Organic & Biomolecular Chemistry

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View Article Online
DOI: 10.1039/C7OB01510K

Journal Name

ARTICLE

Poly(methylhydrosiloxane) as a green reducing agent in organophosphorus-catalysed amide bond formation

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

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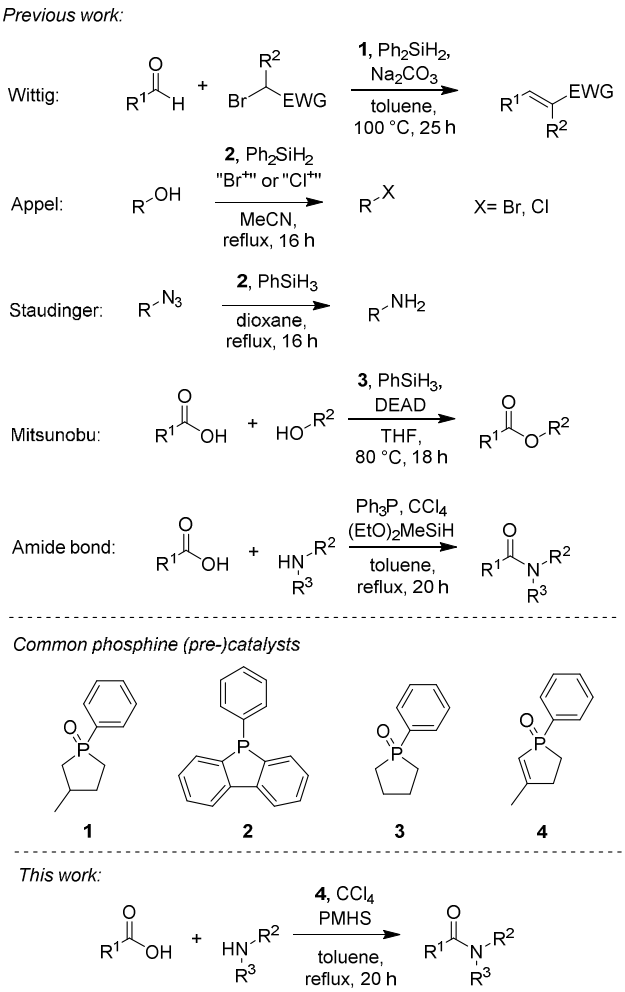
Development of catalytic amide bond formation reactions has been the subject of the intensive investigations in the past decade. Herein we report an efficient organophosphorus-catalysed amidation reaction between unactivated carboxylic acids and amines. Poly(methylhydrosiloxane), a waste product of the silicon industry, is used as an inexpensive and green reducing agent for *in situ* reduction of phosphine oxide to phosphine. The reported method enables the synthesis of a wide range of secondary and tertiary amides in very good to excellent yields.

Over the past decade, there has been a significant interest in the development of catalytic versions of phosphine-mediated reactions that are often used in organic synthesis, including the Staudinger, Mitsunobu, Wittig and Appel reactions.[1] The formation of the relatively strong phosphine oxide bond (P=O, 128 kcal mol^{-1}) is the driving force for the classic versions of these commonly used reactions.[1a] However, the formation of stoichiometric amounts of high molecular weight phosphine oxide waste is highly undesired, as it results in poor overall atom economy, and is often difficult to remove from the desired products. In this regard, the organophosphorus-catalysed reactions heavily rely on the efficient reduction of phosphine oxides to phosphines. Recent reports have shown that organophosphorus catalysis can be achieved by *i*) activation of phosphine species, in this case the oxidation state P^V remains unaffected throughout the reaction[2] or *ii*) P^{III}/P^V redox chemistry, i.e. the formed phosphine oxide (P^V) is reduced *in situ* to the corresponding phosphine (P^{III}).[3]

In the latter case, silanes, such as phenylsilane and diphenylsilane, have been typically employed as reducing agents due to their high reactivity and chemoselective nature.[4] In P^{III}/P^V redox organophosphorus catalysis 5-membered cyclic phosphine oxides are generally used as pre-catalysts (Scheme 1). Cyclic phosphine oxides are more prone to reduction in comparison to triphenylphosphine oxide, whilst the corresponding cyclic phosphines (P^{III}) remain their nucleophilic character against several types of electrophilic reagents, and are therefore still able to effectively mediate various transformations. For example, O'Brien *et al.* employed 3-methyl-1-phenylphospholane-1-oxide **1** in the first



Scheme 1 Organophosphorus-catalysed reactions.

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Electronic Supplementary Information (ESI) available: Synthetic procedures, characterisation of compounds, and NMR spectra. See DOI: 10.1039/x0xx00000x

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DOI: 10.1039/C7OB01510K

organophosphorus-catalysed Wittig reaction.[5] Diphenylsilane was used to selectively reduce **1**, while starting aldehyde and alkene products remained unaffected by the **1**-Ph_2SiH_2 system (Scheme 1). *In situ* reduction of dibenzophosphole oxide, formed from **2**, with diphenylsilane in a catalytic Appel reaction was first reported by van Delft *et al.* (Scheme 1).[6] Dibenzophosphole **2** was later also used in the organophosphorus-catalysed Staudinger reduction.[7] Other 5-membered cyclic phosphines that have been demonstrated to catalyse important chemical transformations include phenyl phospholane oxide **3**, which was used in the catalytic Mitsunobu reaction,[8] and phospholene oxide **4** in the catalytic diaza-Wittig reaction (Scheme 1).[9]

Although numerous procedures for the synthesis of amide bonds are well known and described in literature, most rely on the use of stoichiometric amounts of reagents.[10] In order to circumvent large amounts of unwanted waste (typically ureas), the past decade has witnessed a great success in development of efficient metal-[11] and organocatalysed[12] amide bond formation reactions, starting from readily available starting materials.

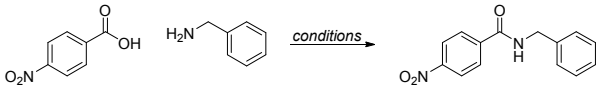
We have recently reported that unactivated carboxylic acids and amines undergo Ph_3P-catalysed direct amidation in the presence of 2 equiv. of CCl_4, 1.5 equiv. of $(EtO)_2MeSiH$ and catalytic amounts (5 mol%) of bis(*p*-nitrophenyl) phosphate.[12f] We envisioned that it would be beneficial to develop a "greener" version of direct amidation of carboxylic acids using an environmentally benign and cheap silane, instead of more reactive methyldiethoxysilane, as a reducing agent for the vital conversion of phosphine oxide to phosphine that provides the key step in catalysis.

Results and discussion

Poly(methylhydrosiloxane) (PMHS) was considered as an attractive candidate due to its low cost and environmentallly friendly characteristics.[13] It has been previously shown for related organophosphorus-catalysed reactions that by implementing PMHS, major reductions in cumulative energy demand (CED) and greenhouse gas (GHG) emmisions can be achieved.[14] In a model reaction, *p*-nitrobenzoic acid and benzylamine reacted in the presence of 0.25 equiv. of Ph_3P, 2.0 equiv. of CCl_4, 9 Si-H equiv. of poly(methylhydrosiloxane) (PMHS, Mw 390 Da) and 0.05 equiv. of bis(*p*-nitrophenyl) phosphate at 110 °C in toluene to yield 48% of *N*-benzyl-*p*-nitrobenzamide **5** (Table 1, entry 1). Use of Ph_3PO instead of Ph_3P afforded 36% of the amide under standard conditions, indicating that an additional reduction step at the beginning of the catalytic cycle lowers the overall yield of the amidation reaction (Table 1, entry 2). Various phosphines that possess either electron-donating or electron-withdrawing groups were then tested, because we conceived that fine-tuning the electronics of the P=O bond could have a significant effect on the rate of silane-mediated phosphine oxide reduction. Different Ph_3P derivatives, however, did not improve the yield of the model reaction (Table 1, entries 3–5).

Next, we tested phosphine oxides that were previously used in other well known organophosphorus-catalysed reactions (Scheme 1). A combination of the fused phospholane **2** and PMHS provided only 30% of amide **5** under standard reaction conditions. We were pleased that five-membered phosphine oxides **1**, **3**, and **4** possess redox properties that are compatible with PMHS-mediated reduction (Table 1, entries 7–9). Saturated phosphine oxides **1** and **3** afforded 47% and 61% of the amide **5** under standard conditions. Notably, we were particularly pleased to observe that the commercially available 3-methyl-1-phenyl-2-phospholene oxide **4**, afforded the amide **5** in excellent 82% NMR yield (Table 1, entry 9).

Table 1 Optimisation of organophosphorus-catalysed amide bond formation.[a]



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Entry	Catalyst	Reagent[b]	NMR Yield[c]
1	Ph_3P	$PMHS_{390}$(9)/phosphate	48
2	Ph_3PO	$PMHS_{390}$(9)/phosphate	36
3	$(p\text{-MePh})_3P$	$PMHS_{390}$(9)/phosphate	50
4	$(p\text{-MeOPh})_3P$	$PMHS_{390}$(9)/phosphate	46
5	$(C_6F_5)_3P$	$PMHS_{390}$(9)/phosphate	15
6	**2**	$PMHS_{390}$(9)/phosphate	30
7	**1**	$PMHS_{390}$(9)/phosphate	47
8	**3**	$PMHS_{390}$(9)/phosphate	61
9	**4**	$PMHS_{390}$(9)/phosphate	82
10	**4**	TMDS(9)/phosphate	79
11	**4**	$PMHS_{10k}$(9)/phosphate	53
12	**4**	$PMHS_{2450}$(9)/phosphate	92
13	**4**	$PMHS_{2450}$(6)/phosphate	74
14	**4**	$PMHS_{2450}$(12)/phosphate	73
15	**4** (15 mol%)	$PMHS_{2450}$(9)/phosphate	82
16	**4** (10 mol%)	$PMHS_{2450}$(9)/phosphate	62
17	**4**	-	trace
18	**4**	$PMHS_{2450}$(9)	67
19[d]	-	$PMHS_{2450}$(9)	13
20	-	$PMHS_{2450}$(9)/phosphate	26
21[e]	-	$PMHS_{2450}$(9)/phosphate	33

[a] Conditions: *p*-nitrobenzoic acid (0.5 mmol), benzylamine 0.65 mmol), phosphine (oxide) (0.125 mmol, 25 mol%), CCl_4 (1.0 mmol), PMHS (0.12 mmol.; 9 Si-H eq.), bis(*p*-nitrophenyl) phosphate (0.025 mmol), 2.5 mL toluene, 110 °C, 20h. [b] PMHS = poly(methylhydrosiloxane); average molecular weight in subscript, Si-H equivalents in parenthesis. [c] NMR yield (%) determined using tri-*tert*-butylbenzene as an internal standard. [d] Reaction performed without CCl_4. [e] 15 mol% phosphate.

PMHS is available in various lengths, therefore we tested whether the shortest analog tetramethyldisiloxane (TMDS, Table 1, entry 10) and longer analogs, with average molecular weights of 10 kDa and 2450 Da (Table 1, entries 11 and 12) resulted in improved yields of the amide bond formation. Similar yields were obtained for TMDS and PMHS (Mw 390),

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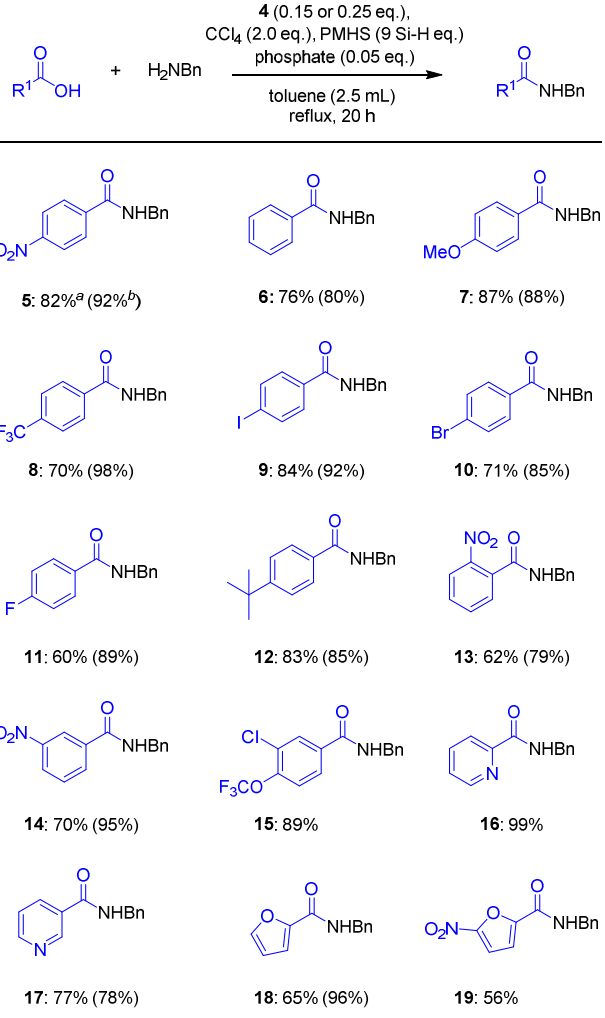
whereas longer PMHS (Mw_{avg} 2450) afforded the amide in substantially increased 92% yield. The longest PMHS analog, with an average molecular weight of 10 kDa, only afforded 53% of amide **5**. Decreasing or increasing the amount of PMHS resulted in lower NMR yields; 6 and 12 hydride equiv. of PMHS afforded 74 and 73% of the target amide, respectively (Table 1, entries 13 and 14). Employing lower amounts (15 mol% and 10 mol%) of phosphine oxide **4** resulted in slightly decreased, but still very good yields of the desired amide (82% and 62%) (Table 1, entries 15 and 16). When the model reaction was carried out in the absence of PMHS/phosphate, we detected only traces of the target amide in ^{1}H NMR spectra (Table 1, entry 17). Importantly, when the model reaction was performed without bis(*p*-nitrophenyl*)* phosphate, only 67% of amide was obtained; this result demonstrates the positive contribution of phosphate to the overall yield (Table 1, entry 18). Due to the fact that silanes have the ability to promote direct amidation of carboxylic acids,[15] we also examined potential PMHS-mediated formation of the target amide **5** under standard conditions. In the presence of PMHS, *p*-nitrobenzoic acid and benzylamine yielded only 13% of amide (Table 1, entry 19); the observed low yield is comparable with our previously observed formation of the amide (9%), when only *p*-nitrobenzoic acid and benzylamine were heated in toluene at 110 °C.[12f] Moreover, in the presence of CCl_4, PMHS, and phosphate, a small amount of amide was formed: 26% in the presence of 5 mol% phosphate, and 33% with 15 mol% phosphate (Table 1, entries 20 and 21).

The most optimal ratios of the reagents (Table 1, entry 12) served as a base for additional experiments in which we examined the role of the solvent, reaction time, and the amount of amine on the catalytic reaction. Among common and high boiling point solvents, toluene was found to be the preferred one; 42–52% of the amide **5** was formed in *n*-heptane, 1,4-dioxane and *o*-xylene (Table S1). Due to fewer catalytic cycles, shorter reaction times also resulted in lower yields (Table S2). Increasing or decreasing the equivalents of benzylamine in the reaction resulted in decreased yields: 81% amide with 1.1 equiv. benzylamine and 72% amide with 2.0 equiv. benzylamine (Table S3).

With the optimised reaction conditions in hand, we set out to explore the scope of the reaction with both 15 and 25 mol% of phosphine oxide **4** (Tables 2 and 3). *N*-Benzylbenzamide **6** was obtained in 76% isolated yield with 15 mol% of **4**, while increasing the catalyst loading to 25 mol% afforded 80% of amide **6**. Various *para*-substituted benzoic acid derivatives, bearing electron-donating and electron-withdrawing functional groups, were reacted with benzylamine (Table 2, **7**-**12**). In general, very good to excellent isolated yields were obtained with both 15 mol% and 25 mol% of **4**. The formed benzamides that bear various halogen substituents at the aromatic ring could be further functionalised employing well established cross-coupling reactions. A moderate yield of 62% was obtained for *o*-nitrobenzoic acid in the presence of 15 mol% of **4**, whereas the yield increased significantly (79%) in the presence of 25 mol% of **4** (Table 2, **13**). For *m*-nitrobenzoic acid, 70% of the corresponding amide was obtained (Table 2, **14**). The reaction between benzylamine and disubstituted *m*-chloro-*p*-trifluoromethoxybenzoic acid proceeded very well and afforded the corresponding disubstituted benzamide in excellent 89% yield (Table 2, **15**). Heteroaromatic carboxylic acids, such as picolinic acid and nicotinic acid, also underwent organophosphorus-catalysed amide bond formation in excellent 99% and 77% yields, respectively (Table 2, **16** and **17**). Furan-2-carboxylic acid and electron-deficient 5-nitrofuran-2-carboxylic acid reacted with benzylamine under standard conditions to provide 65% and 56% of the desired amides, respectively (Table 2, **18** and **19**). In general, organophosphorus-catalysed reaction in the presence of 25 mol% of **4** resulted in increased isolated yields (on average ~15%) of amides, when compared to reactions that used 15 mol% of **4** (Table 2). Aliphatic carboxylic acids were not examined, because they undergo direct amidation at elevated temperatures.[11a]

Table 2 Organophosphorus-catalysed amide bond formation of various carboxylic acids.



[a] Isolated yield, 15 mol% pre-catalyst **4**. [b] Isolated yield, 25 mol% pre-catalyst **4**.

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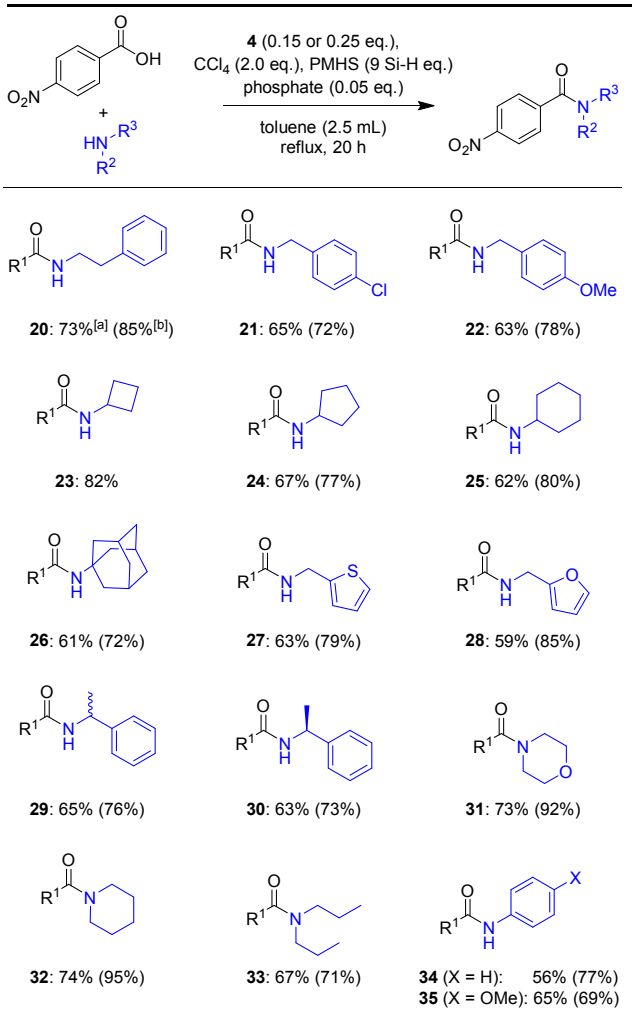
We further explored the scope of the reaction by examining various amines with *p*-nitrobenzoic acid under optimised conditions (Table 3). Primary aliphatic amines, such as phenethylamine, *p*-chlorobenzylamine, *p*-methoxybenzylamine, and cycloalkylamines with various ring size, yielded amides in very good yields, ranging from 62 to 82% (Table 3, **20**–**25**). The reaction also proceeded well with sterically hindered 1-adamantylamine, which afforded the corresponding amide **26** with a yield of 61%. Thiophenemethylamine and furfurylamine gave moderate yields of 63%, and 59%, respectively (Table 3, **27** and **28**). As expected, with racemic and enantriomerically pure 1-phenylethylamine similar yields of amide were obtained: 65% (*R*,*S*) and 63% (*S*), respectively (Table 3, **29** and **30**). We were pleased to find that the reaction proceeds with virtually complete retention of configuration (>98%), as confirmed by chiral HPLC analyses (Figures S1 and S2). Amide bond formation also tolerates the use of secondary amines, as tertiary amides derived from piperidine and morpholine were prepared in 74% and 73% yields, respectively (Table 3, **31** and **32**). Notably, no reduction of tertiary amide **32** to the corresponding tertiary amine was observed under our reaction conditions. Acyclic dipropylamine also reacted under standard conditions to afford the corresponding tertiary amide **33** with 67% isolated yield. Aniline, the simplest example of arylamine, yielded 56% of amide **34**, the result that is likely due to the decreased nucleophilicity of the amine group; our previously established method only afforded 25% of the same isolated amide.[12f] Introducing a *p*-methoxy substituent on aniline increases the nucleophilicity of the amine functionality, and indeed *p*-anisidine gave a slightly increased yield of 65% amide **35**. Again, use of 25 mol%, instead of 15 mol%, of **4** led to increased yields (~15%) of amides (Table 3).

Table 3 Organophosphorus-catalysed amide bond formation of various amines.



[a] Isolated yield, 15 mol% pre-catalyst **4**. [b] Isolated yield, 25 mol% pre-catalyst **4**.

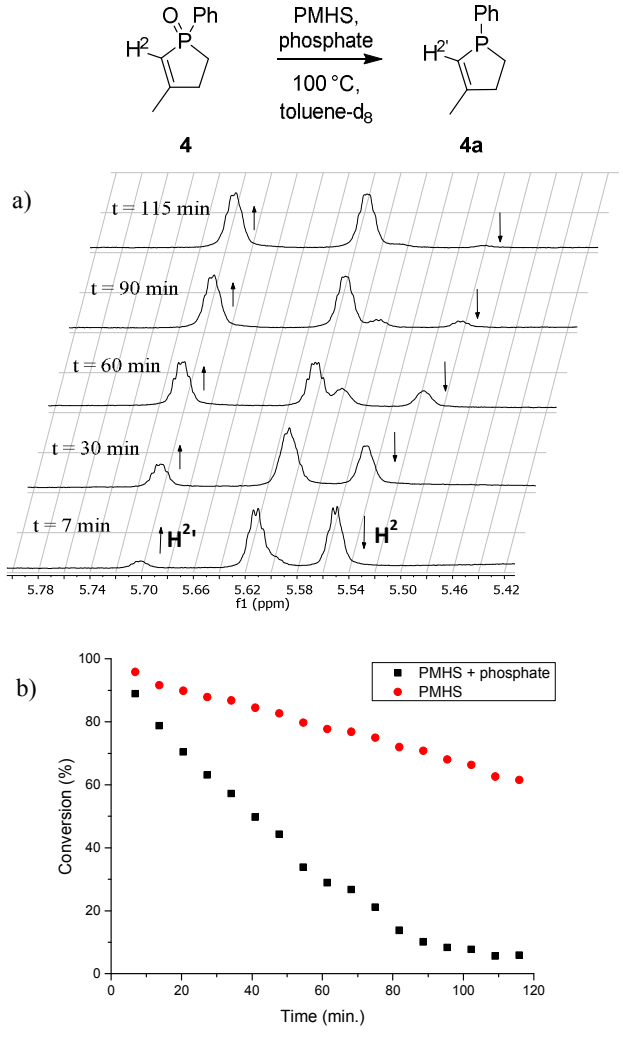


Figure 1 a) Stacked ^{1}H NMR spectra showing the reduction of **4** to **4a** in the presence of PMHS and bis(*p*-nitrophenyl) phosphate and b) conversion of **4** to **4a** plotted against time in the presence of PMHS and bis(*p*-nitrophenyl) phosphate (black squares), and just PMHS (red dots).

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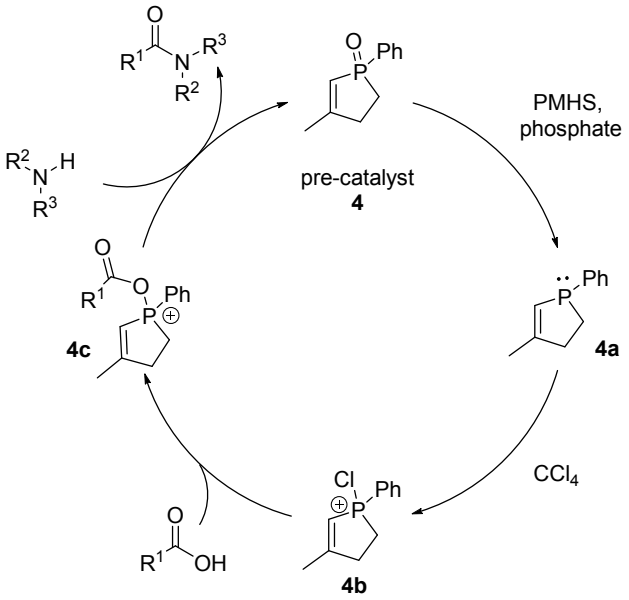
In comparision with our recently reported amidation reaction that is based on the Ph_3P-$(EtO)_2MeSiH$ system,[12f] the method reported here possesses three advantages: *i*) it uses the environmentally benign and cheap PMHS as a reducing agent; *ii*) it uses a low catalyst loading of 15 mol% of phosphine oxide **4** (instead of 25 mol% of Ph_3P); and *iii*) despite using a lower catalyst loading and requiring an additional reduction step at the beginning of the catalytic cycle, the isolated yields for various amides are significantly higher (on average ~15%) when compared with the first version of the reaction.

The rate of reduction of phosphine oxide **4** to the corresponding phosphine **4a** by PMHS and bis(p-nitrophenyl) phosphate was also investigated. For this purpose *in situ* quantitative variable-temperature (VT) ^{1}H NMR spectroscopy (Figures 1, S3, and S4) was used because *i*) we observed a precipitation of phosphine species when the reaction mixture was cooled to room temperature and subsequently analysed in room temperature NMR experiments and *ii*) the rate of reduction was too high for detailed analyses by *in situ* quantitative VT ^{31}P NMR spectroscopy. The ratios between two distinct peaks of the starting phosphine oxide **4** (H^2 δ 5.55 ppm) and the formed phosphine **4a** ($H^{2'}$ δ 5.70 ppm) were followed over time (Figure 1a). In line with our results that show that a combination of **4** and PMHS/bis(*p*-nitrophenyl) phosphate leads to very efficient amide bond formation, we observed almost complete conversion of phosphine oxide **4** to the corresponding phosphine **4a** within 90 minutes at 100 °C in toluene (Figure 1b). In the absence of phosphate, however, only ~40% of phosphine oxide **4** was reduced to phosphine **4a** (Figure 1b), the result that is consistent with our organophosphorus-catalysed amidation reaction (Table 1, entry 18). It is noteworthy that Beller and coworkers demonstrated that bis(*p*-nitrophenyl) phosphate is essential for $(EtO)_2MeSiH$-mediated reduction of phosphine oxides to corresponding phosphines.[4b] As expected, we observed that the rate of PMHS/phosphate-mediated reduction of **4** is even higher at 110 °C (>95% in 20 minutes, Figure S5), the temperature at which the presented amidation reaction is performed.

Although there is in principle a possibility that the reported reaction involves the formation of silyl chloride and/or silyl ester *via* an alternative pathway, our VT NMR experiments demonstrate that the rate of the PMHS-mediated reduction of phosphine oxide **4** into phosphine **4a** is compatible with the yields of the formed amide products. We were not able to detect any clear formation of silyl chloride or related silyl ester in ^{1}H and ^{29}Si NMR spectra of the reaction mixture. In addition, we did not detect any formation of H_2 in ^{1}H NMR during the catalytic reaction,[15b] a result that furthermore suggests that silyl ester is not formed during the reported organophosphorus-catalysed amide bond formation reaction.

Based on methodological and mechanistic investigations of related organophosphorus-catalysed reactions, our ^{1}H NMR studies, and control experiments, a proposed catalytic cycle is outlined in Scheme 2. First, a pre-catalyst **4** is reduced to the corresponding phosphine **4a** in the presence of PMHS and bis(*p*-nitrophenyl) phosphate. Phosphine **4a** then reacts with carbon tetrachloride (CCl_4) to form the chlorophosphonium intermediate **4b** that possesses the P^V oxidation state. Nucleophilic substitution of **4b** by a carboxylate anion subsequently leads to a new intermediate **4c**, in which the carboxylate is now converted into a good leaving group. The formed **4c** is susceptible towards nucleophilic attack by an amine, thereby forming the desired amide product and phosphine oxide **4**. It is also possible that **4c** first reacts with chloride ion to yield **4** and acyl chloride,[16] which then reacts with amine to afford the amide product. The formed **4** is subsequently used in the new catalytic cycle.



Scheme 2 Proposed catalytic cycle.

Conclusions

In conclusion, we have developed a green version of organophosphorus-catalysed amide bond formation between unactivated aromatic carboxylic acids and amines. The commercially available pre-catalyst 3-methyl-1-phenyl-2-phospholene oxide **4** is reduced *in situ* by inexpensive and environmentally benign poly(methylhydrosiloxane) and bis(*p*-nitrophenyl) phosphate. With our newly developed method a wide variety of secondary and tertiary amides could be synthesised in very good to excellent yields. It is envisioned that organophosphorus catalysis will be a subject of extensive investigations in the upcoming years. Moreover, we believe that poly(methylhydrosiloxane) will find practical applications in several other common reactions in organic chemistry.

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Experimental

A Radleys tube equipped with a magnetic stirbar was charged with carboxylic acid (0.5 mmol, 1.0 equiv.), phosphine oxide **4** (0.075 mmol or 0.125 mmol; 0.15 or 0.25 equiv.), and bis(*p*-nitrophenyl) phosphate (0.025 mmol, 0.05 equiv.). Subsequently toluene (2.5 mL, 0.2 M) was added, and to the formed suspension were added benzylamine (0.65 mmol, 1.3 equiv.), CCl_4 (1.0 mmol, 2.0 equiv.), and poly(methylhydrosiloxane) (Mw 2450 Da, 0.12 mmol, 9 Si-H equiv.). The reaction was stirred at 110 °C for 20 hours. After cooling to room temperature, toluene was removed under reduced pressure and the crude product was resuspended in ethyl acetate (20 mL). The organic phase was washed with sat. aqueous $NaHCO_3$ (2 x 20 mL), brine (1 x 20 mL), dried over Na_2SO_4, filtered, and evaporated. The crude product was purified by silica column chromatography (ethyl acetate and *n*-heptane) to afford the desired amide.

Conflicts of Interest

There are no conflicts of interest to declare.

Acknowledgements

We thank Dr. Paul White for technical assistance with in situ VT ^{1}H NMR and ^{31}P NMR experiments.

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In situ reduction of phosphine oxide by poly(methylhydrosiloxane) leads to efficient amidation reaction between carboxylic acids and amines.