Organocatalysis

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Enantioselective Organocatalytic Hydrophosphination of α,β-Unsaturated Aldehydes**

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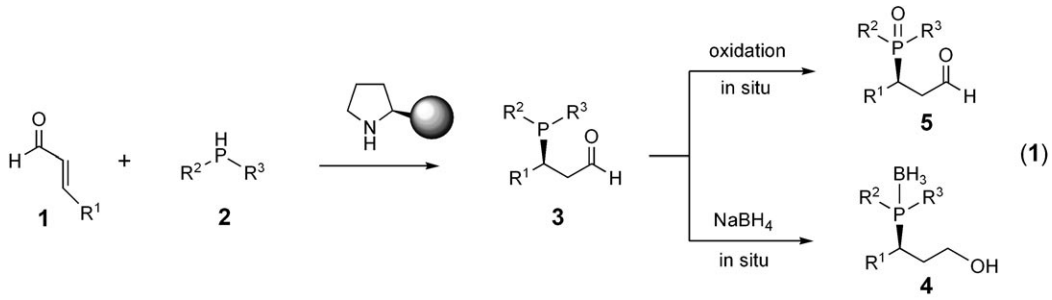
Chiral phosphines are highly valuable ligands for metal-catalyzed enantioselective transformations[1] and can be used as catalysts in organocatalytic reactions.[2] They are generally prepared by resolution—by employing stoichiometric amounts of chiral auxiliaries or enantiopure substrates.[3] Thus, there is an important need for the development of more efficient catalytic methods.[4] The asymmetric hydrophosphination (AHP)[5] of trivalent phosphine compounds with a P–H bond to electron-deficient olefins provides a direct route to useful chiral phosphine ligands containing different chemical functionalities. However, there are only a few catalytic asymmetric methods for this transformation;[6–8] for example, Togni and co-workers reported a highly enantioselective reaction catalyzed by a Lewis acid,[6] and, during our initial studies, Melchiorre and co-workers reported an elegant AHP of nitrostyrenes catalyzed by a chiral organic base that proceeds with good enentioselectivity.[8]

Aminocatalysis has proven to be a powerful procedure[9] within the field of organocatalysis[10] for the enantioselective transformation of carbonyl compounds. In this context, iminium activation[11a] has been successfully demonstrated in Michael-type β-functionalizations for carbon-,[11] hydrido-,[12] sulfur-,[13] nitrogen-,[14] and oxygen nucleophiles.[15] On the basis of this research and the importance of developing AHP reactions, we envisioned a direct route to functionalized optically active β-formyl- and γ-hydroxyphosphines and derivatives thereof by amine-catalyzed stereoselective reactions between trivalent phosphine compounds and enals [Eq. (1), gray sphere = chiral group]. However, there are inherent difficulties in this type of transformation because of the reversibility of the nucleophilic attack and competition between 1,2- and 1,4-addition to the enal (Scheme 1).



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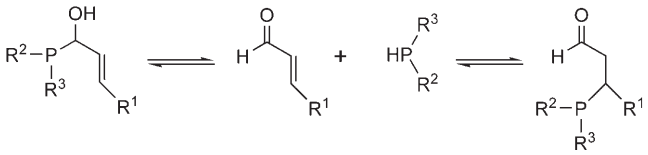
Herein we present the highly chemo- and enantioselective organocatalytic β-hydrophosphination of α,β-unsaturated aldehydes.



Scheme 1. Difficulties encountered when attempting AHP of enals.

After extensive screening of catalysts and different suitable phosphine sources for the AHP of cinnamic aldehyde (**1a**), we found that diphenylphosphine (**2a**) had the right properties to achieve product formation. Some of the results from the screening of the reaction conditions and catalysts for the enantioselective reaction of enal **1a** and **2a** in $CHCl_3$ are shown in Table 1.[16] The corresponding β-formylphosphine **3a** was reduced in situ with $NaBH_4$ to the air-stable alcohol derative **4a** to facilitate the purification process as well as to generate a more stable product.[17]

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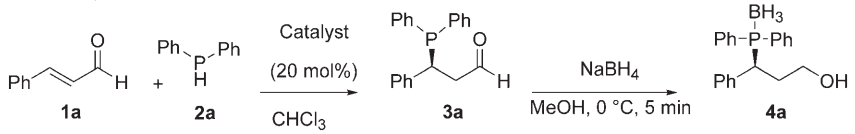
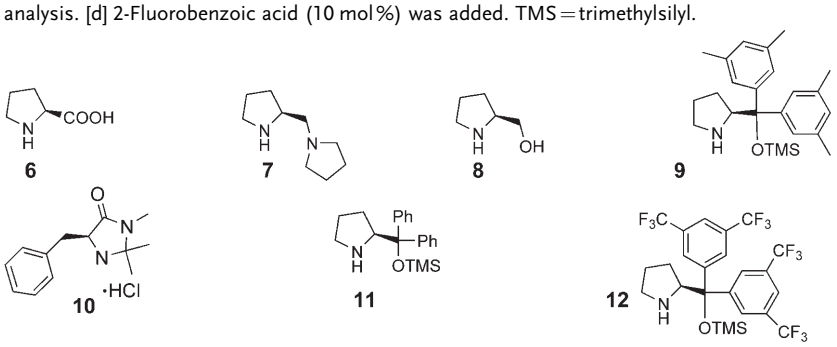
Table 1: Catalyst screen for the reaction between **1a** and **2a**.[a]



Entry	Catalyst	*T* [°C]	*t* [min]	Conv [%][b]	*ee* [%][c]
1	**6**	RT	60	53	0
2	**7**	RT	60	55	14
3	**8**	RT	60	59	12
4	**9**	RT	60	>99	38
5	**10**	RT	60	81	18
6	**11**	RT	60	>99	50
7	**12**	RT	60	>99	56
8	**11**	RT	10[d]	>99[d]	40[d]
9	**11**	4	20[d]	>99[d]	83[d]
10	**12**	4	20[d]	>99[d]	73[d]
11	**11**	−10	60[d]	45[d]	79[d]

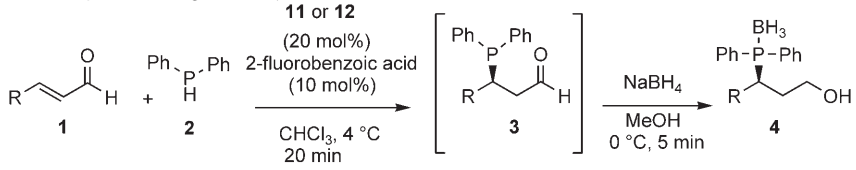
[a] Experimental conditions: A mixture of **1a** (0.25 mmol) and catalyst (20 mol%) in $CHCl_3$ (1.0 mL) was flushed with argon. Next, **2** (0.30 mmol) was added and the reaction mixture stirred at the temperature for the time indicated. In situ reduction of **3a** with $NaBH_4$ gave the corresponding γ-alcohol **4a**. [b] Conversion into product **3a** as determined by NMR analysis. [c] Determined by chiral-phase HPLC analysis. [d] 2-Fluorobenzoic acid (10 mol%) was added. TMS = trimethylsilyl.

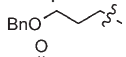
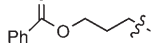


We found that chiral amines **6**–**12** catalyzed the AHP of enal **1a** with high efficiency and with *ee* values ranging from 0–56% *ee*. Chiral protected diarylprolinols **7**, **11**,[18] and **12**[11j,g,13a,c,15a] were the most efficient catalysts under our reaction conditions and mediated the formation of **3a** with high chemoselectivity (entries 4, 6, and 7). Notably, we found that the reaction was significantly accelerated by the addition of a benzoic acid additive, which probably promoted the formation of the iminium ion. Of the benzoic acids tested, 2-fluorobenzoic acid (10 mol%) gave the best results without significantly affecting the enantioselectivity (entry 8). Under these conditions, chiral amine **11** catalyzed the asymmetric formation of **3a** with 83% *ee* and complete conversion at 4°C within 20 minutes (entry 9). Decreasing the temperature to −10°C did not improve the enantioselectivity and reduced the efficiency of the reaction (entry 11). On the basis of these results we decided to investigate the enantioselective AHP of enals **1** with diphenylphosphine (**2a**) catalyzed by amine **11** and **12** under these conditions (Table 2).

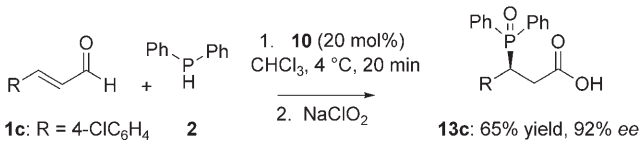
The organocatalytic AHP reactions were highly chemo- and enantioselective and the corresponding formylphosphines **3** were converted in situ into the corresponding alcohols **4** or phosphine oxides **5** by in situ reduction or oxidation, respectively. For example, β-phosphine alcohols **4b**–**4g** were isolated with 90–99% *ee*. The reaction was efficient and highly enantioselective for α,β-unsaturated aldehydes **1** with either aliphatic or aromatic functional groups. Moreover, the α,β-unsaturated aldehydes **1** could also be converted in a one-pot reaction into the corresponding β-phosphine oxide acids **13** (Scheme 2). For example, β-phosphine oxide carboxylic acid **13c** was obtained in 65% yield and 92% *ee*. If desired, the phosphine oxide derivatives can be readily converted into the hydrophosphines by reduction with silanes.[19] The absolute configuration of the phosphorus-containing compounds was 2*S* (R = Ar), as established by X-ray analysis of a single crystal of the diphosphine oxide derivative **14d** (Figure 1),[20] which was formed by decomposition of the isolated pure phosphine oxide aldehyde **3d** after more than 16 h at room temperature.

Table 2: Scope of the organocatalytic AHP.[a]



Entry	Catalyst	R	Prod.	Yield [%][b]	*ee* [%][c]
1	**11**	Ph	**4a**	85	83
2	**11**	4-$NO_2C_6H_4$	**4b**	87	99
3	**12**	4-ClC_6H_4	**4c**	79	92
4	**12**	4-BrC_6H_4	**4d**	78	90
5	**12**	2-Naph	**4e**	85	98
6	**12**		**4f**	70	91
7	**12**		**4g**	72	95

[a] Experimental conditions: A mixture of **1** (0.25 mmol), 2-fluorobenzoic acid (10 mol%), and catalyst **11** or **12** (20 mol%) in $CHCl_3$ (1.0 mL) was flushed with argon. Next, **2** (0.30 mmol) was added and the reaction mixture stirred for 20 min at 4°C. Next, in situ reduction of **3** with $NaBH_4$ gave the corresponding alcohol **4**. [b] Yield of isolated pure product aldehyde **5** after in situ oxidation of **3** with I_2. [c] Determined by chiral-phase HPLC analysis.



Scheme 2. One-pot asymmetric synthesis of β-phosphine oxide acid **13c**.

To shed more light on the origin of the enantioselectivity we performed density functional theory (DFT) calculations on the P–C bond-forming step. The calculations were performed using the Gaussian 03 software package[21] and the B3LYP functional.[22] Geometries were optimized with the 6-31G(d,p) basis set, and characterized with frequency calculations. Final energies were obtained with the larger basis set 6-311 + G-(2d,2p) and corrected for zero point effects obtained from the frequency calculations. The effect of solvation in $CHCl_3$ was calculated using a polarizable conductor model (CPCM).[23] As a representative case for the calculations, we considered the reaction of diphenylphosphine (**2a**) with the iminium species formed from cinnamic aldehyde (**1a**) and catalyst **11** (Figure 2).[24] The transition state leading to the *S* product (**TS-*S***) was calculated to have the lowest energy. The attack takes place at the face of the *E*-iminium ion that is not shielded by the bulky group of the catalyst. The attack on the shielded face of the *E*-iminium ion (**TS-*R***), which yields the 2*R* product, is 1.5 kcal mol^{-1} higher in energy (2.9 kcal mol^{-1} including solvation effects). Although the energy difference suggests a somewhat higher enantioselectivity than the one observed experimentally for this specific reaction, it is qualitatively in agreement with the experimental findings and supports the prediction that the bulky group of **11** shields the *Re* face (R = Ar)[25] of the *E*-iminium ion, which leads to *Si* facial attack. The *Z*-iminium ion was previously found to be less stable than the *E*-iminium ion.[14e] We have calculated that the different transition states for the phosphine attack on the *Z*-iminium ion have 3–5 kcal mol^{-1} higher energies than those formed by attack on the *E*-iminium ion, and are not considered further here. This finding is also in accordance with previous conjugate additions catalyzed by catalysts **11** and **12**.[13–15]

In summary, we have reported the unprecedented example of a highly chemo- and enantioselective organocatalytic hydrophosphination of α,β-unsaturated aldehydes. The reaction is catalyzed efficiently by simple chiral pyrrolidine derivatives and gives the corresponding phosphine derivatives in high yields and in up to 99% *ee*. The synthetic utility of the novel catalytic AHP was exemplified by the one-pot asymmetric synthesis of β-phosphine oxide acids. DFT calculations showed that the lowest energy transition state led to the *S* product. Mechanistic studies, synthetic applications of this transformation, as well as development of other enantioselective AHP reactions based on this concept are ongoing.

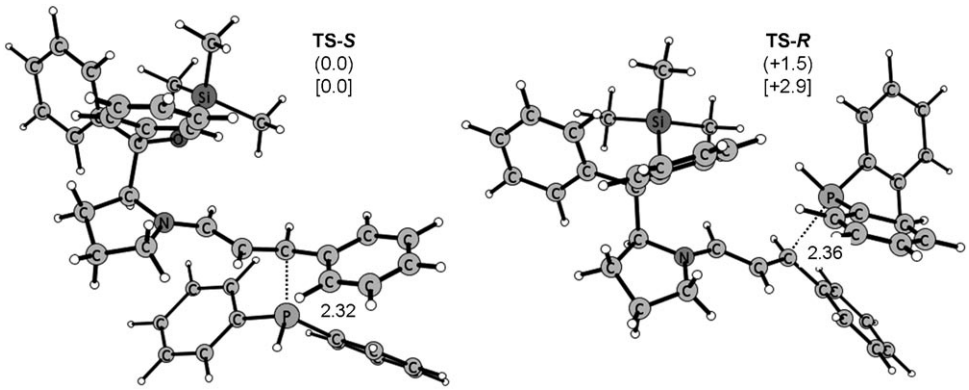


Figure 2. Optimized transition-state structures for phosphine attack on an *E*-iminium ion. **TS-*S*** arises from attack on the unshielded face of the iminium ion and has lower energy than when the attack is on the shielded face (**TS-*R***). Relative energies [kcal mol^{-1}] in the gas phase (in parentheses) and solvated [in brackets] are given. Distances are in Ångstroms.

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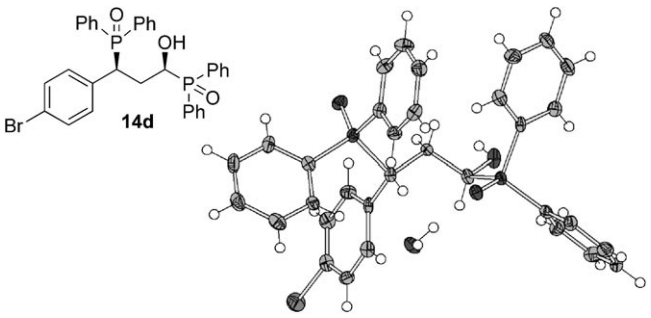

Figure 1. ORTEP picture of the crystalline di(phosphine oxide) compound **14d**.

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