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Organocatalytic Asymmetric Hydrophosphination of α,β-Unsaturated Aldehydes: Development, Mechanism and DFT Calculations

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Abstract: The development and mechanism of the highly chemo- and enantioselective organocatalytic hydrophosphination reaction of α,β-unsaturated aldehydes is presented. The reactions are catalyzed by protected chiral diarylprolinol derivatives and give access to optically active phosphine derivatives in high yields with up to 99% *ee*. The organocatalytic addition of other phosphorus nucleophiles was also investigated. The origin of the high enantioselectivity for the reaction with diphenylphosphine as the nucleophile is investigated by density functional theory calculations.

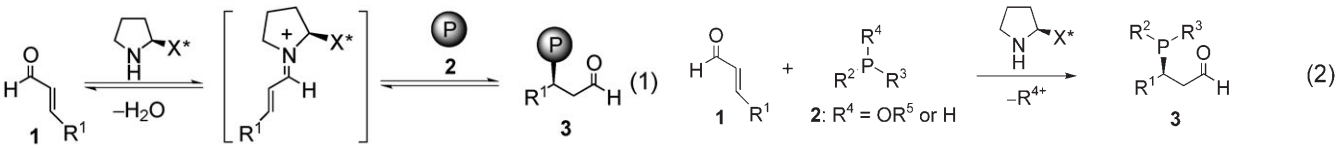
Keywords: asymmetric catalysis; chiral phosphines; DFT calcuations; hydrophoshination; organocatalysis; α,β-unsaturated aldehydes

Introduction

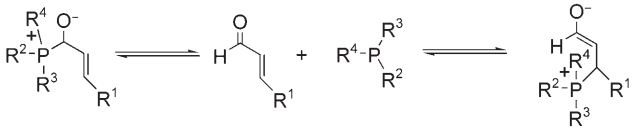
Optically active compounds with a chiral phosphorus-carbon bond such as phosphines and phosphonates are very important for chemical applications.[1–3] For example, chiral phosphines are highly valuable ligands for metal-catalyzed asymmetric transformations[1] and can be utilized as nucleophilic catalysts for organocatalytic transformations such as the Morita–Baylis–Hillman reaction.[2] Chiral phosphonates are, for example, important as precursors of optically active phosphonic acids and can be used as pharmaceuticals and pesticides.[3]

Chiral phosphines are generally prepared by resolution, employment of stoichiometric amounts of chiral auxiliaries and the use of enantiopure substrates.[4] Thus, it is highly desirable to develop more efficient catalytic methods for the enantioselective synthesis of optically active compounds with a chiral carbon atom having a P–C bond.[5] In this context, the asymmetric hydrophosphination (AHP)[6] of trivalent phosphine compounds with a P–H bond to electron-deficient olefins provides a direct route to useful chiral molecules with a P–C bond such as ligands for asymmetric catalysis. However, there are only a few methods based on catalytic asymmetric synthesis.[7,8] For example, Togni has reported a highly enantioselective HP reaction catalyzed by a Lewis acid.[7]

Organocatalysis is a rapidly growing research subfield within the area of asymmetric catalysis.[9] In this context, asymmetric aminocatalysis has proven to be a powerful procedure for the enantioselective transformations of carbonyl compounds.[9,10] This type of catalysis is based on enamine,[10e] iminium,[10d,f] singly occupied molecular orbital (SOMO)[11] or nucleophilic amine activation[10a,12] and combinations thereof.[9–12] Iminium activation of enals has been successfully demonstrated in Michael-type β-functionalizations for carbon,[13] hydrido,[14] sulfur,[15] nitrogen[16] and oxygen nucleophiles,[17] and should be a suitable strategy for the addition of P nucleophiles to activated olefins. Based on this research and our previous experience in organocatalysis,[18] we envisioned a direct route to functionalized optically active compounds **3** with a chiral carbon atom having a P–C bond by amine-catalyzed stereoselective reactions between phosphorus nucleophiles **2** and enals **1** [Eq. (1)]. However, there are inherent difficulties in this type of transformation due to the reversibility of the nucleophilic attack and



competition between 1,2- and 1,4-addition to the enal (Scheme 1).[3f,8b]



Scheme 1. Difficulties encountered when attempting addition of P nucleophiles to enals.

Notably, during our initial studies, Melchiorre and co-workers disclosed the first chiral organic base-catalyzed AHP of nitrostyrenes that proceed with good enantioselectivity.[19] Our group[20a] and Melchiorre's[20b] group have recently simultaneously reported the first direct enantioselective hydrophosphination of α,β-unsaturated aldehydes.[20] After our reports, Terada et al.[21a] as well as Wang[21b] and co-workers presented a chiral amine-catalyzed asymmetric phosphonylation (AP) of nitrostyrenes.[21] Moreover, Jørgensen and co-workers reported an elegant organocatalytic AP of enals.[22] In this paper, we describe our findings, including the scope, density functional theory (DFT) calculations and mechanism of the catalytic addition of trivalent phosphorus compounds to unmodified α,β-unsaturated aldehydes with a focus on the AHP transformation.

Results and Discussion

In our initial experiments, we performed an extensive screening of catalysts and different suitable phosphorus sources **2** for the asymmetric addition to enals **1** [Eq. (2)]. We decided to focus on the AHP reaction since it would be a direct catalytic route to functionalized optically active β-formyl- and γ-hydroxyphosphines and derivatives thereof [Eq. (3)].

Catalyst Screen

The catalyst screen was performed with cinnamic aldehyde **1a** as the acceptor and diphenylphosphine **2a** as the trivalent phosphorus source in chloroform (Table 1). The corresponding β-formylphosphine **3a** were not air stable. Hence, we decided to reduce the β-formylphosphine **3a** *in situ* with $NaBH_4$ to furnish the air- and more stable phosphine borane alcohol derivative **4a**. Moreover, the deprotection of phosphine boranes can be readily accomplished.[23]

The screen showed that all the chiral amines **6**–**12** catalyzed the AHP of enal **1a** with high efficiency and chemoselectivity. No 1,2-addition product was observed and the corresponding product **3a** was formed with 0–56% *ee* at room temperature. Proline **6**, diamine **7** and prolinol **8** catalyzed the reaction with poor enantioselectiviy (0–14% *ee*). MacMillan's catalyst **9** was more efficient and catalyzed the reaction with higher stereoselectivity (entry 4). To our delight, diarylprolinols **10**, **11** and **12** were highly efficient and complete conversion was achieved within 60 min and the enantioselectivity of the AHP was moderate (38–56% *ee*, entries 5–8). Notably, the reaction was significantly accelerated by the addition of benzoic acid (10 mol%), which promotes the formation of the iminium intermediate shown in Eq. (1) (entry 8). Under these conditions the reaction was completed within 10 min. However, the enantioselectivity of the reaction decreased.

Organic Acid Additive Screen

The significant acceleration of the protected chiral diarylprolinol-catalyzed reactions by benzoic acid encouraged us to perform a screen of different organic acids for their ability to improve the efficiency and enantioselectivity of the reaction. Thus, the influence of the addition of different acid additives to the AHP

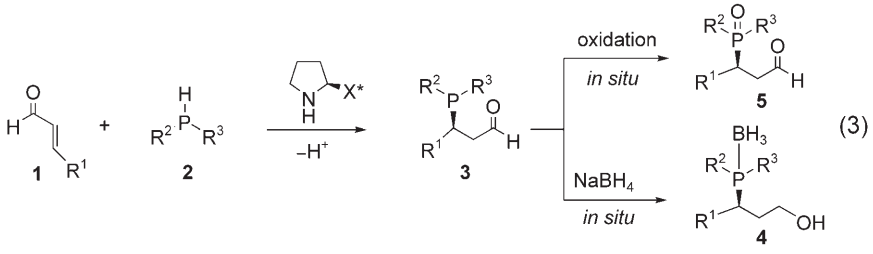
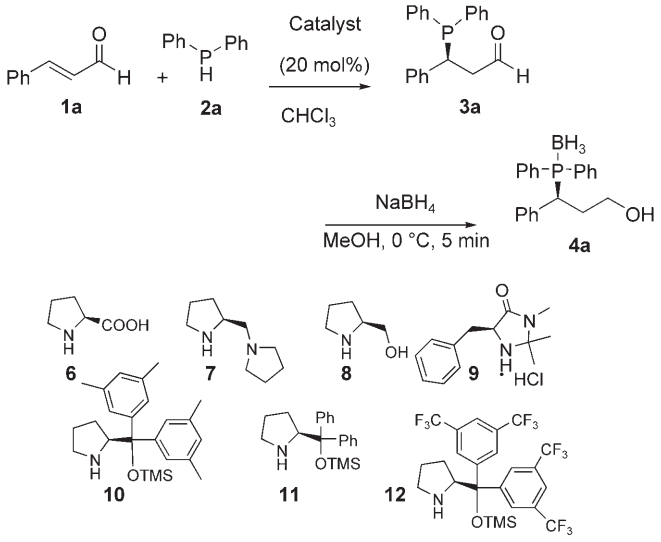


Table 1. Catalyst screen for the reaction between **1a** and **2a**.[a]



Entry	Catalyst	T [°C]	t [min]	Conversion [%][b]	*ee* [%][c]
1	**6**	r.t.	60	53	0
2	**7**	r.t.	60	55	14
3	**8**	r.t.	60	59	12
4	**9**	r.t.	60	81	18
5	**10**	r.t.	60	>99	38
6	**11**	r.t.	60	>99	50
7	**12**	r.t.	60	>99	56
8	**11**	r.t.	10	>99[d]	38[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, **2a** (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.

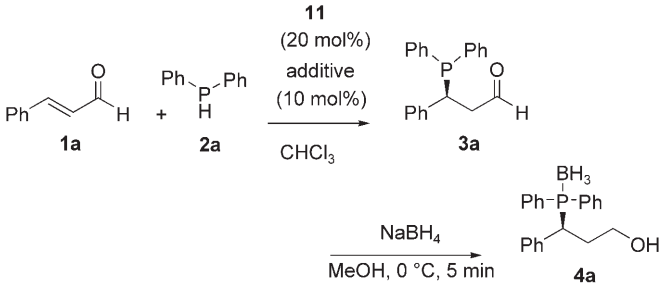
[c] Determined by chiral-phase HPLC analysis.

[d] Benzoic acid (10 mol%) was added. TMS = trimethylsilyl.

of enal **1a** in the presence of catalysts **11** and **12** was investigated (Table 2).

We found that the use of benzoic acid derivatives significantly increased the reaction rate. The use of 2-fluorobenzoic acid (10 mol%, pK_a of 3.27 in H_2O) gave the best result without affecting the enantioselectivity at room temperature (entry 3). In comparison, the use of 2-nitrobenzoic acid (pK_a = 2.17 in H_2O) and benzoic acid (pK_a = 4.20 in H_2O) decreased the stereoselectivity. Thus, we decided to further optimize the reaction conditions by using 2-fluorobenzoic acid as the additive. Moreover, 4-nitrobenzoic acid (pK_a = 3.44 in H_2O) is also a very good additive.[20b] Hence, the p*K*a of the acid additive was an important factor. To our delight, decreasing the reaction temperature increased the enantioselectivity of the reaction

Table 2. Organic acid additive screen for the chiral amine **11**- and **12**-catalyzed reaction between **1a** and **2a**.[a]



Entry	Additive	T [°C]	t [min]	Conversion [%][b]	*ee* [%][c]
1	none	r.t.	60	>99	50
2	$PhCO_2H$	r.t.	10	>99	38
3	2-$FC_6H_4CO_2H$	r.t.	10	>99	40
4	CH_3CO_2H	r.t.	120	traces	2
5	2-$NO_2C_6H_4CO_2H$	r.t.	30	70	26
6	2,5-$(NO_2)_2C_6H_3CO_2H$	r.t.	20	>99	18
7	2-$FC_6H_4CO_2H$	4	20	>99	83
8	none	r.t.	60	>99[d]	56[d]
9	2-$FC_6H_4CO_2H$	4	20	>99[d]	73[d]
10	2-$FC_6H_4CO_2H$	−10	60	45	79

[a] *Experimental conditions:* A mixture of **1a** (0.25 mmol), acid (10 mol%) and catalyst (20 mol%) in $CHCl_3$ (1.0 mL) was flushed with argon. Next, **2a** (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.

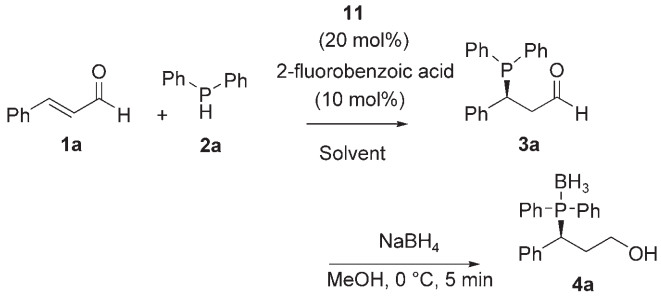
[d] Reaction performed with catalyst **12** (20 mol%).

without considerably affecting the efficiency (entries 7, 9 and 10). The highest enantioselectivity was achieved at 4 °C whereby chiral amines **11** and **12** catalyzed the formation of **3a** after 20 min in full conversion with 83 and 79% *ee*, respectively (entries 7 and 9). It should be mentioned that the lower enantioselectivity at room temperature might be due to an unselective background reaction between **2a** and **1a**.[8b]

Solvent Screen

We also performed a solvent screen and found that the AHP reaction was possible in all solvents investigated. The fastest reaction rate was achieved in $CHCl_3$ and the highest enantioselectivity was observed in toluene followed by $CHCl_3$ and Et_2O (Table 3, entries 1–3). The reaction rate in toluene was similar to the one in CH_2Cl_2. The reaction was slower and moderate enantioselectivity was observed in CH_3CN and THF.

Table 3. Solvent screen.[a]



Entry	Solvent	T [°C]	t [min]	Conversion [%][b]	*ee* [%][c]
1	$CHCl_3$	4	20	>99	83
2	toluene	4	20	62	84
3	Et_2O	4	45	55	81
4	CH_3CN	r.t.	240	38[d]	45[d]
5	CH_3CN	4	120	56	24
6	CH_2Cl_2	4	20	69	76
7	DMF	4	120	24	n.d.
8	THF	4	120	32	42
9	THF	r.t.	240	60[d]	46[d]

[a] *Experimental conditions:* A mixture of **1a** (0.25 mmol), 2-fluorobenzoic acid (10 mol%) and catalyst **11** (20 mol%) in $CHCl_3$ (1.0 mL) was flushed with argon. Next, **2a** (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.

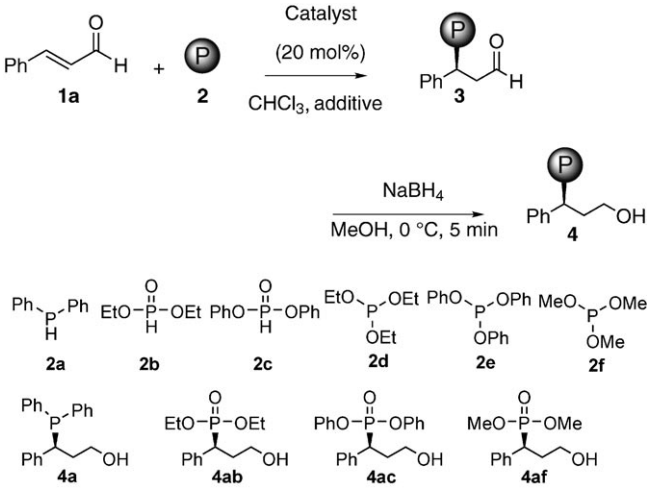
[d] No 2-fluorobenzoic acid was added. n.d. = not determined.

Nucleophile Screen

We also screened different phosphorus compounds **2** for their ability to be used as nucleophiles in the chiral amine-catalyzed stereoselective conjugate addition to enal **1a** (Table 4).

We found that the asymmetric conjugate additions only gave the corresponding product when compounds with a trivalent P atom were used as nucleophiles. The organocatalytic reaction with phoshine **2a** exhibited the highest stereoselectivity. The use of the pentavalent P compounds **2b** and **2c** did not furnish the corresponding phoshonates **2ab** and **2ac**, respectively. This is due to the lower nucleophilicity of these compounds. Moreover, the equilibrium of the phosphonate with its phosphite form lowers the pK_a as compared to the diarylphosphine **2a**, which favors the reversible reaction after the initial addition step and regenerates the starting materials (Scheme 3). The chiral amine-catalyzed reactions with phosphites **2d–f** were successful when trialkyl phosphites such as **2d** and **2f** were employed as nucleophiles. In these cases,

Table 4. Screen for the reaction between **1a** and different phosphorus compounds **2**.[a]



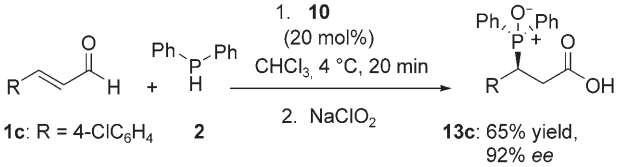
Entry	Catalyst	2	Product	T [°C]	t [h]	Conversion [%][b]	*ee* [%][c]
1	**11**	**2a**	**4a**	4	0.33	>99	83
2	**11**	**2b**	**4ab**	r.t.	48	<5	n.d.
3	**11**	**2c**	**4ac**	r.t.	48	0	n.d.
4	**11**	**2d**	**4ab**	4	24	45[d]	14
5	**12**	**2d**	**4ab**	r.t.	24	46[d]	10
6	**11**	**2e**	**4ac**	4	24	0	n.d.
7	**12**	**2f**	**4af**	r.t.	24	47[d]	12

[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 **3** with $NaBH_4$ gave the corresponding γ-alcohol **4**.

[b] Conversion into product **3** as determined by NMR analysis.

[c] Determined by chiral-phase HPLC analysis.

[d] 2-Fluorobenzoic acid (100 mol%) was added. TMS = trimethylsilyl.



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

the corresponding phosphonates **4ab** and **4af** were furnished with low enantioselectivity. Thus, the organocatalytic asymmetric addition of P nucleophiles to enals can also be used for the synthesis of phosphonates. We decided not to further optimize these results since an elegant report appeared which describes this reaction using catalysts **11** and **12**.[22]

Scope of the Reaction

On the basis of the results from the catalyst, acid additive and solvent screens, we decided to investigate the catalytic AHP of enals **1** with diphenylphosphine **2a** in $CHCl_3$ at 4 °C utilizing amines **11** and **12** as the catalysts, respectively (Table 5).

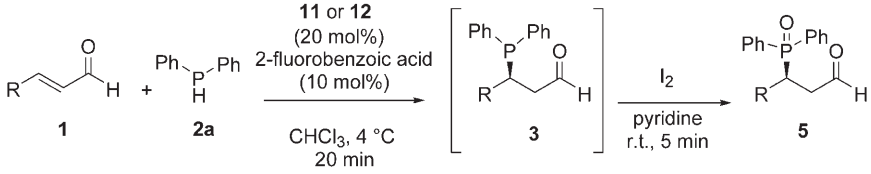
The organocatalytic AHP were highly chemo- and enantioselective and the corresponding formylphosphines **3** were converted *in situ* to the corresponding alcohols **4** or phosphine oxides **5** by *in situ* reduction or oxidation, respectively. For example, aldehydes **5a–j** were isolated in high yields and β-phosphine alcohols **4b–j** were isolated with up to 99% *ee*. The reaction was efficient and highly enantioselective for α,β-unsaturated aldehydes **1** with both aliphatic and aromatic functionalities. Having an electron-donating group on the aromatic moiety of the enal decreased the *ee* of the reaction under our reaction conditions (entry 9). Moreover, the α,β-unsaturated aldehyde **1a** was also converted in one-pot to the corresponding β-diphenylphosphoryl acid **13** in 65% yield with 92% *ee* (Scheme 2, Figure 1).

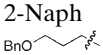
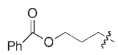
These phosphine oxide derivatives can be readily converted to the hydrophosphines by reduction with silanes.[24] The absolute configuration of the phosphorus-containing compounds was 2*S* (R = Ar) as established by X-ray analysis of a single crystal of diphosphine oxide derivative **14d** (Figure 1).[25] This compound was formed as a side product from the isolated pure compound **3d** during the slow crystallization process. Thus, initial decomposition of **3d** followed by 1,2-addition of the liberated phosphine and subsequent oxidation by air gave unexpectedly **14d** as the crystalline side product.

Mechanistic Considerations

The mechanism of the organocatalytic AHP reaction is shown in Scheme 3. Thus, iminium activation of enal **1** is followed by enantioselective conjugate addition of the P nucleophile to the unshielded face of the iminium intermediate **I** (*Si*-face when R = Ar; *Re*-face when R = alkyl). This step is reversible and it is important that the proton gets abstracted in order to avoid racemization or low conversion. In fact, our experimental results showed that the enantioselectivity of the reaction can drop at prolonged reaction times. Next, interconversion of the *in situ* generated enamine to the iminium intermediate **II** followed by hydrolysis gives the corresponding β-formylphosphine **3** and releases the catalyst. We believe that the acid additive has an important role in accelerating the catalytic cycle by facilitating the formation of iminium intermediates **I** and **II**. This will also push the equilibrium towards product formation. As discussed above (see Table 4), it was essential that the P nucleophile had a trivalent phosphorus in order to achieve product formation. The similar mechanism for the AP of α,β-unsaturated aldehydes is depicted in Scheme 4. The difference is that irreversible nucleophilic substi-

Table 5. Scope of the organocatalytic AHP.[a]

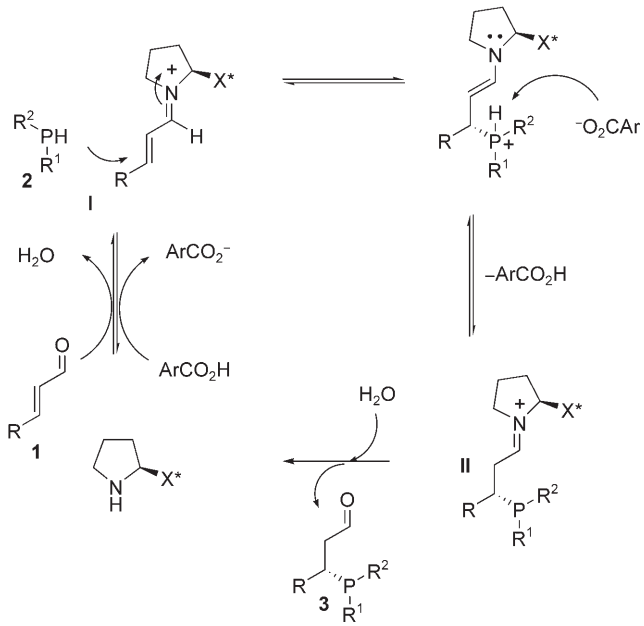


Entry	Catalyst	R	Product	Yield [%][b]	*ee* [%][c]
1	**11**	Ph	**5a**	85	83
2	**11**	4-$NO_2C_6H_4$	**5b**	87	99
3	**12**	4-ClC_6H_4	**5c**	79	92
4	**12**	4-BrC_6H_4	**5d**	78	90
5	**12**	2-Naph	**5e**	85	98
6	**12**		**5f**	70	91
7	**12**		**5g**	72	95
8	**11**	3-$NO_2C_6H_4$	**5h**	84	98
9	**12**	4-$MeOC_6H_4$	**5i**	67	76
10	**11**	3-BrC_6H_4	**5j**	86	83

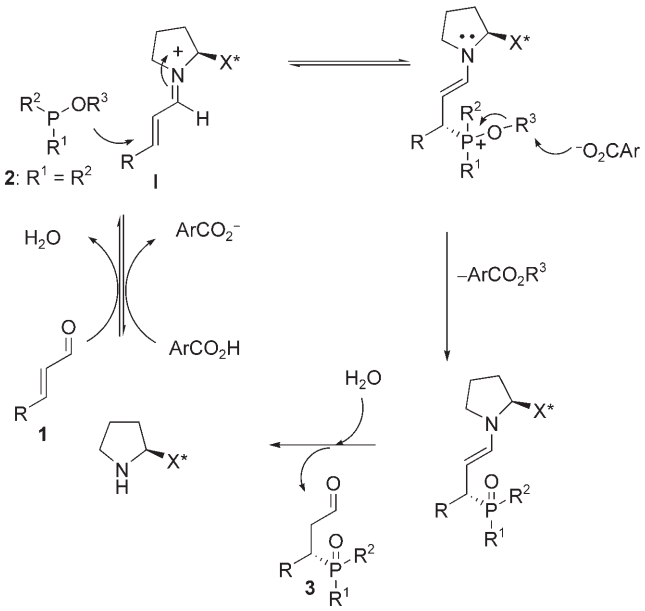
[a] *Experimental conditions:* A mixture of **1** (0.25 mmol), 2-fluorobenzoic acid (10 mol%) and catalyst **11** or **12** (20 mol%) in $CHCl_3$ (1.0 mL) was flushed with argon. Next, **2a** (0.30 mmol) was added and the reaction mixture stirred for 20 min at 4 °C. *In situ* reduction of **3** with $NaBH_4$ gave the corresponding γ-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 3. Proposed catalytic cycle for the AHP reaction.



Scheme 4. Proposed catalytic cycle for the AP reaction.

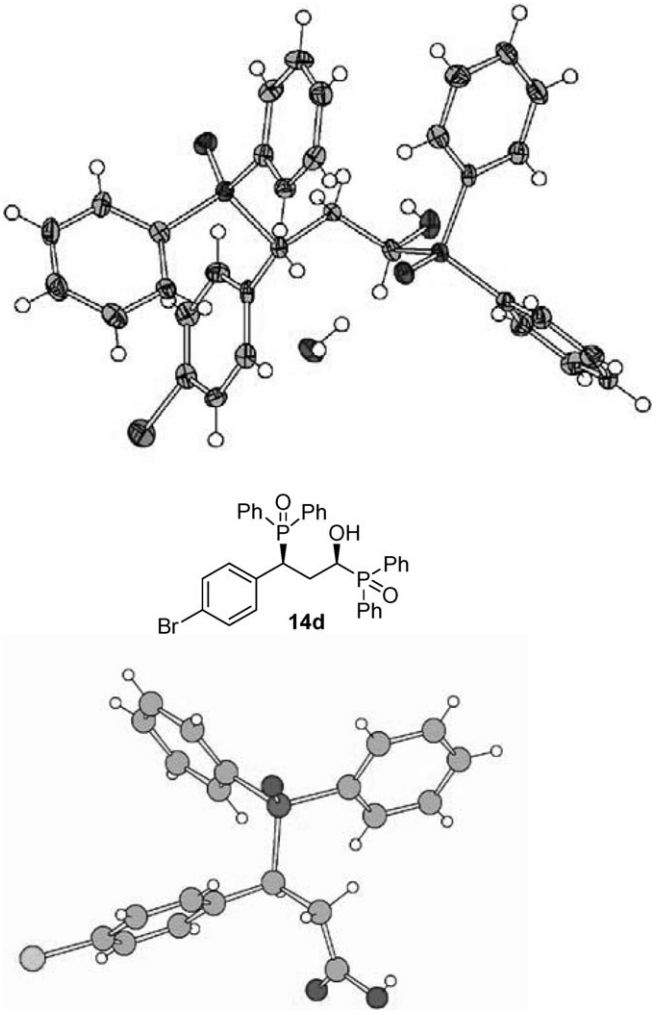


Figure 1. ORTEP pictures of the crystalline diphosphine oxide compound **14d** (top) and acid **13c** (bottom).

tution by the benzoic acid derivative drives the reaction forward after the initial reversible stereoselective P conjugate attack.[22] Thus, when the R^3 group of the P nucleophile in Scheme 4 is equal to an aryl group the substitution does not occur and no product is formed (see Table 4).

We also performed DFT calculations on the chiral amine **11** catalyzed AHP of enals. In order to verify the conformation of the ground state of the catalyst-iminium intermediate and reduce the number of transition states to consider for the phosphination, we initially optimized the iminium conformations shown in Figure 2.

We found that the *E*-isomer **Ia** is lowest in energy. For the catalyst studied, diphenylprolinol derivative **11**, there are three rotamers **Ia–c** regarding the bulky group of the amine catalyst **11**, which all lie within 2.4 kcal mol^{-1} (Figure 2). All rotamers are expected to give similar shielding of the iminium ion, which is why only the lowest of these rotamers is considered further for the other conformations and transition states. The *Z*-isomer **II** is higher by 3.5 kcal mol^{-1} (2.0 kcal mol^{-1} with solvation correction). This correlates well with the work of Dinér et al. who calculated this difference to 1.4 kcal mol^{-1} using 2-pentenal as the enal and chiral prolinol **12** as the catalyst.[16e] The *cis*-conformations of type **III** are considerably higher, *E*-**III** has an energy of 5.2 (4.8) kcal mol^{-1} relative to *E-trans*-**Ia**, while Z-**IV** is 12.3 (11.6) kcal mol^{-1} higher in energy. In Figure 3, the optimized transition states for the stereointroducing step are shown. For the most accessible iminium conformer (**Ia**) we have considered the attack by diphenylphosphine on the unshielded as well as the shielded face. The attack on

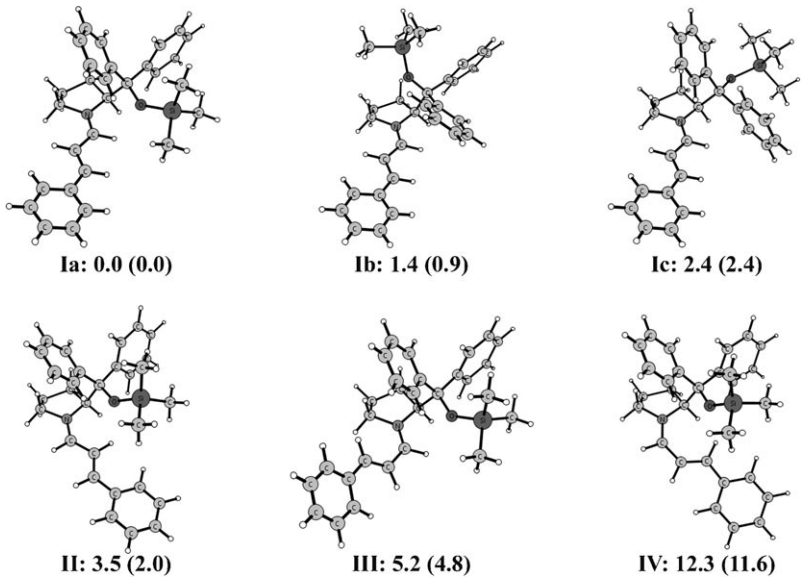


Figure 2. Conformations of catalyst-iminium intermediate. Values in the label are energies relative to **Ia**, in kcal mol^{-1} (solvation corrected energy in parentheses).

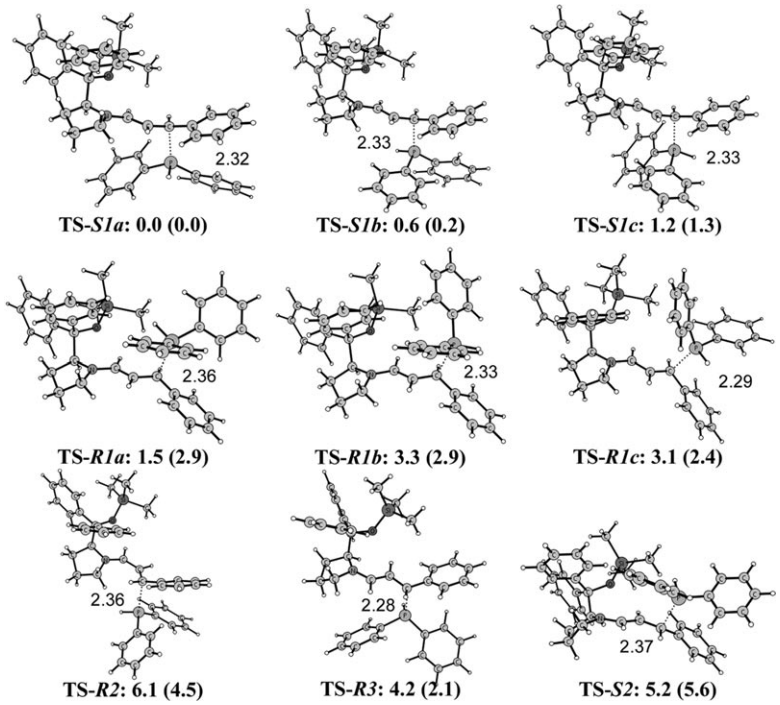


Figure 3. Transition state structures for the phosphination. Values in the label are energies relative to **TS-*S1a***, in kcal mol^{-1} (solvation corrected energy in parentheses). The P–C distances are given in Å.

the unshielded face, **TS-*S1a***, leads to the observed 2*S*-product, and is indeed lowest in energy among all transition states located (Figure 3). The forming P–C bond in **TS-*S1a*** is 2.32 Å. We have also located all transition states obtained by different rotations of phosphine **2a**. The two less favored rotameric transition states **TS-*S1b*** and **TS-*S1c*** are 0.6 (0.2) kcal mol^{-1} and 1.2 (1.3) kcal mol^{-1} higher in energy, respectively, as compared to the optimal **TS-*S1a*** due to higher steric effects between the phenyl groups of the P nucleophile and the cinnamyl moiety of the imminium complex. The P–C distances of these transition states are almost the same (2.33 Å). The attack on the shielded face of the iminium complex **Ia**, **TS-*R1a***, is higher in energy by 1.5 (2.9) kcal mol^{-1} due to the steric repulsion with the bulky group of the catalyst

11. In this transition state the P–C distance is also slightly longer (2.36 Å). The other transition states **TS-*R1b*** and **TS-*R1c*** of the rotameric possibilities of the *Re*-facial attack on iminium complex **Ia** are 3.1 (2.4) and 3.3 (2.9) kcal mol^{-1}, respectively, higher in energy as compared to **TS-*S1a***. The *Z*-iminium conformer **II** and the *cis*-conformer **III** of the catalyst-iminium complex both expose the *Re*-face, which upon attack gives the corresponding minor 2*R*-enantiomer product. In order to verify that the unshielded attack on these iminium intermediates have higher transition states energies compared to transition state **TS-*S1a***, we also investigated these possibilities. The *R*-transition state involving *cis*-**III**-iminium intermediate, **TS-*R2***, was found to be 6.1 kcal mol^{-1} (4.5 with solvation added) less favored than **TS-*S1a***. One other transition state rotamer was optimized, also having similar energy, 6.6 (6.6) kcal mol^{-1}, in agreement with **III** being 5 kcal mol^{-1} higher in energy. This hence rules out these transition states as viable options. The transition state **TS-*R3*** of the *Z*-iminium **II** complex was found to be 4.2 kcal mol^{-1} higher in the gas phase. However, when the effect of solvation in the form of a dielectric continuum is added, the energy difference decreases to only 2.1 kcal mol^{-1}, which is less than **TS-*R1a–c***. Thus, **TS-*R3*** has a competitive energy, indicating that increasing the bulkiness of the catalyst would not increase the enantiomeric excess significantly. This is confirmed by the experimental data in Table 1 where the enantioselectivity for the AHP reaction was not increased when using the more bulky catalyst **10** as compared to catalyst **11**. The *Si*-facial attack in **TS-*S2***, which leads to the *S*-product but is shielded by the bulky group is raised by 5.2 (5.6) kcal mol^{-1} as compared to **TS-*S1a*** due to both the Z-conformation sterics and the apparent proximity of the attacking phosphine **2a** to the bulky chiral group of the catalyst. Transition states involving the *Z*-iminium **IV** was not considered since this structure is considerably higher in energy.

Conclusions

In summary, we report the development and mechanism of the chemo- and enantioselective organocatalytic hydrophosphination of α,β-unsaturated aldehydes. The catalytic AHP of enals was highly enantioselective and efficiently catalyzed by simple chiral pyrrolidine derivatives. The corresponding phosphine derivatives such as γ-alcohols **4** and aldehydes **5** were isolated in high yields with up to 99% *ee*. Our study revealed that trivalent phosphorus nucleophiles were essential in order to achieve product formation. Extensive DFT calculations of the AHP reaction gave the lowest energy transition state **TS-*S1a*** and revealed the origins of the enantioselectivity. The high stereoselectivity originated from a combination of the orientations of the iminium complexes, with *E-trans*-**Ia** being the most favored, and efficient steric shielding of *Re*-face (R = Ar) of this iminium complex by the bulky chiral group of the protected diarylprolinol catalysts.

Experimental Section

Computational Study

In order to rationalize the enantioselectivity, we have performed DFT calculations on the chiral iminium complexes as well as the phosphine addition transition states. All calculations were performed using the B3LYP functional[26] implemented in Gaussian 03.[27] Geometries were optimized with 6–31G(d,p) basis set, and energies calculated with the more accurate basis set 6–311+G(2d,2p) and corrected for zero point vibrational energies from frequency calculations, also confirming the nature of the stationary points. The effect of solvation was treated as a single point correction to the final energy obtained from polarizable continuum model, CPCM,[28] calculation with the smaller basis set on the optimized structures, specifying $CHCl_3$ as solvent.

Typical Experimental Procedure for the the Optimized Organocatalytic AHP Reactions

To a stirred solution of catalyst (20 mol%) and 2-fluorobenzoic acid (10 mol%) in $CHCl_3$ (1.0 mL) at 4 °C, was added 0.25 mmol (1.0 equiv) of α,β-unsaturated aldehyde **1**. The reaction mixture was then flushed with Ar, and 0.3 mmol (1.2 equiv.) of diphenylphosphine was added. The reaction mixture was stirred at 4 °C for the time reported in Table 2. Next, the product was oxidized or reduced *in situ*. Thus, 1.5 equiv. of I_2 in 2% H_2O in pyridine (1.2 mL) were added. The crude mixture was purified by column chromatography to afford the pure phosphine oxide aldehydes **5**. In order to determine the *ee*, the crude material was reduced *in situ* by $NaBH_4$ in MeOH, and the crude product was purifed by column chromatography to afford the corresponding phosphine alcohol derivatives **4**.

Typical Experimental Procedure for the Direct Enantioselective Catalytic Hydrophosphination of α,β-Unsaturated Aldehydes and *in situ* Oxidation to Acid

To a stirred solution of catalyst (20 mol%) and 2-fluorobenzoic acid (10 mol%) in $CHCl_3$ (1.0 mL) at 4 °C, was added 0.25 mmol (1.0 equiv.) of α,β-unsaturated aldehyde. The reaction mixture was then flushed with Ar, and 0.3 mmol (1.2 equiv.) of diphenylphosphine was added. The reaction mixture was stirred at 4 °C for the time reported in Table 2. Next, isobutene (0.1 mL), *tert*-butanol (0.4 mL), H_2O (0.2 mL) KH_2PO_4 (54.4 mg, 4 mmol), and $NaClO_2$ (36 mg, 4 mmol) were added sequentially. The reaction mixture was allowed to reach room temperature and was stirred overnight. The crude material was purified by column chromatography (pentane/ethyl acetate mixtures) to afford the desired acid.

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