalysts with optimal electronic and steric properties in these enantioselective transformations.[2,5] This feature, together with their strong Lewis basicity, makes secondary phosphoramides containing a P(=O)–N bond ideal candidates in such catalytic applications.[6]

Apart from their important applications in catalysis, *N*,*N*-disubstituted phosphoramidate derivatives, **1**, can be regarded as protected secondary amines, and thus can be transformed into this important class of compounds, which are commonly present in the pharmacological and natural product kingdoms, by simple deprotection (Scheme 1).[7] Acidic removal of the P(=O)–$(R/OR)_2$ moiety is known to proceed under mild conditions to give the corresponding amine, **2**, in a virtually quantitative yield (Scheme 1).[8] An efficient synthetic route to obtain these derivatives would also allow straightforward access to secondary amines, as traditional syntheses are sometimes accompanied by intrinsic problems, including harsh reaction conditions, low yields, poor chemoselectivity, overalkylation and labour-intensive purification.[7,9]

We now report a process that allows direct access to *N*,*N*-disubstituted phosphoramidates, **1**, from organic azides *via* a two-step/one-pot process (Scheme 1). The reaction sequence firstly includes the reaction of an azide with phosphites to give phosphorimidates, **3**, which are analogous to the iminophosphoranes, **4**, formed during the Staudinger reaction of azides with phosphines.[10] In the following reaction step, the crude phosphorimidates, **3**, undergo rearrangement to their corresponding phosphoramidates by Lewis acid activation. Whereas the nucleophilicity of iminophosphoranes is well employed in synthetic transformations, such as the Staudinger reduction of azides to primary amines (Scheme 1), the aza-Wittig reaction and the Staudinger ligation,[11,12] reactions of *O*-substituted P=N species have only recently found a synthetic application.[12] These phosphorimidates are able to undergo, depending on the substituents at the phosphorus, an inter- or intramolecular rearrangement.

Chen and Mapp[13] have demonstrated that allylic phosphorimidates are able to undergo a thermally induced intramolecular [3,3]-sigmatropic rearrangement, leading to the selective formation of an N–C bond and, after acidic treatment, to the synthesis of allylic amines. The intermolecular thermal rearrangement was pioneered by Challis and co-workers.[14] They reported in particular that the very slow thermal rearrangement of phosphorimidates, **3**, to the corresponding phosphoramidates, **1** ($T_{\frac{1}{2}}$ = 30 d for R_1 = Ph and R_2 = Et), could be accelerated by the presence of a consistent amount (20–40%) of an alkyl halide, in which the alkyl moiety matched the phosphite substituent. In view of the importance of phosphoramidates in organic synthesis and being intrigued by the observation of Challis *et al.*, we decided to investigate the capabilities of different additives to promote a more efficient catalytic cycle, regardless of the phosphite substituents. Our attention especially focused on the rearrangement of simple phosphorimidates derived from the reaction of organic azides with commercially available phosphites such as trimethyl- or triethylphosphite. *N*-Benzyl-trimethylphosphorimidate (**6**), obtained by the reaction of trimethylphosphite with benzyl azide for 2 h at 80 °C in benzene, was selected as a model substrate.



Scheme 1 Synthesis of primary and secondary amines *via* the Staudinger reduction or the phosphorimidate rearrangement.

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† This paper is dedicated to Prof. Helmut Schwarz on the occasion of his 65th birthday.

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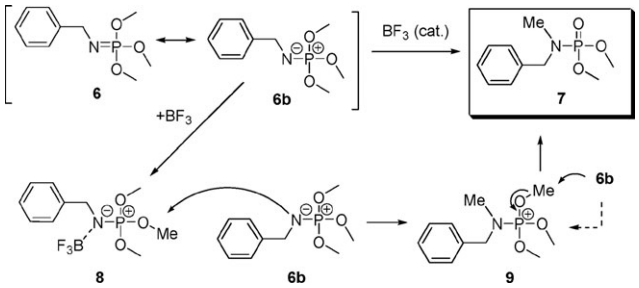
Our study was initiated by the observation that no detectable amount of the rearrangement product could be observed after refluxing compound **6** for 5 h in benzene (Table 1, entry 1). The use of DMF as solvent resulted in a moderate improvement in the reaction, affording the rearranged product in a 41% yield (Table 1, entry 2).[15] However, when **6** was refluxed in benzene in presence of molecular sieves, a smooth reaction took place and the desired *N*,*N*-disubstituted phosphoramidate was isolated in 70% yield (Table 1, entry 3).

Further Lewis acid screening revealed that $BF_3{\cdot}Et_2O$ and TMSOTf were *very* effective catalysts for the target rearrangement, and quantitative turnover could be achieved with even 1 mol% of catalyst under the reaction conditions used (Table 1, entries 4–6). Moreover, benzene, DMF and CH_2Cl_2 could also be used as solvents in the $BF_3{\cdot}Et_2O$-catalyzed rearrangement; however, the yield was generally lower (Table 1, entries 7 and 8). None of the other Lewis acids tested matched $BF_3{\cdot}Et_2O$ or TMSOTf in reactivity (Table 1, entries 9–13). It is worth noting that during the reaction sequence, no work-up was performed between the phosphorimidate formation and rearrangement steps. However, anhydrous reaction conditions were required for the rearrangement to occur in order to prevent BF_3 hydrolysis.

In agreement with previous mechanistic investigations and theoretical calculations regarding the BF_3-catalyzed polymerization[16] of cyclic phosphorimidates, we suggest that BF_3 is coordinated to the negatively-charged nitrogen, as visualized in the aza-ylide resonance form of the phosphorimidate, **6b**, thus accelerating the rearrangement process (Scheme 2). This coordination in complex **8** enhances the electrophilicity of the adjacent methyl group, which allows a subsequent attack of the nitrogen lone pair of another **6b**, leading to the charged species **9**. Compound **9** is prone to nucleophilic attack by a further **6b**, whereby the catalytic cycle is closed, simultaneously resulting in the alkylation of the nitrogen and formation of the P═O double bond in the resulting phosphoramidate, **7**.

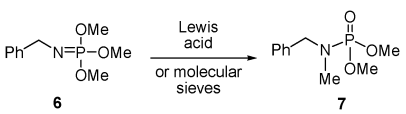


Scheme 2 Mechanism of the $BF_3{\cdot}Et_2O$-catalyzed intermolecular rearrangement of phosphorimidate **6**.

Finally, we investigated the substrate scope for the transformation of different azides, **10**, into the corresponding *N*-methyl substituted phosphoramidates, **11**, *via* the two-step protocol described above, using 1 mol% of $BF_3{\cdot}Et_2O$ as the catalyst. To our delight, we found that the reaction sequence allowed the synthesis of phosphoramidates of great structural diversity in high isolated chemical yields between 78 and 98% (Table 2). Benzylic, phenylic, allylic and aliphatic azides could all be used as substrates, whilst no work-up at the phosphorimidate stage was needed. Of particular note is the fact that even hindered tertiary azides and substrates containing ester functionalities could be transformed in very good overall yields. In addition to methyl transfer, we also probed the rearrangement of *N*-triethylphosphorimidates. These derivatives also delivered the corresponding phosphoramidates in high yields. However, an extended reaction time of 5–6 h was needed to ensure high overall yields.

In conclusion, we have developed a new protocol for the preparation of secondary phosphoramidates from azides and commercially available phosphites *via* a one-pot procedure, including the formation of phosphorimidates and their subsequent Lewis acid-catalyzed rearrangement. This reaction sequence tolerates a wide range of substrates and offers the possibility of synthesizing phosphoramidates in good yields and in high purity. Considering the importance of these

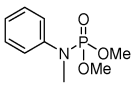
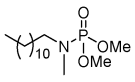
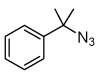
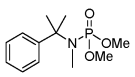
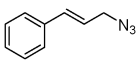
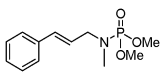
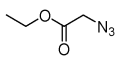
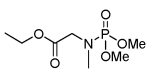
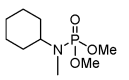
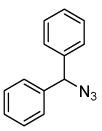
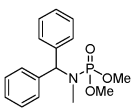
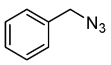
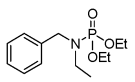
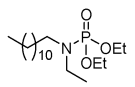
Table 1 Catalyst screening for the rearrangement



Entry	Additive[a]	Concentration (mol%)	Reaction time/h	Temperature/°C	Solvent	Yield (%)
1	—	—	5	80[b]	Benzene	—
2	—	—	5	80[b]	DMF	41
3	Molecular sieves (4 Å)	—	4	80[b]	Benzene	70
4	$BF_3{\cdot}Et_2O$	10	2	80	Benzene	93
5	$BF_3{\cdot}Et_2O$	1	2	80	Benzene	98
6	TMSOTf	1	2	80	Benzene	99
7	$BF_3{\cdot}Et_2O$	1	2	40	CH_2Cl_2	70
8	$BF_3{\cdot}Et_2O$	1	2	80	DMF	62
9	TMSI	1	2	80	Benzene	12[c]
10	TMSI	10	4	80	Benzene	40
11	TMSBr	1	2	80	Benzene	24[c]
12	TMSCl	1	2	80	Benzene	—
13	$AlCl_3$	10[d]	4	80	Benzene	37[c]

[a] Conditions: Catalyst was added to the pre-formed phosphorimidate (1 equiv. BnN_3, 1 equiv. $P(OMe)_3$, 2 h, 80 °C, DMF/benzene or 2 h, 40 °C CH_2Cl_2). For more details see the ESI. [b] The rearrangement was performed directly with 1 equiv. BnN_3 and 1 equiv. $P(OMe)_3$. [c] Conversion determined by ^{1}H-NMR. [d] $AlCl_3$ was not soluble under the reaction conditions.

Table 2 Substrate scope with 1 mol% $BF_3{\cdot}Et_2O$ in benzene

Azide **10**	Phosphite	Reaction conditions[a]	Time/h	Temperature/°C	Yield (%)	Product **11**
	$P(OMe)_3$	A B	2 2	80 80	85	
	$P(OMe)_3$	A B	2 2	80 80	89	
	$P(OMe)_3$	A B	2 2	80 80	88	
	$P(OMe)_3$	A B	2 2	80 80	84	
	$P(OMe)_3$	A B	2 2	80 80	78	
	$P(OMe)_3$	A B	2 2	80 80	84	
	$P(OMe)_3$	A B	2 2	80 80	80	
	$P(OEt)_3$	A B	5 5.5	80 80	98[b]	
	$P(OEt)_3$	A B	12 5	25 80	63	

[a] Conditions: (A) 1 equiv. azide, 1 equiv. $P(OMe)_3$ or $P(OEt)_3$. (B) 1 mol% $BF_3{\cdot}Et_2O$, benzene. The catalyst was added directly to the phosphorimidate without intermediate work-up. For more details see the ESI. [b] TMSOTf as catalyst.

compounds in catalysis and in organic synthesis as precursors to secondary amines, this transformation is of high utility and complements the Staudinger reduction pathway, which directly converts azides into primary amines.

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