Organocatalysis

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

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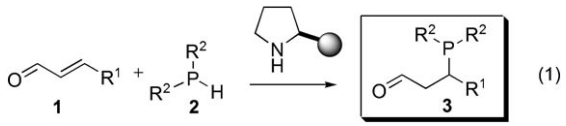
Optically active aldehydes constitute an important class of versatile precursors for the synthesis of chiral molecules. It is not surprising, therefore, that in the rapidly expanding field of asymmetric organocatalysis[1] great attention has been focused on their preparation either by enamine[2] or by iminium-ion[3] activation through chiral secondary amine catalysis.[4] Over the past few years, enormous progress has been achieved in the asymmetric functionalization of aldehydes with a wide range of electrophiles and nucleophiles. The organocatalytic enantioselective introduction of carbon-,[5] oxygen-,[6] sulfur-,[7] hydrogen-,[8] nitrogen-,[9] and halogen-based[10] reagents has thus been efficiently developed. However, it is intriguing to note that not all of the non-inert elements classified as "nonmetals" in the Periodic Table have been stereoselectivily incorporated into aldehydes; surprisingly, the asymmetric introduction of P-based compounds has not been reported, despite the high synthetic potential of the phosphorus adducts. Furthermore, an organocatalytic approach, in contrast to a metal-catalyzed process, prevents product inhibition arising from the coordination ability of the phosphorus atom.

Herein we document the successful exploitation of the iminium-ion activation strategy for the direct enantioselective addition of secondary phosphines to α,β-unsaturated aldehydes catalyzed by a readily available chiral secondary amine. To our knowledge, this study represents the first example of the asymmetric hydrophosphination (AHP) of aldehydes, which affords direct access to highly enantioenriched β-phosphine aldehydes **3** [Eq. (1)] which, after simple manipulations, can provide potentially useful bidentate P ligands.



(1)

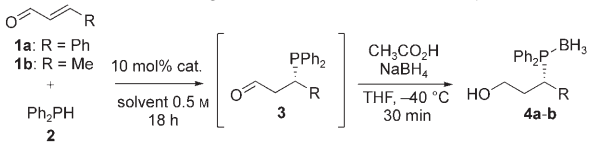
Chiral phosphines, which are valuable ligands for metal-catalyzed enantioselective transformations, are generally prepared by resolution or by using a stoichiometric amount of chiral auxiliaries.[11] Thus, the development of more efficient catalytic methods for the enantioselective synthesis of optically active phosphines is currently of pressing importance.[12] In this context, an organocatalytic AHP of α,β-unsaturated aldehydes is clearly highly desirable.

Recently, we demonstrated the capability of a chiral tertiary amine to act as a basic catalyst for the asymmetric addition of diphenylphosphine to nitroolefins.[13] Given the known capability of iminium catalysis to lower the lowest unoccupied molecular orbital (LUMO) and impart high chemo- and enantioselectivity in conjugate additions,[3a] we considered this tactic as suitable for accomplishing the desired hydrophosphination of α,β-unsaturated aldehydes.

To assess the feasibility of such an organocatalytic hydrophosphination strategy we focused on the use of chiral secondary amines to catalyze the addition of diphenylphosphine (**2**) to cinnamaldehyde (**1a**) in toluene (Table 1). The sequential one-pot formation of the air-stable phosphine-borane-alcohol derivative **4a**, generated in situ by employing a trivial procedure,[14] facilitates the purification process, as the adduct is stable for a long time.

The reaction was screened with some of the most widely employed chiral secondary amines; in the presence of catalyst **B**·$PhCO_2H$ (TMS = trimethylsilyl, the desired product could be obtained in 52% *ee* (entry 2). To our delight, better enantiocontrol was achieved with catalyst **C**·$PhCO_2H$[15]

Table 1: Selected screening results for the AHP of aldehydes.



Entry	R	Catalyst	Solvent	*T* [°C]	Conv.[a] [%]	*ee*[b] [%]
1	Ph	**A**·TFA	toluene	RT	76	0
2	Ph	**B**·$PhCO_2H$	toluene	RT	>95	52
3	Ph	**C**·$PhCO_2H$	toluene	RT	>95	75
4	Ph	**C**·$PhCO_2H$	MeOH	RT	<5	–
5	Ph	**C**·$PhCO_2H$	CH_2Cl_2	RT	>95	32
6	Ph	**C**·$PhCO_2H$	Et_2O	RT	>95 (88)	87
7	Me	**C**·$PhCO_2H$	Et_2O	RT	>95	19
8	Me	**C**·$PhCO_2H$	Et_2O	−30	>95	30
9[c]	Me	**C**·*p*$NO_2C_6H_4CO_2H$	Et_2O	−30	85 (60)	84
10[c]	Ph	**C**·*p*$NO_2C_6H_4CO_2H$	Et_2O	−10	>95 (72)	94

[a] Conversion determined by ^1H NMR analysis; the yield of the isolated product is given in brackets. [b] Determined by chiral HPLC analysis. [c] $[\mathbf{2}]_0 = 0.125$ M.

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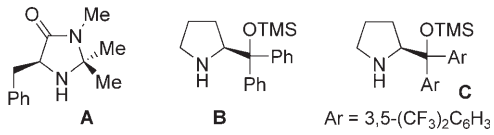
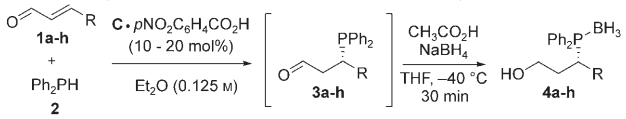
(entry 3, 75% *ee*); a survey of the reaction media revealed that Et_2O induced better selectivity (entry 6, 87% *ee*).



Unfortunately, exposure of crotonaldehyde (**1b**) to **2** under the same reaction conditions did not provide the desired adduct **4b** in satisfactory enantiopurity, even at low temperature (entries 7 and 8). Further optimization of the standard reaction parameters revealed that the nature of the acidic additive and the reagent concentration were the crucial factors for obtaining a highly efficient and general catalytic system with both aromatic and aliphatic aldehydes. Carrying out the reaction in the presence of **C**·*p*$NO_2C_6H_4CO_2H$ at lower concentration ($[\mathbf{2}]_0 = 0.125$ M) afforded both adducts **4a** and **4b** in high enantiomeric excess (entries 9 and 10). Thus, the superior level of induction and reaction efficiency exhibited by this system prompted us to select these conditions to explore the scope of the organocatalytic AHP of aldehydes.[16]

As highlighted in Table 2, the method proved successful for a wide range of enal substituents, including aryl, heteroaryl, alkyl, and alkenyl groups, with the desired products **4** being isolated in high to excellent enantiomeric excess (75–94% *ee*) and good yields.

Table 2: Scope of the AHP of α,β-unsaturated aldehydes.[a]

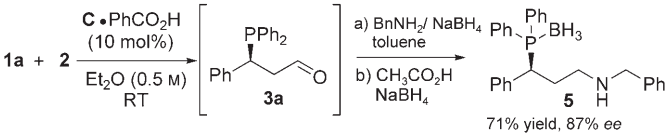


Entry	R	*T* [°C]	*t* [h]	Yield[b] [%]	*ee*[c] [%]
1	Ph, **1a**	−10	24	**4a**: 72	94
2	Ph, **1a**	−10	24	**4a**: 75	−94[d]
3	Me, **1b**	−30	36	**4b**: 60	84[e]
4	2-furyl, **1c**	−30	48	**4c**: 64	90
5	*p*MeO-C_6H_4, **1d**	−30	24	**4d**: 67	93
6	*o*Cl-C_6H_4, **1e**	−30	44	**4e**: 62	81
7	Et, **1f**	−30	44	**4f**: 82	80
8	*i*Pr, **1g**	0	24	**4g**: 92	79
9	$CH_3CH{=}CH$, **1h**	0	36	**4h**: 68	75

[a] Reactions performed on a 0.2-mmol scale with 1.5 equiv of enal **1**. [b] Yield of isolated product. [c] Determined by HPLC analysis. [d] (*R*)-**C** was used as the catalyst. [e] Absolute configuration determined to be *R* by comparison of the specific optical rotation with the value reported in the literature.[17]

The sense of asymmetric induction, based on the absolute configuration (*R*) of compound **4b**,[17] is consistent with a "steric control approach"[15a] in which the efficient shielding of the chiral fragment in **C** determines the selective engagement of **2** with the *Re* face of the iminium intermediate.[18]

A demonstration of the utility of this novel organocatalytic AHP is presented in the one-pot (two-step) conversion of simple aldehydes into enantioenriched 3-aminophosphine derivatives; the AHP of **1a** under our catalytic conditions, followed by in situ reductive amination, provided the product **5** in 71% overall yield without erosion of the enantiomeric excess (Scheme 1). The easy switch from



Scheme 1. Asymmetric one-pot synthesis of 3-aminophosphines.

potentially useful chiral P,O ligands to P,N ligands,[19] by means of a simple and short manipulation, demonstrates the high synthetic potential of this transformation. In a broader sense, the organocatalytic AHP could provide a bridge between the two complementary areas of asymmetric catalysis: organo- and metal-catalyzed transformations.

In summary, we have disclosed the first organocatalytic asymmetric β-functionalization of aldehydes with a P-centered nucleophile; the presented AHP constitutes an easy and efficient method for the direct preparation of highly enantioenriched phosphines. A full account of this survey will be forthcoming.

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