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Sustainable organophosphorus-catalysed Staudinger reduction

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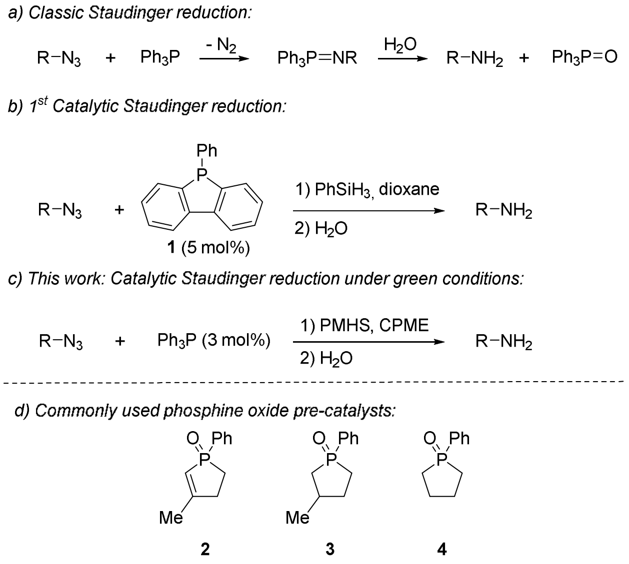
A highly efficient and sustainable catalytic Staudinger reduction for the conversion of organic azides to amines in excellent yields has been developed. The reaction displays excellent functional group tolerance to functionalities that are otherwise prone to reduction, such as sulfones, esters, amides, ketones, nitriles, alkenes, and benzyl ethers. The green nature of the reaction is exemplified by the use of PMHS, CPME, and a lack of column chromatography.

Organic azides are important intermediates in the synthesis of various classes of nitrogen containing molecules. For instance, azides are used in the azide-alkyne Huisgen cycloaddition, various related strain promoted click reactions, Aza-Wittig reaction, Staudinger ligation, and Staudinger reduction.[1] The transformation of organic azides to amines can be achieved by means of catalytic hydrogenation in the presence of H_2 and transition metal catalyst, such as Pd.[2] Also, strong reducing agents, such as lithium aluminium hydride ($LiAlH_4$), efficiently reduce azides to amines.[3] Under these conditions, however, functional group tolerance is severely hampered; catalytic hydrogenation typically results in reduction of the nitro group, and alkene and alkyne functionalities, whereas with $LiAlH_4$ carboxylic acids and esters are reduced. Another commonly used approach in converting azides to amines is the Staudinger reduction (also known as Staudinger reaction) (Scheme 1a). In the classic Staudinger reaction, stoichiometric amounts of triphenylphosphine react with the azide to form a phosphazide intermediate, which subsequently loses N_2 to form an aza-ylide; in the presence of water, this aza-ylide forms the desired amine and triphenylphosphine oxide by-product.[4]



Scheme 1 [a] Classic Staudinger reduction in the presence of stoichiometric amounts of triphenylphoshphine. [b] Catalytic Staudinger reduction in the presence of 5 mol% 1-phenyl-dibenzophosphole **1** with phenylsilane as a reducing agent. [c] This work: Catalytic Staudinger reduction in the presence of 3 mol% triphenylphosphine and poly(methylhydrosiloxane) (PMHS) as a green reducing agent in cyclopentylmethyl ether (CPME) as a green solvent. [d] Phosphine oxides **2–4** that are commonly used in organophosphorus catalysis.

The formation of large amounts of phosphine oxide by-product under stoichiometric conditions is highly undesirable, as it results in poor overall atom economy and separation from the desired products can be troublesome.[5] To circumvent the formation of significant amounts of phosphine oxide waste, a catalytic Staudinger reduction was reported by van Kalkeren *et al*. in 2012.[6] *In situ* reduction of the formed aza-ylide intermediate by phenylsilane, followed by an aqueous work-up afforded the desired amine product and reformation of dibenzophosphole **1** (Scheme 1b).

Besides the Staudinger reduction, various other phosphine-catalysed transformations, including the Appel, Mitsunobu, Wittig, Staudinger ligation and amide-bond formation reactions have been developed recently.[7] In contrast to the catalytic Staudinger reduction, most of these reactions appear to rely on *in situ* reduction of phosphine oxides, which are formed during the reaction, to phosphines. Because the

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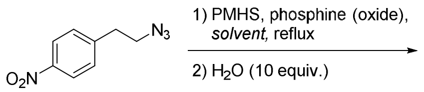
reduction of triphenylphosphine oxide is difficult and often requires harsh conditions (*i.e.* elevated temperature, reactive silane as reducing agent),[8] triphenylphosphine has typically been replaced by other phosphines (or phosphine oxide pre-catalysts), which are more prone to reduction. For instance, 3-methyl-1-phenyl-2-phospholene 1-oxide **2** was used in the catalytic aza-Wittig reaction[9] and very recently by our group in the catalytic amidation between carboxylic acids and amines (Scheme 1d).[7f] In addition, phosphine oxides **3** and **4**, were used as catalysts in the catalytic Wittig and Mitsunobu reactions, respectively.[7b, 7d]

To date, most, if not all, reported catalytic organophosporus reactions are lacking sufficiently green characteristics, mainly due to uses of environmentally problematic solvents and reducing agents. Here we report the development of a sustainable and highly efficient organophosphorus-catalysed Staudinger reduction using poly(methylhydrosiloxane) (PMHS) as a green reducing agent and cyclopentylmethyl ether (CPME) as a renewable solvent (Scheme 1c).[10]

We started our investigations by testing whether the previously reported dibenzophosphole **1** was compatible with poly(methylhydrosiloxane) as a reducing agent in the catalytic Staudinger reduction in toluene. We were pleased to find that 79% of 4-nitrophenethylamine was obtained from 4-nitrophenethyl azide in the presence of 3 mol% of **1** and 6 Si-*H* equivalents of PMHS (M_w 2450 Da) (Table 1, entry 1). When phosphine oxide **2** was used, 82% of amine was obtained under the same conditions (Table 1, entry 2). Cyclic phosphine oxide pre-catalysts **3** and **4** were also evaluated; similar NMR yields of 70 and 72% of amine were obtained (Table 1, entries 3-4). We were particularly pleased to find that use of cheap and commercially available triphenylphosphine resulted in the formation of 94% 4-nitrophenethylamine (Table 1, entry 5). Triphenylphosphine appears to be a comparatively better catalyst than **2**-**4**, likely because these are actually precatalysts that exist in the forms of phosphine oxides, thus requiring another catalytic cycle in the presence of PMHS. Decreasing the reaction temperature to 80 °C in toluene drastically decreased the yield, as only 29% of amine was formed (Table 1, entry 6). Thus, we tested various solvents with high boiling points, and found that the reaction proceeded very poorly in both 1,4-dioxane (11%) and *n*-heptane (24%) (Table 1, entries 7-8).

Table 1 Optimisation of the catalytic Staudinger reduction[a]



Entry	Phosphine (equiv.)	Solvent	Yield (%)[b]
1	**1** (0.03)	Toluene	79
2	**2** (0.03)	Toluene	82
3	**3** (0.03)	Toluene	70
4	**4** (0.03)	Toluene	72
5	Ph_3P (0.03)	Toluene	94
6[c]	Ph_3P (0.03)	Toluene	29
7	Ph_3P (0.03)	Dioxane	11
8	Ph_3P (0.03)	*n*-Heptane	24
9	Ph_3P (0.03)	2-MeTHF	0
10	Ph_3P (0.03)	CPME	97
11[d]	Ph_3P (0.03)	CPME	91
12[e]	Ph_3P (0.03)	CPME	58
13[f]	Ph_3P (0.03)	CPME	69
14	Ph_3P (0.02)	CPME	94
15	Ph_3P (0.01)	CPME	54
16[c]	Ph_3P (0.03)	CPME	28
17	Ph_3PO (0.03)	CPME	<1
18	Ph_3PO (0.10)	CPME	<1
19	-	CPME	0
20[g]	Ph_3P (0.03)	CPME	2

[a] 4-nitrophenethyl azide (0.5 mmol), PMHS (M_w 2450 Da, 0.08 mmol, 6 Si-H equiv.), phosphine (oxide), solvent (2.5 mL, 0.2 M), for 20 hours at reflux; [b] NMR yield using 1,3,5-trimethoxybenzene as an internal standard; [c] reaction at T = 80 °C; [d] 9 Si-H equiv. PMHS (0.12 mmol); [e] 3 Si-H equiv. PMHS (0.04 mmol); [f] 8 hours reaction time; [g] no PMHS added.

We were particularly curious to explore whether the model catalytic reaction works well in 2-methyltetrahydrofuran (2-MeTHF) and cyclopentylmethyl ether (CPME), both being green and sustainable solvents produced from biomass.[10b, 11] No amine product was observed when the reaction was carried out in 2-MeTHF, likely due to lower reaction temperature (Table 1, entry 9). However, we were indeed very pleased to find that the catalytic Staudinger reduction proceeds very well in CPME; nearly quantitative NMR yield (97%) of amine was achieved under standard conditions (*i.e.* 3 mol% Ph_3P, 6 Si-H equiv. PMHS, 106 °C, 20 h) (Table 1, entry 10). Increasing the amount of PMHS did not improve the yield of the reaction (Table 1, entry 11), whereas decreasing PMHS to 3 Si-H equivalents resulted in a lower production (58%) of amine (Table 1, entry 12). Thus we decided to use 6 Si-H equivalents of PMHS in all subsequent experiments (0.08 mmol of total PMHS). Shortening the reaction time to 8 hours led to the formation of 69% of amine, indicating that the reaction is relatively fast in the first few hours (Table 1, entry 13). A more detailed time course of the reaction was also investigated (Figure S1). Interestingly, even in the presence of 2 mol% of Ph_3P, 94% of amine was obtained, whereas decreasing the catalyst loading to 1 mol% produced the amine in a somewhat lower, but still comparatively good 54% yield under standard conditions (Table 1, entries 14-15). Lowering the reaction temperature resulted in a significantly lower yield; *i.e.* at 80 °C only 28% of amine was formed (Table 1, entry 16). Notably, when triphenylphosphine was replaced by triphenylphosphine oxide, hardly any amine was formed at 3 mol% and 10 mol% loadings (<1%, Table 1, entries 17-18). This observation suggests that PMHS does not possess the ability to reduce Ph_3PO to Ph_3P, and as a result, yields no amine product; this result is in agreement with Beller's work.[8b] To confirm this observation, we performed a control experiment in which we attempted to reduce triphenylphosphine oxide (0.1 mmol) by PMHS (0.16 mmol) under our reaction conditions. In line with our expectations, no reduction of phosphine oxide was observed by ^{31}P NMR (Figure S2). With the aim of providing better insight into the molecular requirements for the catalytic reaction, we also carried out two important control experiments. No amine product was

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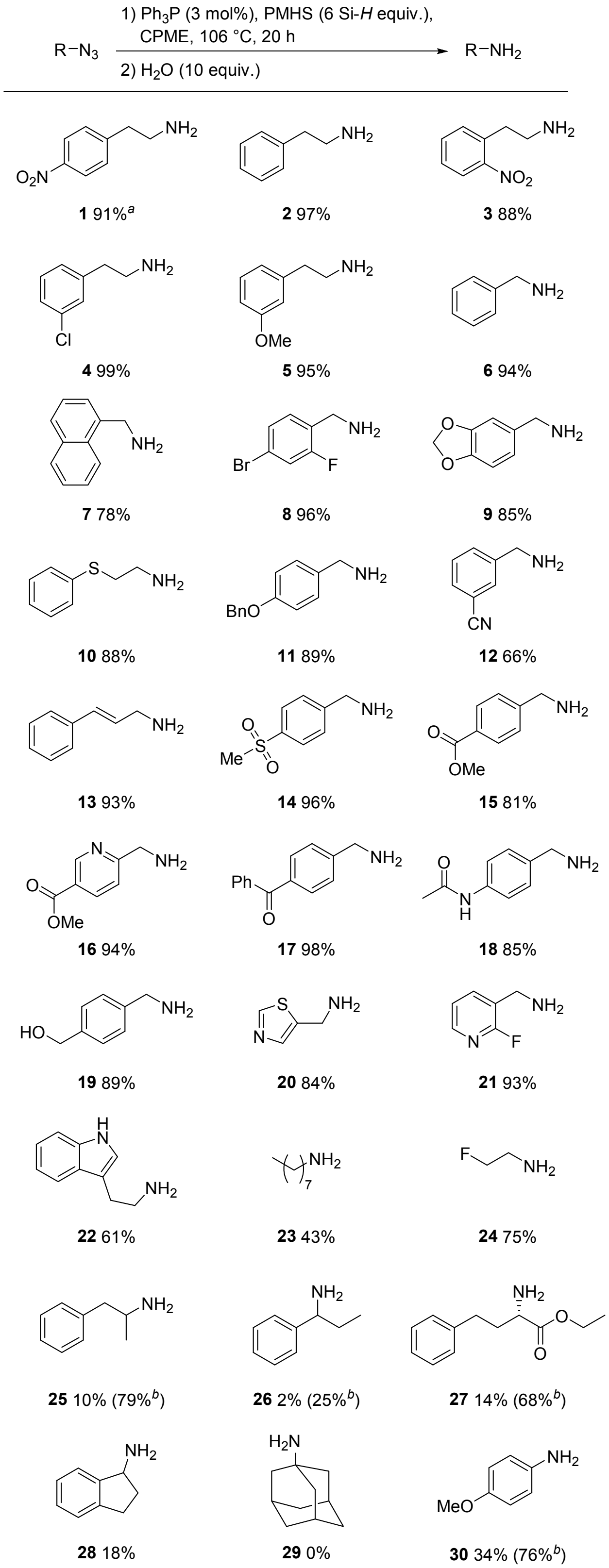
formed when the reaction was carried out in the presence of PMHS, but in the absence of triphenylphosphine (Table 1, entry 19). Similarly, we only observed traces (2%) of conversion of azide to amine in the presence of 3 mol% of Ph_3P and in the absence of PMHS (Table 1, entry 20).

Having identified the optimal reaction conditions for the Ph_3P-catalysed Staudinger reduction, we set out to explore the scope of the reduction on various organic azides. In addition to carrying out the reactions under green conditions, as exemplified by the use of reducing agent PMHS and solvent CPME, we also successfully attempted to produce amine products directly from precipitation as hydrochloride salts, thus eliminating a purification step (*e.g.* extraction and/or column chromatography) that typically requires large amounts of environmentally problematic solvents. 4-Nitrophenethylamine and phenethylamine were obtained in excellent 91% and near quantitative 97% isolated yields, respectively (Scheme 2, compounds **1** and **2**). The reduction of 2-nitrophenethyl azide produced 2-nitrophenethylamine with an 88% isolated yield (Scheme 2, compound **3**). It is noteworthy that no reduction of the nitro group was observed for compounds **1** and **3** under these conditions, demonstrating that our catalytic reaction has good chemoselectivity and presents an advantage compared to the H_2-mediated conversion of azides to amines, a method that also reduces the nitro group to an amino group.[12] 3-Chlorophenethyl azide and 4-methoxyphenethyl azide underwent virtually quantitative (99% and 95%) conversions to corresponding amines (Scheme 2, compounds **4** and **5**).

Benzyl azide underwent excellent conversion (94%) to benzylamine (Scheme 2, compound **6**). The reaction also proceeded well with 1-naphthylmethyl azide, which was successfully reduced and produced 78% 1-naphthylmethylamine (Scheme 2, compound **7**). The organophosphorus-catalysed Staudinger reduction under green conditions also works well for disubstituted benzyl azides; 2-fluoro-4-bromobenzylamine and piperonylamine were obtained with 96% and 85% yields, respectively (Scheme 2, compounds **8** and **9**). A thioether containing azide was efficiently reduced to produce 88% of the corresponding amine (Scheme 2, compound **10**).

Having shown that the nitro group remains unaffected by our organocatalytic reaction conditions (*vide supra*), we further explored the chemoselective nature of the reaction. The reduction of benzyloxy-substituted benzyl azide only took place on the azide site (89% yield), whereas the benzyloxy protecting group was not removed under our conditions; again, this result highlights the advantage of our developed method over the alternative hydrogenation method (Scheme 2, compound **11**). 3-Cyanobenzyl azide was efficiently reduced to 3-cyanobenzylamine (66% yield), while the reduction-prone cyano group remained intact (Scheme 2, compound **12**). The chemoselective nature of our method reported here was furthermore demonstrated by a highly selective reduction of the azide functional group in the presence of alkene functionality (93% yield, Scheme 2, compound **13**), and a complete inability of reduction of the sulfone moiety in 4-



Scheme 2 Substrate scope for the organophosphorus-catalysed Staudinger reduction. Amines obtained as hydrochloride salts upon precipitation with 4.0 M HCl in dioxane; [a] isolated yield; [b] isolated yield in the presence of 10 mol% triphenylphosphine.

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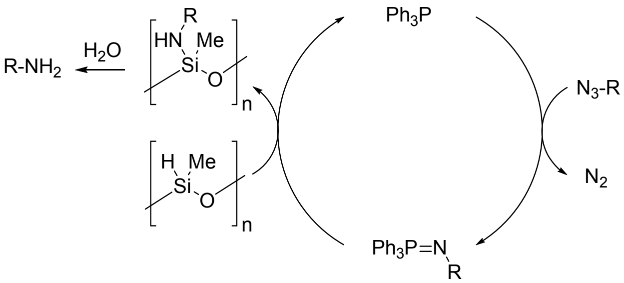
methylsulfone-substituted benzyl azide (Scheme 2, compound **14**, 96% yield). No reduction of the carboxylic ester, ketone and amide functional groups was observed: esters **15** and **16** were obtained with excellent yields of 81% and 94% respectively, ketone **17** with 98%, and amide **18** with 85% isolated yield. These results are important because they show that the ester, ketone, and amide functionality remains intact under our conditions; in contrast, a common reducing agent $LiAlH_4$ reduces both the azide and these functional groups.[13]

Reduction of an azide that contains a free alcohol, (4-hydroxymethyl)benzyl azide, also proceeded very well; (4-hydroxymethyl)benzylamine **19** was obtained with 89% isolated yield. This observation could shorten synthetic pathways as no alcohol protecting group manipulations need to be performed. Heterocycle-containing azides were tolerated well in the catalytic Staudinger reaction; the reduction of 5-(azidomethyl)thiazole produced 84% of amine **20**. Moreover, pyridine- and indole-derived amines **21** and **22** were obtained with 93% and 61% isolated yields. We also examined two entirely aliphatic azides, 1-octylazide and 2-fluoroethyl azide, which were reduced to give 43% and 75% of corresponding amines in the form of hydrochloride salt, respectively (Scheme 2, compounds **23** and **24**). Sterically hindered secondary azides reacted poorly; at 3 mol% triphenylphosphine only 10% of 1-phenyl-2-aminopropane **25** and 2% of 1-phenyl-1-aminopropane **26** were obtained. The reduction of ethyl (*S*)-2-azido-4-phenylbutanoate proceeded slightly better to afford 25% of amine **27**, whereas only 18% of 1-aminoindane **28** was isolated in the presence of 3 mol% triphenylphosphine. To investigate whether the yield for secondary amines could be improved, we performed the catalytic reduction of several secondary azides in the presence of 10 mol% triphenylphosphine and obtained significantly better yields of 79% (amine **25**), 25% (amine **26**), and 68% (amine **27**). For tertiary 1-azidoadamantane, the reaction did not yield any amine product **29**, possibly due to an increased sterics effect. The catalytic reduction of 4-azidoanisole, an example of aromatic amine, in the presence of 3 mol% yielded 34% of 4-anisidine **30**. Increasing the amount of triphenylphosphine to 10 mol%, however, significanly improved the yield of **30** to 76%.

To show the applicability of our newly developed methodology, we carried out organophosphorus-catalysed Staudinger reduction of two representative azides on a multigram scale. 4-Nitrophenethyl azide (25 mmol, 4.8 gram) and phenethyl azide (25 mmol, 3.7 gram) were successfully reduced under standard reaction conditions. From these reactions, 4.9 grams (97% isolated yield) of 4-nitrophenethylamine **1** and 3.3 grams (88% isolated yield) of phenethylamine **2** were obtained as hydrochloride salts. Again, no work-up and column chromatography were required, and the products were obtained in excellent (>98%) purity as assessed by analytical HPLC (Figure S3 and S4).

Based on the previous report[6] and the observation that PMHS is unable to reduce triphenylphosphine oxide to triphenylphosphine (Figure S2), a plausible mechanism for the PMHS-mediated organophosphorus catalysed Staudinger reduction is proposed in Scheme 3. First, triphenylphosphine reacts with the azide to form an aza-ylide intermediate and nitrogen gas is released from the reaction mixture. The aza-ylide is then reduced by PMHS to form a silylamine species and triphenylphosphine, which can re-enter the catalytic cycle. Upon the addition of water, the silylamine is hydrolysed and the desired amine product is obtained.



Scheme 3 Proposed mechanism for the PMHS-mediated organophosphorus-catalysed Staudinger reduction.

In summary, we have developed a highly efficient and sustainable organophosphorus-catalysed Staudinger reduction, which has several advantages over the existing method.[6] It uses *i*) cheap and commercially available triphenylphosphine in very small amounts (3 mol%); *ii*) poly(methylhydrosiloxane), as a green reducing agent; *iii*) cyclopentylmethyl ether, a sustainable solvent produced from renewable sources; and *iv*) no column purification is required to obtain pure products, as amines are produced as hydrochloride salts upon precipitation. Our newly developed green and catalytic Staudinger reduction enables the preparation of a wide range of amines in excellent isolated yields (up to 99%). Notably, we demonstrate the chemoselective nature of the reaction, by showing an excellent functional group tolerance; *i.e.* nitro-, cyano-, alkene, ester, amide, ketone, benzyl ether, and sulfonyl groups were not reduced by PMHS. Furthermore, the reaction is amenable to multi-gram scale. We hope that this work will inspire the development of other important organophosphorus-catalysed reactions under green conditions.

Conflicts of interest

There are no conflicts to declare.

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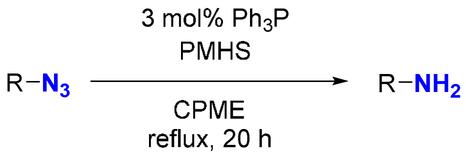

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- No column chromatography
- tolerance functional group tolerance
- Amenable to gram-scale synthesis