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A Catalyst-Free Synthesis of Phosphinic Amides Using *O*-Benzoylhydroxylamines

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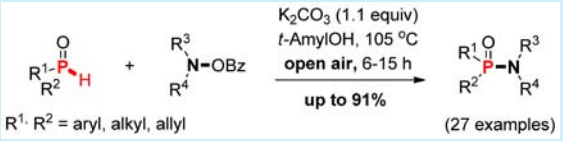
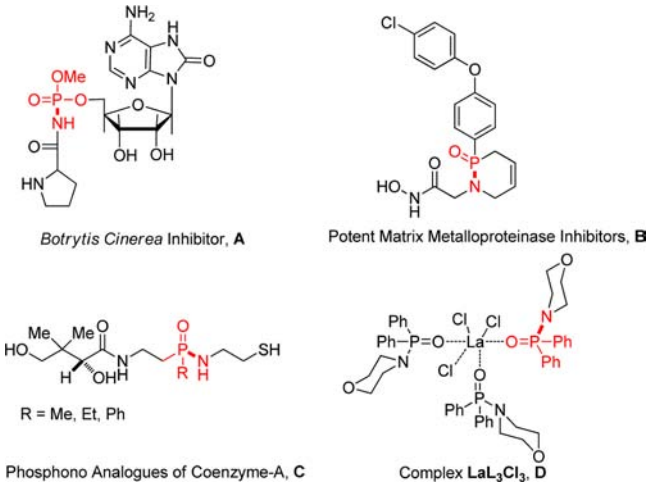
Supporting Information

ABSTRACT: A practical approach for the synthesis of phosphinic amides via the coupling of secondary phosphine oxides (SPOs) with *O*-benzoylhydroxylamines has been reported. Simply heating the mixture of SPOs and *O*-benzoylhydroxylamines in the presence of K_2CO_3 gave the phosphinic amides in moderate to excellent yields under an open air system. This method provides a practical and catalyst-free method for the synthesis of various synthetically valuable phosphinic amides.



Significant attention has been paid to organic molecules containing P(=O)−N bonds since they have been discovered to have widespread utilities in modern organic chemistry, as well as in biological chemistry.[1−3] For example, phosmidosine (compound **A**) exhibits specific inhibitory activity against spore formation of *Botrytis cinerea*.[1a] Sørensen and co-workers found that cyclic phosphinic amides, such as compound **B**, strongly inhibited matrix metalloproteinase (Scheme 1, **A** and **B**).[1c] Phosphinic amides are indispensable

Scheme 1. Representative Useful Phosphoramidates and Phosphinic Amides



structural motifs in a variety of bioactive products. Phosphono analogues of coenzyme-A (such as compound **C**) have been an important aspect of peptides research in recent decades (Scheme 1, **C**).[3c] Morpholinodiphenylphosphine oxide was a good ligand for lanthanide, and stable LaL_3Cl_3-complex **D** could be readily prepared (Scheme 1, **D**).[2e] Phosphinic amides show good performance as flame retardants[4] and extractants for liquid and membrane extraction.[5] Moreover, phosphinic amides are useful precursors for the preparation of aminophosphine borane adducts via the reduction by oxalyl chloride/$NaBH_4$, developed by Gilheany and co-workers.[6]

Traditional routes for syntheses of phosphinic amides involve the treatment of amines with appropriate phosphorus halides (Scheme 2, eq 1) or two-step synthesis: coupling phosphine chlorides with amines followed by the oxidation of P(III) to P(V) (Scheme 2, eq 2).[7,8] Phosphinic amides could be obtained from phosphinic acids and amines by utilizing *n*-propane-phosphonic acid anhydride (T3P) (Scheme 2, eq 3).[9] An interesting synthesis of phosphinic amides via thermal radical rearrangement of P(III)−O−N into P(O)−N was observed by Ranks and Hudson (Scheme 2, eq 4).[10] However, these syntheses require anaerobic reagents and were conducted under anhydrous and inert conditions.[11] Furthermore, the preparation of phosphorus halides or phosphine chlorides suffered from tedious fuming reaction conditions, such as the use of SO_2Cl_2. Jenkins and co-workers reported an interesting synthesis of diphenylphosphinoylhydrazine-1,2-dicarboxylates via a direct nucleophilic addition of SPO to azodicarboxylates (Scheme 2, eq 5).[12] Herein, we report a new practical synthesis of phosphinic amides via a direct amination reaction between bench stable phosphine oxides and *O*-benzoylhydroxylamines (Scheme 2, eq 6).

Our initial plan was to study palladium-catalyzed Catellani *ortho*-amination followed by phosphorylation using aryl halides, diphenylphosphine oxide, and *N*-benzoyloxylmorpholine. To our surprise, in the absence of aryl halides, the reaction afforded the unexpected phosphinic amide **3a** in toluene or DME in 21% or 36% isolated yield, respectively (Table 1, entries 1−2). Interestingly, in the absence of a palladium catalyst, the reaction proceeded uneventfully with 39% of **3a** being isolated (Table 1, entry 3). Under radical conditions, BPO with irradiation, only a trace amount of product was observed (Table 1, entry 4). The addition of 4 Å MS did not alter the outcome (Table 1, entry

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Scheme 2. Synthesis of Phosphinic Amides

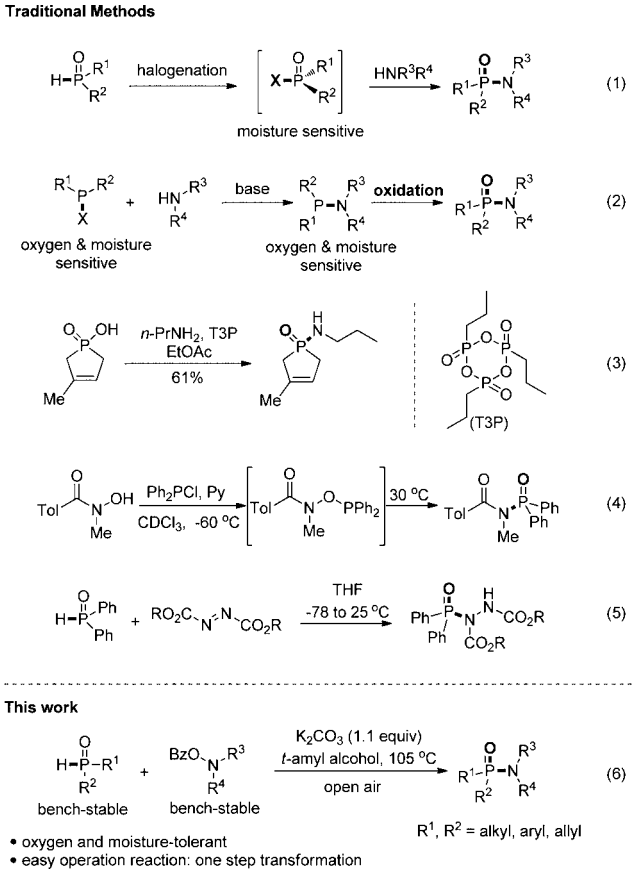
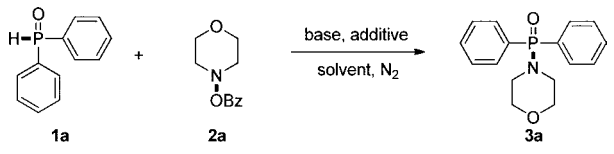


Table 1. Reaction Conditions Optimization[a]



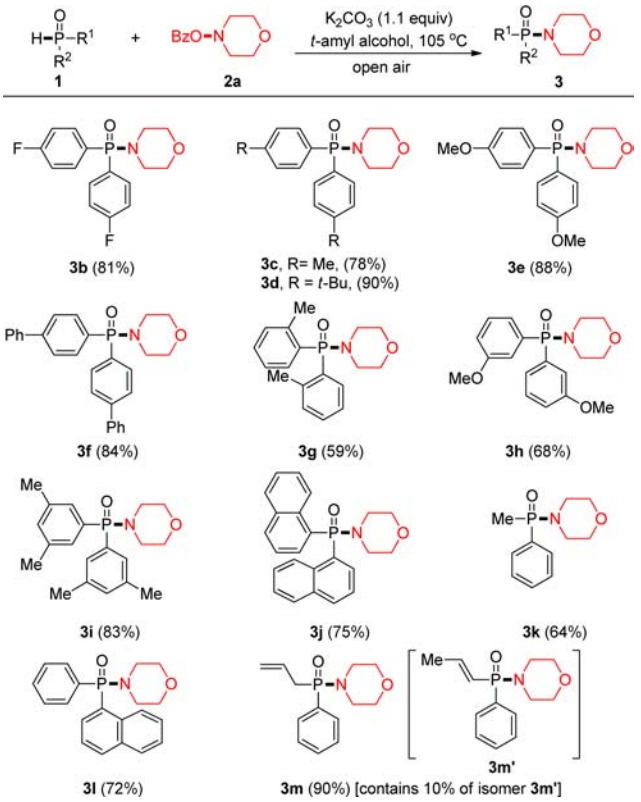
entry	base	solvent	t (°C)	yield of **3a**[b] (%)
1[c]	K_2CO_3	toluene	110	21
2[c]	K_2CO_3	DME	110	36
3	K_2CO_3	DME	105	39
4[d]	K_2CO_3	DME	80	<5
5[e]	K_2CO_3	DME	105	35
6	K_2CO_3	PhF	105	–
7	K_2CO_3	1,4-dioxane	105	–
8	K_2CO_3	*t*-AmylOH	105	86
9	K_2CO_3	*t*-AmylOH	100	70
10	Na_2CO_3	*t*-AmylOH	105	59
11	lutidine	*t*-AmylOH	105	–
12	Cs_2CO_3	*t*-AmylOH	105	30
13[f]	K_2CO_3	*t*-AmylOH	105	68
14[g]	K_2CO_3	*t*-AmylOH	105	85

[a]The reaction was conducted with **1a** (0.20 mmol, 1.0 equiv), **2a** (0.24 mmol, 1.2 equiv), base (0.22 mmol, 1.1 equiv) in solvent (0.10 M). [b]Isolated yields. [c]5 mol % of $Pd(OAc)_2$ and 10 mol % of XPhos were added. [d]Under irradiation of 5 W white light, 10 mol % of BPO was added. [e]4 Å M.S. (50 mg) was added. [f]K_2CO_3 (0.40 mmol, 2.0 equiv) was added. [g]The reaction was conducted under an open air system.

5). A significant solvent effect was observed for this transformation, and no desired product was detected when switching the solvent from toluene to fluorobenzene or 1,4-dioxane (Table 1, entries 6–7). Significantly, it was found that *tert*-amyl alcohol gave high conversion (Table 1, entry 8), and indeed this solvent was utilized for all subsequent studies. Meanwhile, the use of comparatively weaker or stronger bases such as sodium carbonate, 2,6-lutidine, or cesium carbonate decreased the yields dramatically (Table 1, entries 10–12). It should be noted that increasing the loading of K_2CO_3 to 2.0 equiv only showed a negative effect and the yield dropped to 68% (Table 1, entry 13). Furthermore, the reaction was not sensitive to moisture or oxygen, and it could be conducted under an open air system without affecting the yield (Table 1, entry 14).

We evaluated this protocol by applying a series of disubstituted phosphine oxides to the optimum conditions to synthesize various phosphinic amides. Substrates with *para*-substituents on the phenyl rings proceeded smoothly. As illustrated in Scheme 3, the reaction of 4-fluoro, 4-methyl, 4-

Scheme 3. Substrate Scope of Phosphine Oxides[a]



[a]The reaction was conducted with **1** (0.20 mmol), **2a** (0.24 mmol), K_2CO_3 (0.22 mmol) in *t*-AmylOH (0.10 M) at 105 °C.

tert-butyl, 4-methoxyl, and 4-phenyl benzenes gave the desired products in moderate to excellent yields (**3b**–**3f**) (Scheme 3). A compound with an *ortho*-methyl on the phenyl ring afforded the aim product **3g** in relatively lower yield (59%), perhaps for steric reasons. Substrates with electron-donating *meta*-substituents on the phenyl rings were tolerated under these reaction conditions, with the yields being 68% and 83% respectively (**3h**–**3i**). The reaction of di(*α*-naphthyl)phosphine oxide gave a 75% yield of the corresponding product **3j**. It should be noted that the electronic property of the substituents on the phenyl rings has little effect on the yields. Phosphine oxides with two different substituents were also tested. The

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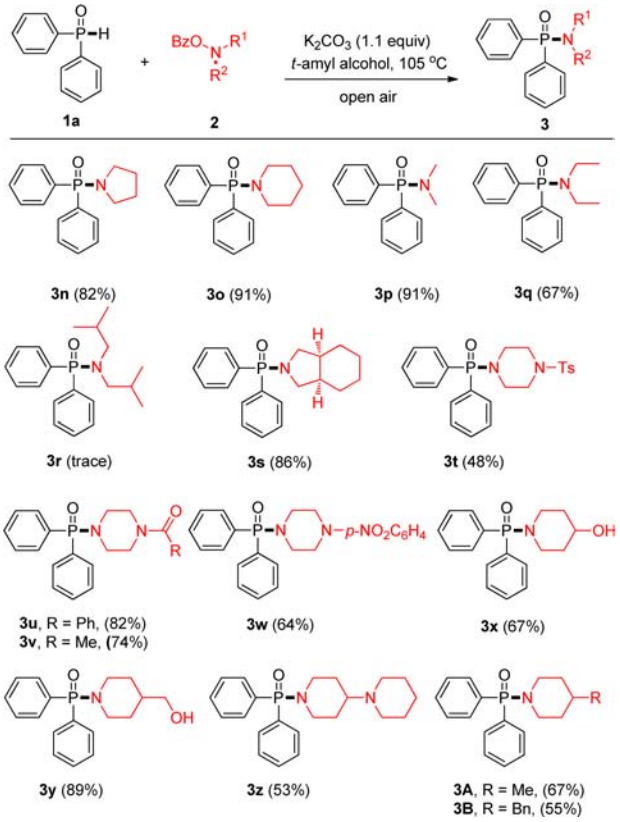
unsymmetric phosphine oxides, such as 1-naphthyl(phenyl)-phosphine oxide and methyl(phenyl)phosphine oxide worked uneventfully to deliver the corresponding products in moderate yields (**3k**–**3l**). Allyl-substituted **3m** was formed with some isomerization. However, the use of dicyclohexyl phosphine oxides as the substrate, the reaction did not deliver any isolable product.

To further explore the generality of this reaction, different substituted *O*-benzoylhydroxylamines were investigated as well (Scheme 4). Both *O*-benzoylhydroxylamines derived from

Scheme 4. Substrate Scope of *O*-Benzoylhydroxyl Amines[a]

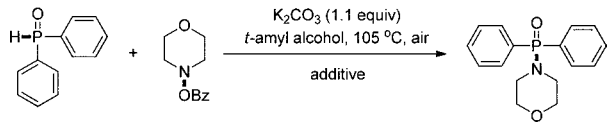


[a]The reaction was conducted with **1a** (0.20 mmol), **2** (0.24 mmol), and K_2CO_3 (0.22 mmol) in *t*-AmylOH (0.10 M) at 105 °C.

pyrrolidine and piperidine provided the desired amination products in high yields (**3n**–**3o**). The reactions of dimethylamine, diethylamine, and *cis*-octahydroisoindole derivatives resulted in moderate to excellent yields (**3p**, **3q**, and **3s**). However, the reaction would not take place upon the use of *O*-benzoyl-*N*,*N*-diisobutylhydroxylamine as the reagent (**3r**), possibly due to the steric hindrance of the two isobutyl groups. Piperazine derivatives with a tosyl, benzoyl, and acetyl protecting group or *para*-nitrophenyl functionality were well tolerated, and moderate to good yields could be achieved (**3t**–**3w**). Free alcohols, including primary and secondary hydroxyl groups, were compatible (**3x** and **3y**). Other substituted piperidine analogues, such as **3z**, **3A**, and **3B**, could also be formed in decent yields.

To gain some mechanistic insight, some control reactions were performed by the addition of radical trapping reagents. With 1.0 equiv of TEMPO, the reaction was completely inhibited, while the use of 0.20 equiv of TEMPO, BHT (1.0 equiv), or diphenylethene (1.0 equiv) resulted in partial inhibition of the reaction (Scheme 5). EPR signals were observed at the early stage of the reaction; however, it is unclear

Scheme 5. Radical Trap Reactions

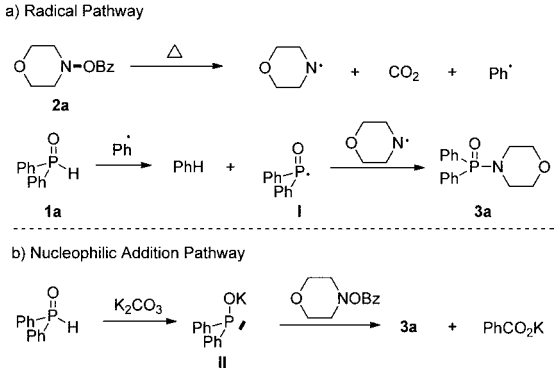


additive (equiv)	yield
Tempo (1.0 equiv)	trace
Tempo (0.20 equiv)	41%
2,6-dibutylhydroxytoluene (1.0 equiv)	18%
1,1-diphenylethene (1.0 equiv)	27%

if that corresponded to the nitrogen, oxygen, or phosphorus radical (see Supporting Information).[13]

Tentatively two plausible pathways with diphenylphosphine oxide and *O*-benzoylhydroxyl morpholine as representative substrates were proposed in Scheme 6. Homolytic bond

Scheme 6. Plausible Reaction Pathways



cleavage of **2a** would generate two radical species by releasing CO_2.[14] Hydrogen abstraction of diphenylphosphine oxide by a phenyl radical to form radical **I**, which gave the product via radical–radical coupling (Scheme 6a). Alternatively, the *O*-benzoyl hydroxylamines are well-known as electrophilic nitrogen reagents.[15] Deprotonation of diphenylphosphine oxide by K_2CO_3 gave **II**, which underwent nucleophilic addition to **2a** to deliver the final product (Scheme 6b). The steric hindrance of the *N*,*N*-(di-isobutyl)amine moiety accounted for the poor yield for phosphinamide **3r**. The isolation of benzoic acid after acidifying the reaction mixture further supported the latter pathway.

In conclusion, a convenient and practical amination of SPOs for the synthesis of phosphinic amides has been reported. In contrast to conventional methods, this newly developed protocol has good functional group tolerance and is compatible with a wide variety of phosphine oxides.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03056.

Experimental procedures, characterization data, and ^{1}H, ^{13}C, ^{19}F, and ^{31}P NMR spectra for new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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