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Triphenylphosphine-catalysed amide bond formation between carboxylic acids and amines†

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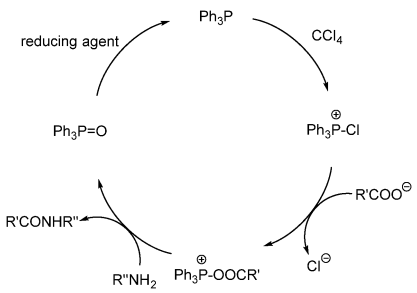
Unactivated carboxylic acids and amines undergo organocatalytic Ph_3P/CCl_4-mediated amide bond formation by employing *in situ* reduction of triphenylphosphine oxide to triphenylphosphine in the presence of diethoxymethylsilane and bis(4-nitrophenyl)phosphate.

The amide bond is ubiquitous in all forms of life. Amide bonds constitute the skeleton of biologically important proteins, several drugs, including penicillin and paracetamol, and also widely used synthetic polymers, such as nylon.[1,2] Amides are most often prepared from carboxylic acids and amines, either *via* formation of more reactive carboxylic acid anhydrides or acyl chlorides, or *via* activation with coupling reagents. Most of the current synthetic methods for the formation of the amide bond are, however, limited to the use of stoichiometric amounts of reagents that activate carboxylic acids.[3,4]

The formation of the amide bond under catalytic conditions is considered as one of the grand challenges of modern organic chemistry.[5,6] Recent endeavours have demonstrated the promise that amides can be synthesised from various readily available starting materials, including the most preferred pair of carboxylic acids and amines.[7,8] For instance, direct coupling between carboxylic acids and amines has been achieved under organocatalytic conditions in the presence of functionalised arylboronic acids.[9–11] In addition, several metal-catalysed methods for the formation of amide bonds have been established using Zr-, Ti-, Zn-, Fe- and Sn-based catalysts.[12–17]

We envisaged that it might be possible to synthesise amides from carboxylic acids and amines in the presence of catalytic amounts of phosphines by employing *in situ* reduction of phosphine oxides. Recently, several methods have been developed for the efficient conversion of triphenylphosphine oxide ($Ph_3P{=}O$) to triphenylphosphine (Ph_3P), either by utilising (i) diethoxymethylsilane and bis(4-nitrophenyl)phosphate,[18] (ii) tetramethyldisiloxane (TMDS) and copper(II) triflate,[19] or (iii) TMDS and indium(III) bromide.[20] Early studies showed that amides can almost quantitatively be obtained by the reaction between carboxylic acids and amines in the presence of 2 equiv. of Ph_3P and CCl_4 under reflux in THF *via* a variation of the Appel reaction.[21,22] Thus, we hypothesised that a system that consists of a carboxylic acid, an amine, Ph_3P and CCl_4 could be a good starting point to develop the 'first generation' organocatalytic amide bond formation. In this proposed method, which uses catalytic amounts of Ph_3P, the $Ph_3P{=}O$ product has to be reduced back to Ph_3P by the appropriate reducing agent(s) (Scheme 1). Such *in situ* reduction of phosphine oxides has been employed in several catalytic reactions, including the Appel, Wittig, and Staudinger reactions.[23–26] Notably, related catalytic organophosphorus reactions based on the P(V)/P(III) or P(V) cycle have also been developed recently.[27–32]

Initially, we explored reaction conditions for the model reaction between 4-nitrobenzoic acid and benzylamine to afford the corresponding amide in toluene at 110 °C. Under stoichiometric conditions in the presence of 2 equiv. of CCl_4 and 1 or 2 equiv. of Ph_3P, 92 and 100% of amides were obtained, respectively (Table 1, entries 1 and 2). In the presence of 0.25 equiv. of Ph_3P and 2.0 equiv. of CCl_4, 4-nitrobenzoic acid and benzylamine reacted to afford 24% of the amide (Table 1, entry 3). A recent study by Williams *et al.* demonstrated that unactivated aliphatic carboxylic acids and aliphatic amines, unlike their aromatic counterparts,



Scheme 1 Proposed catalytic amide bond formation cycle.

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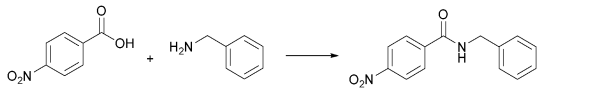
† Electronic supplementary information (ESI) available: Synthetic procedures, characterisation of compounds, and chiral HPLC data. See DOI: 10.1039/c4cc01861c

Table 1 Optimisation of conditions for amide bond formation[a]



Entry	Reagent	Catalyst	Conv.[b] (yield)[c]
1	CCl_4/Ph_3P[d]	—	92 (73)
2	CCl_4/Ph_3P[e]	—	100 (87)
3	CCl_4/Ph_3P[f]	—	24 (19)
4	—	—	5 (1)
5	CCl_4/Ph_3P	Silane (1.5)/phosphate (0.05)[g]	84 (64)
6	CCl_4/Ph_3P	Silane (4.0)/phosphate (0.05)	63 (37)
7	CCl_4/Ph_3P	Silane (1.5)/phosphate (0.1)	71 (51)
8	CCl_4/Ph_3PO[h]	Silane (1.5)/phosphate (0.05)	60 (44)
9	—	Silane (1.5)	10 (2)
10	—	Silane (1.5)/phosphate (0.05)	11 (10)
11	Ph_3P (0.25)	Silane (1.5)/phosphate (0.05)	13 (11)
12	CCl_4/Ph_3P	TMDS (1.5)/$Cu(OTf)_2$ (0.04)	22 (15)
13	CCl_4/Ph_3P	TMDS (1.5)/$InBr_3$ (0.02)	28 (21)
14	CBr_4/Ph_3P[i]	Silane (1.5)/phosphate (0.05)	58 (26)
15	$CBrCl_3/Ph_3P$[j]	Silane (1.5)/phosphate (0.05)	49 (18)

[a] Conditions: 4-nitrobenzoic acid (1 mmol), benzylamine (1.3 mmol), anhydrous toluene (5 mL), 110 °C, 20 h. [b] Conversion determined by GC. [c] Isolated yield. [d] CCl_4 (2.0)/Ph_3P (1.0). [e] CCl_4 (2.0)/Ph_3P (2.0). [f] CCl_4 (2.0)/Ph_3P (0.25). [g] Silane/phosphate = $(EtO)_2MeSiH$ and bis-(4-nitrophenyl)phosphate. [h] CCl_4 (2.0)/Ph_3PO (0.25). [i] CBr_4 (2.0)/Ph_3P (0.25). [j] $CBrCl_3$ (2.0)/Ph_3P (0.25).

undergo direct coupling reactions in toluene at 110 °C in the absence of a catalyst, and in many cases, the amide was formed quantitatively.[13] Thus, we had to test whether 4-nitrobenzoic acid and benzylamine react in the absence of activating agents; in the control experiment, only traces of amides (5%) were formed after 20 hours at 110 °C (Table 1, entry 4).

Having shown that the model reaction gives excellent conversions in the presence of an excess of Ph_3P, and poor conversion in the presence of the catalytic amounts of Ph_3P, we investigated whether the yield for the reaction that is catalytic in Ph_3P can be increased in the presence of the appropriate reducing reagent(s). A combination of diethoxymethylsilane ($(EtO)_2MeSiH$) and bis-(4-nitrophenyl)phosphoric acid was found to improve the conversion of the model reaction. The conversion increased significantly from 24% to above 60% (Table 1, entries 5–7). Optimisation of the ratios between $(EtO)_2MeSiH$ and bis(4-nitrophenyl)phosphoric acid provided the most optimal reaction conditions for the formation of amides. In the presence of 1.5 equiv. of $(EtO)_2MeSiH$ and 0.05 equiv. of bis(4-nitrophenyl) phosphoric acid, 84% of the target amide was formed. Replacing Ph_3P by $Ph_3P{=}O$ under standard conditions resulted in a decrease of the conversion to 60%, indicating that one additional reduction step at the beginning of the catalytic cycle is not completely quantitative (Table 1, entry 8). Moreover, control experiments for the amidation of 4-nitrobenzoic acid and benzylamine in the absence of PPh_3/CCl_4, but in the presence of $(EtO)_2MeSiH$ and bis(4-nitrophenyl)phosphate showed that only 11% of the amide was formed (Table 1, entries 9 and 10). In addition, the standard reaction in the absence of CCl_4 affords only 13% of the amide (Table 1, entry 11).

Previous studies also demonstrated that $Ph_3P{=}O$ can be reduced to Ph_3P in the presence of other reducing agents.[18–20] In contrast to the $(EtO)_2MeSiH$ and bis(4-nitrophenyl)phosphoric acid, a combination of TMDS and copper(II) triflate was not compatible with the conditions for the catalytic amide bond formation; only 22% of the amide product was formed (Table 1, entry 12). Similarly, Ph_3P/CCl_4-mediated amide bond formation, coupled to putative TMDS/$InBr_3$-catalysed reduction of $Ph_3P{=}O$ to Ph_3P, did not afford improved yields of the desired amide; 28% conversion of the amide was found (Table 1, entry 13). In addition to CCl_4, we evaluated two other common halogen-donor reagents; under standard reaction conditions, but in the presence of CBr_4 and $CBrCl_3$, only 58 and 49% conversions to the amide were observed, respectively (Table 1, entries 14 and 15).

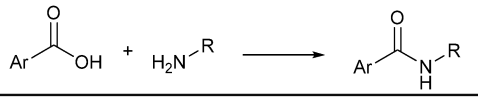
Several reports showed that amides can be reduced to amines in the presence of various reducing agents, including silanes.[33–35] In a control experiment, the amide did not react with $(EtO)_2MeSiH$ nor with a mixture of $(EtO)_2MeSiH$ and bis(4-nitrophenyl) phosphoric acid in dry toluene at 110 °C; 99% of the amide was recovered.

The influence of the solvent on the conversion was then investigated. Performing the reaction at reflux in solvents with high boiling points could potentially allow a good recovery of Ph_3P by the reduction of $Ph_3P{=}O$. Among several common solvents, dry toluene gave the best yield for the model reaction. In *o*-xylene, acetonitrile, 1,4-dioxane, and THF, the amide product was formed in lower conversions relative to toluene (see ESI†). Interestingly, the amide was formed in higher conversions when the reaction was performed at higher temperatures, hence suggesting the direct uncatalysed reaction.

We next explored the scope of the organocatalytic amide bond formation. A diverse set of unactivated *para*-substituted benzoic acids was reacted with benzylamine to afford the corresponding amides in very good to excellent conversions (70–90%) (Table 2, entries 1–7). Isolated yields for the amides obtained under catalytic conditions were found to be in the range of 54–76%, while reactions under uncatalytic conditions (*i.e.* in the absence of $(EtO)_2MeSiH$ and bis(4-nitrophenyl)phosphate) afforded amides in isolated yields below 20% (conversions 17–25%). Only 4-methoxybenzoic acid gave comparatively lower conversions for the reaction with benzylamine (52%) (Table 2, entry 8). Picolinic and quinaldic acids were also converted into amides in 99 and 72% yields, whereas under non-reducing conditions less than 10% of amides was formed (Table 2, entries 9 and 10). Overall, these results imply that $(EtO)_2MeSiH$ and bis(4-nitrophenyl)phosphate facilitate the Ph_3P/CCl_4-mediated amide bond formation reaction by reducing the $Ph_3P{=}O$ product to Ph_3P, which is subsequently used in the next catalytic cycle.

In addition, 4-nitrobenzoic acid reacted with 4-methoxy benzylamine under catalytic conditions to afford the corresponding amide in 82% conversion (53% yield) (Table 2, entry 11). 2-(Aminomethyl)thiophene, 2-phenylethylamine, and cyclohexylamine gave 71, 96, and 65% conversions, respectively (Table 2, entries 12–14). Aniline was found to afford only 35% of the amide; we attribute the relatively low reaction conversion to the lower nucleophilic character of aniline when compared to aliphatic amines (Table 2, entry 15). Notably, reactions with secondary amines, including piperidine and morpholine, proceeded with 81–87% conversions (52–77% isolated yields), demonstrating that our standard

Table 2 Scope of the organocatalytic[a] and uncatalytic[b] amidation of carboxylic acids and amines



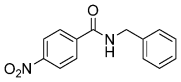
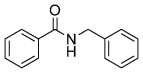
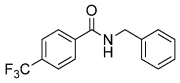
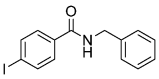
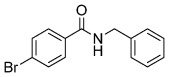
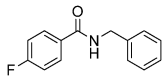
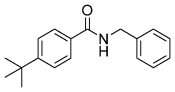
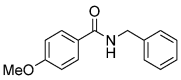
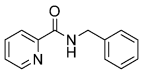
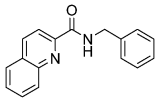
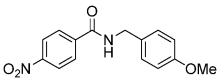
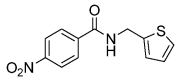
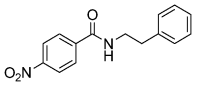
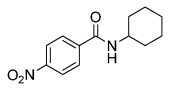
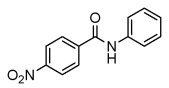
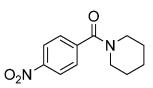
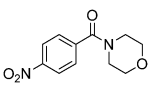
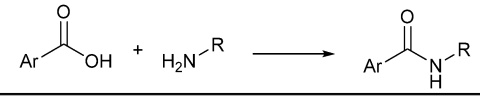
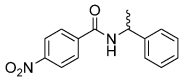
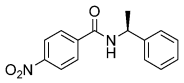
Entry	Amide	Catalytic conversion (yield)	Uncatalytic conversion (yield)
1		84[c] (64)[d]	24 (19)
2		81 (60)	24 (12)
3		77 (58)	21 (13)
4		72 (61)	25 (19)
5		71 (68)	20 (6)
6		90 (54)	17 (11)
7		80 (75)	22 (19)
8		52 (46)	5 (3)
9		99 (76)	28 (6)
10		72 (69)	13 (10)
11		82 (53)	14 (7)
12		71 (58)	9 (5)
13		96 (75)	28 (20)
14		65 (48)	8 (5)
15		35 (25)	16 (10)
16		81 (77)	17 (8)
17		87 (52)	22 (8)

Table 2 (*continued*)



Entry	Amide	Catalytic conversion (yield)	Uncatalytic conversion (yield)
18		98 (52)	20 (14)
19		91 (51)	21 (15)

[a] Conditions: carboxylic acid (1 mmol), amine (1.3 mmol), Ph_3P (0.25 mmol), CCl_4 (2.0 mmol), $(EtO)_2MeSiH$ (1.5 mmol), bis-(4-nitrophenyl)phosphate (0.05 mmol), anhydrous toluene (5 mL), 110 °C, 20 h. [b] Conditions as in catalysis, but in the absence of silane and phosphate. [c] Determined by GC. [d] Isolated yield.

conditions are also applicable to the synthesis of tertiary amides (Table 2, entries 16 and 17). Background reactions under uncatalytic conditions for this set of amines only gave poor conversions of amides. In all cases, conversions and isolated yields were observed to be below 30%.

Racemic and enantiomerically pure (*S*)-1-phenylethylamine afforded the amides in >90% conversion under catalytic conditions; the background reaction gave only 15% conversion (Table 2, entries 18 and 19). Notably, the amide bond formation under our conditions results in complete retention of the configuration (see ESI†). Racemic 1-phenylethylamine formed racemic amides (1 : 1 ratio between the enantiomeric amides), while (*S*)-1-phenylethylamine gave only the (*S*)-amide products (>99.9%).

In conclusion, we have successfully demonstrated the feasibility of organocatalytic amide bond formation between unactivated aromatic carboxylic acids and amines. This reaction proceeds in the presence of a catalytic amount of Ph_3P and a two-fold excess of CCl_4, employing *in situ* reduction of $Ph_3P{=}O$ to Ph_3P using $(EtO)_2MeSiH$ and bis(4-nitrophenyl)phosphate. Considering the importance of the amide bond, we hope that our new approach may inspire researchers to develop alternative catalytic methods for the formation of amide bonds in the coming years.

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