Asymmetric Synthesis

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Asymmetric Organocatalytic Electrophilic Phosphination**

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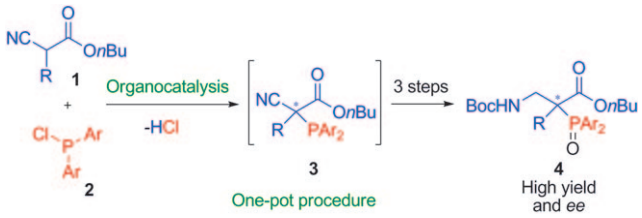
The asymmetric incorporation of phosphorus-containing groups into target molecules is an important goal in diverse areas of synthetic chemistry. Organophosphorus compounds are used in various fields such as the synthesis of natural products[1] and their analogues,[2] ligands in organometallic catalysis,[3] organocatalysis,[4] and in general synthetic chemistry.[5] Hence, the development of asymmetric organocatalytic approaches towards optically active organophosphorus molecules is highly important.[6] A synthetic limitation is that previously the asymmetric catalytic formation of stereogenic carbon centers bonded to phosphorus (C*–P) has only been performed using nucleophilic phosphorus compounds.[7] Herein we present the first asymmetric catalytic C*–P bond formation employing a phosphine electrophile. By reacting α-substituted cyanoacetates (**1**)[8] with diaryl phosphine chlorides (**2**) under organocatalytic conditions,[9] optically active α-phosphinated cyanoacetates (**3**), which contain a stereogenic quaternary carbon center, are obtained (Scheme 1).



Scheme 1. One-pot electrophilic phosphination and formation of α-quaternary α-phosphino β-amino esters **4** by an asymmetric organocatalytic key step. Boc = *tert*-butoxycarbonyl.

Furthermore, **3** is transformed into protected chiral α-quaternary α-phosphino β-amino acids[10] (**4**) by using a one-pot procedure. This class of compounds might also be regarded as precursors for novel P,N ligands.[3f]

Initially, we focused on the formation of α-phosphinated cyanoacetates (**3**), in which an equivalent of HCl is produced during the course of the reaction. Previously, phase-transfer catalysis (PTC) has been shown to be a useful protocol for this type of reaction.[11] However, several attempts using PTC failed to produce any traceable amounts of **3**.[12] We therefore turned our attention to the use of cinchona alkaloids. Pleasingly, using a stoichiometric amount of $(DHQD)_2PYR$ (**5**; Table 1) led to a 77% conversion within 30 minutes under ambient reaction conditions. However, only traces of **3** were formed when 0.1 equivalent of **5** was employed, which was attributed to the protonation of the catalyst. We anticipated that this problem could be solved by employing a base capable of scavenging the acid. Indeed, the addition of an excess of proton sponge (1,8-bis(dimethylamino)naphthalene)[13] when using 10 mol% of **5** led to full conversion after 6 hours under ambient reaction conditions.

Having established a catalytic system, extensive screening[12] resulted in the development of the reaction shown in Table 1, in which step a with subsequent oxidative protection of the phosphine (step b), nitrile reduction, and then N protection (step c),[14] provided highly enantioenriched **4** (up to 93% *ee*) in good yields (>85% for each reaction step). The scope of this reaction was studied by carrying out a range of reactions, in which both the R and the ester substituents in **1**, and the aryl substituents in **2** were varied (Table 1). All the yields reported in Table 1 are for the formation of **4** from **1**, and are thus the result of four steps performed in a one-pot fashion.

Initially, it was shown that employing either $(DHQD)_2PYR$ (**5**) or $(DHQ)_2PYR$ (dihydroquinine 2,5-diphenyl-4,6-pyrimidinediyl diether, **5′**) as catalysts gave similar results for the formation of **4a** and *ent*-**4a** (Table 1, entries 1 and 2). Therefore both enantiomers of the α-quaternary α-phosphino β-amino acids (**4**) are accessible, thus increasing the synthetic value of this reaction. A careful investigation of bases and other additives revealed that in order for the reaction to proceed, the proton sponge is necessary. An acceptable reaction rate was observed when the reaction was run using 5 equivalents of the proton sponge at −40 °C. The reaction also proceeded with a lower amount of proton sponge; at −20 °C the reaction of **1a′** with **2a** (in reference to entry 11 in Table 1) proceeded to full conversion with 3 equivalents of the proton sponge to provide the adduct with a slight decrease in enantioselectivity (82% *ee*, see the Supporting Information).

These initial observations were followed by an investigation into the range of different aryl groups in **2** that could be tolerated in this reaction (Table 1, entries 1, 3, and 4). Substituents in both the 4- and 3-positions were well tolerated and the products were isolated with yields ranging from 52 to 55% and enantioselectivities from 88 to 92% *ee*. Also, the presence of an electron-donating group, for example in the form of a methoxy group in the 4-position, led to a smooth reaction, giving **4c** in a 54% yield with an 88% *ee* (entry 4). Unfortunately, electron-withdrawing groups were found to be unsuitable and led to degradation reactions during step b.

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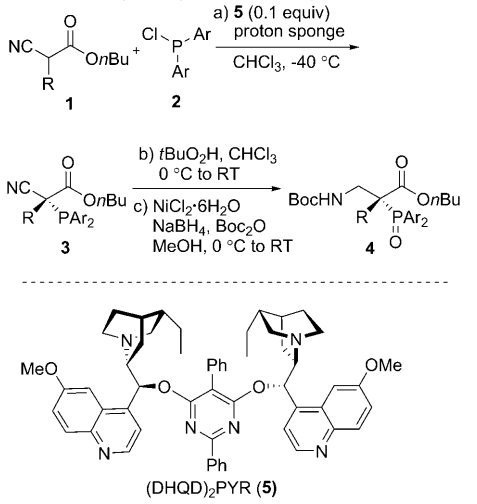
Table 1: One-pot formation of α-quaternary α-phosphino β-amino acids **4** by reaction of **1** with **2** catalyzed by **5** and subsequent transformations.[a]



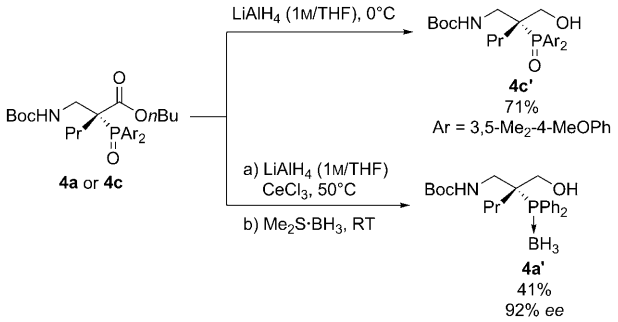
Entry	**1** (R)	**2** (Ar)	Overall Yield [%][b]	*ee* [%][c]
1	**1a** (Pr)	**2a** (Ph)	55 (**4a**)	92
2[d]	**1a**	**2a**	52 (*ent*-**4a**)	93
3	**1a**	**2b** (4-MeC_6H_4)	52 (**4b**)	92
4	**1a**	**2c** (3,5-Me_2-4-MeOC_6H_2)	54 (**4c**)	88 (*R*)
5	**1b** (Me)	**2a**	56 (**4d**)	87
6	**1c** (Et)	**2a**	60 (**4e**)	93
7	**1d** (Hex)	**2a**	53 (**4f**)	92
8	**1d**	**2b**	54 (**4g**)	92
9	**1e** (MeOCH_2CH_2)	**2a**	46 (**4h**)	85
10	**1f** (Bn)	**2a**	36 (**4i**)	92
11[e]	**1a′**[e]	**2a**	41 (**4j**)	90

[a] All reactions were performed in one pot. Reaction conditions: a) **1** (0.25 mmol), **2** (1.5 equiv), **5** (0.10 equiv), and proton sponge (5.0 equiv) in $CHCl_3$ (0.25 mL) at −40 °C; b) *t*BuO_2H (5.5 M in decane, 3.9 equiv) at 0 °C to RT; c) $NiCl_2·6H_2O$ (4.0 equiv), Boc_2O (2.6 equiv), and $NaBH_4$ (until reaction is considered complete by thin-layer chromatography) in MeOH at 0 °C to RT. [b] Yield of **4** isolated from **1**. [c] Determined by HPLC analysis using a chiral stationary phase. [d] Catalyst: **5′**. [e] **1a′** is the corresponding ethyl ester of **1a** (i.e. *n*Bu is replaced by Et). Ar = aryl, Bn = benzyl.

By varying the R substituent in **1**, the reaction was shown to be unaffected by the length of the aliphatic chain, with enantioselectivities of 87–93% *ee* and yields of 52–60% (Table 1, entries 1 and 5–7). The only minor outlier is the methyl substituent that led to 87% *ee* (Table 1, entry 5). An ether group (**1e**) led to slightly inferior results with **4h** being isolated with an 85% *ee* and a 46% yield (Table 1, entry 9). A benzyl group (**1f**) led to **4i** being isolated in 36% yield (corresponding to a 77% yield for each reaction step) and a 92% *ee* (Table 1, entry 10). Changing the *n*-butyl ester to an ethyl ester gave **4j** in a 41% yield with 90% *ee* (Table 1, entry 11), thus showing that the reaction is unaffected by the aliphatic ester moiety employed.

The absolute configuration was determined to be *R* by X-ray crystal structure analysis of the reduced alcohol derivative of **4c** (Scheme 2, top; also see the Supporting Information).[15]

To enhance the developed reaction, the concomitant reduction of the ester and phosphine oxide in **4**, with a subsequent borane protection of the trivalent phosphine was performed. This led to **4a′** in a 41% yield over the three steps, and, more importantly, the enantiomeric excess was maintained at 92% *ee*.



Scheme 2. The reduction of **4a** to **4a′** (bottom) and of **4c** to **4c′** (top). Crystal structure analysis was performed on **4c′**.

We were surprised that the reaction did not proceed under PTC conditions. This observation led us to speculate whether the catalyst partially functions by nucleophilic activation of **2**,[16] which would lead to an activated intermediate containing an ammonium-ion-based N–P bond.[17]

^{31}P NMR measurements were performed to obtain more information on the reaction mechanism (Figure 1). When the ^{31}P NMR spectrum of **2** (Figure 1, spectrum a) is compared with those of mixtures of **2** with quinuclidine and with **5**

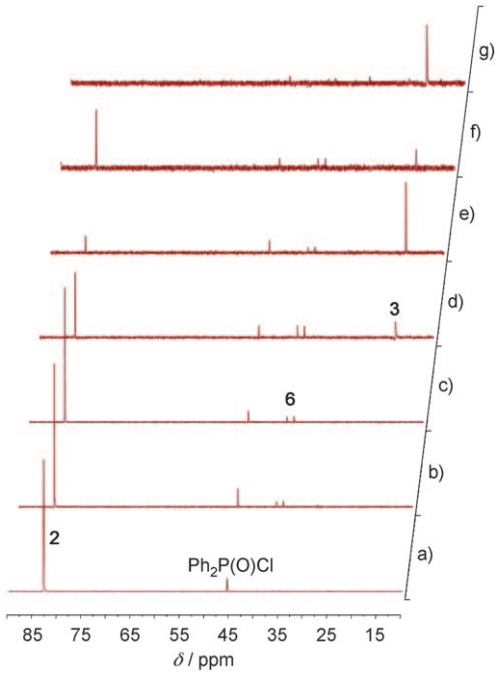
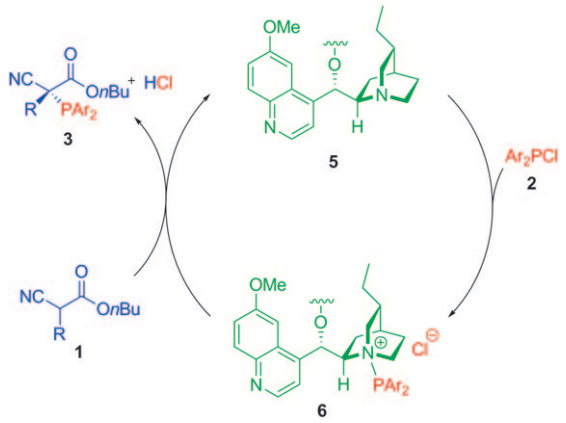


Figure 1. ^{31}P NMR investigations: a) **2**, b) mixture of **2** with quinuclidine, c) mixture of **2** with **5**, d) standard reaction at room temperature after 10 min, e) standard reaction at room temperature after 6 h, f) standard reaction with excess of **1** at room temperature after 10 min, g) standard reaction with excess of **1** at room temperature after 3 h. All solutions were at 1 M concentration.

(Figure 1, spectrum b and c, respectively), two new signals ($\delta = 36$ and 37 ppm) are seen, indicating that a new species is formed (**6**). To verify that this species is also present during the reaction of **1** with **2** when it is catalyzed by **5**, ^{31}P NMR spectra of the crude reaction mixture were measured after 10 minutes and after 6 hours (Figure 1, spectrum d and e, respectively), by which time the full conversion of **1** was observed. As expected, over time the signal for **2** decreased in intensity and the signal for **3** ($\delta = 18$ ppm) increased. The peaks assigned to the intermediate **6** (see Scheme 3 for the structure) were seen throughout the course of the reaction, as anticipated when using an excess of **2** (1.5 equiv) in this reaction. To verify that intermediate **6** is not a "parasitic" or "benign" species, the reaction between **1** and **2** using an excess of **1**, was performed. Under these conditions, the peaks assigned to **6** were observed after 10 minutes (Figure 1, spectrum f). However, as the reaction proceeded these peaks decreased in intensity and disappeared after 3 hours (Figure 1, spectrum g) by which time the full conversion of **2** was observed. The fact that this only occurred when using an excess of **1** suggests that **6** is involved in the catalytic cycle. If **6** was degraded by other mechanisms, its disappearance would also have been expected under the standard reaction conditions, which use an excess of **2**.

These observations combined with the fact that quinuclidine also catalyzes the reaction between **1** and **2** led us to the plausible conclusion that the quinuclidine moiety is responsible for this N–P bond formation.[18] Furthermore, initial screening results showed the enantioselectivity to be independent of the catalyst loading,[12] suggesting a unimolecular action of $(DHQD)_2PYR$ (**5**).[19]

On the basis of these results, we suggest the catalytic cycle shown in Scheme 3. Initially, the catalyst $(DHQD)_2PYR$ (**5**) reacts with **2** in a nucleophilic substitution manner, leading to intermediate **6**, which contains a more electrophilic phosphorus moiety. This increased phosphine electrophilicity then allows the base-induced nucleophilic displacement of the catalyst through another nucleophilic substitution reaction. This step leads to the C*–P bond formation and the creation of the α-phosphinated cyanoacetate **3** and the HCl produced is absorbed by the proton sponge. The suggested reaction mechanism constitutes, according to our knowledge, the first example of a cinchona alkaloid catalyzed enantioselective nucleophilic activation of a substituted electrophile directly on the reactive center.[20]



Scheme 3. The suggested catalytic cycle for the reaction between **1** and **2** leading to **3** catalyzed by **5**.

In conclusion, we have demonstrated the first asymmetric catalytic C*–P bond formation employing electrophilic phosphorus compounds. By applying catalytic amounts of $(DHQD)_2PYR$) in combination with the proton sponge and a subsequent one-pot process, α-quaternary α-phosphino β-amino acids were synthesized with high stereoselectivities and good yields. These compounds were also subjected to further transformations. A range of ^{31}P NMR experiments allowed us to propose a novel reaction mechanism with a cinchona alkaloid catalyzed nucleophilic activation of the phosphorus electrophile.

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