

Catalytic Asymmetric Hydrophosphinylation of α,β -Unsaturated *N*-Acylpyrroles: Application of Dialkyl Phosphine Oxides in Enantioselective Synthesis of Chiral Phosphine Oxides or Phosphines

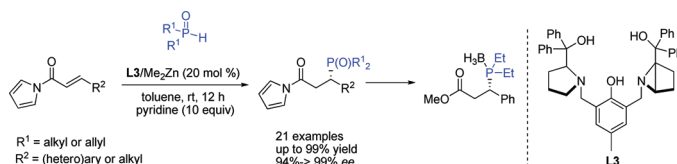
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ABSTRACT



Dialkyl phosphine oxides were introduced in catalytic asymmetric transformations for the first time. An unprecedented phospho-Michael reaction of dialkyl phosphine oxide with α,β -unsaturated *N*-acylpyrroles was disclosed. Excellent enantioselectivities (94–99% ee) and chemical yields (up to 99%) were achieved with a broad substrate scope of the *N*-acylpyrroles. Importantly, pyridine was found to be critical to achieve good results for the present reaction.

Chiral phosphorus-containing compounds have attracted intense interest in recent years owing to their wide applications as ligands for metal-catalyzed asymmetric reactions¹ and their potential biological activities.² These compounds are generally prepared by resolution, employing stoichiometric amounts of chiral auxiliaries or enantiopure substrates. The catalytic asymmetric addition of phosphorus nucleophiles to electrophiles is one of the most powerful methods to provide such compounds.³ Indeed, numerous reports have been focused on the asymmetric additions of dialkyl phosphites [(RO)₂P(O)H]^{3a–d} in the past decades, and recently

secondary phosphines⁴ (R₂PH) have been applied in synthesis of chiral phosphines. However, few reports have been focused on other phosphorus nucleophiles such as secondary phosphine oxides [R₂P(O)H].⁵ To date, Shibasaki's hetero-bimetallic catalyst^{5a} and chiral guanidines^{5b–d} were success-

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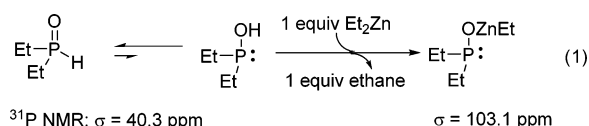
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fully used to synthesize chiral phosphine oxides employing diaryl phosphine oxides. However, less reactive dialkyl phosphine oxides, in comparison with diaryl phosphine oxides, are still challenging for chemists and no report has been presented yet. Herein, we report for the first time the application of dialkyl phosphine oxides in catalytic asymmetric reactions.

It is commonly accepted that secondary phosphine oxides undergo phosphine oxide-phosphinous acid (R_2POH) tautomerism with the phosphinous acid tautomer as the nucleophilic form and the phosphine oxide tautomer as the almost exclusively favored but non-nucleophilic form under neutral conditions (eg, $R = Et$, eq 1).⁶ Thus, the activation of phosphine oxide employing an appropriate base is expected to be an effective approach to activate the nucleophile since the equilibrium could shift toward the reactive phosphinous acid form under such conditions. In connection with our previous work on zinc catalyzed phospho-Michael reactions of dialkyl phosphite,⁷ we chose Et_2Zn as a base to investigate the hydrophosphinylation reaction of dialkyl phosphine oxides.



The preliminary study indicated that diethyl phosphine oxide underwent deprotonation in the presence of Et_2Zn with liberation of 1 equiv of ethane (eq 1). Intrigued by this phenomenon, we tried to monitor this process using ^{31}P NMR. When diethyl phosphine oxide was mixed with Et_2Zn (1 equiv) in toluene, the original signal at 40.3 ppm underwent a significant downfield shift to 103.1 ppm, which indicated the formation of the corresponding zincate.⁸ This intermediate is highly nucleophilic and it undergoes addition to α,β -unsaturated N -acylpyrroles—an equivalence of Weinreb amide.⁹

Encouraged by this finding, we envisioned the catalytic version. The preliminary study indicated (*S,S*)-ProPhenol **L3**¹⁰ was the best ligand among the ligands investigated (95%, 68% *ee*). The following examination of solvents suggested toluene was the best solvent with respect to

Table 1. Optimization of the Phospha-Michael Reaction

entry ^a	additive (mol %)	solvent	yield (%) ^b	<i>ee</i> (%) ^c
1	none	toluene	95	68
2	none	THF	71	60
3	none	ether	90	67
4	none	hexane	90	33
5 ^d	none	toluene	99	94
6	4 Å MS (100 mg)	toluene	83	64
7	<i>i</i> PrOH (20)	toluene	84	60
8	<i>p</i> -cresol (20)	toluene	trace	n.d.
9	PhCOOH (20)	toluene	5	70
10	ZnCl ₂ (20)	toluene	n.r.	—
11	AlCl ₃ (20)	toluene	n.r.	—
12	Ph ₃ PO (20)	toluene	84	68
13	Ph ₃ PS (20)	toluene	83	68
14	Et ₃ N (20)	toluene	83	62
15 ^e	NMI (20)	toluene	59	64
16	2,2'-bipyridine (20)	toluene	91	60
17	pyridine (20)	toluene	85	86
18	pyridine (1 equiv)	toluene	99	93
19	pyridine (5 equiv)	toluene	99	94
20	pyridine (10 equiv)	toluene	95	95
21 ^f	pyridine (10 equiv)	toluene	99	97

^a All reactions were carried out with **1a** (0.375 mmol, 1.5 equiv), **L3**/ Et_2Zn (20 mol %) and **2a** (0.25 mmol) in 2.5 mL solvent at rt for 12 h.

^b Yield of isolated product. ^c The enantiomeric excess was determined by HPLC analysis. ^d One equivalent of **L3**/ Et_2Zn was employed. ^e NMI = *N*-methyl-imidazol. ^f Reaction was carried out with **L3**/ Me_2Zn and 4.0 mL toluene at rt for 12 h.

enantioselectivity. In order to test the chiral inducing ability of the catalyst, 1 equiv **L3**/ Et_2Zn was employed. We were pleased to find the enantioselectivity increased remarkably to 94% *ee* (Table 1, entry 5). On the basis of the result, we speculated that the product formed in the reaction may have a negative feedback to the catalyst and thereby affected the enantioselectivity. So an additional reagent might be required in the reaction to prevent the unfavorable binding of the product to the catalyst. After careful screening of a series of additives,¹¹ including molecular sieves, alcohols, carboxylic

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(8) For details, see Figure S1 in the Supporting Information.

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Table 2. Substrate Scope of the Phospha-Michael Reaction

entry ^a	R ¹	R ²	product	yield (%) ^b	ee (%) ^c
1	Et	Ph	3a	99	97
2	Et	4-MeC ₆ H ₄	3b	98	97
3	Et	4-MeOC ₆ H ₄	3c	98	99
4	Et	3-MeOC ₆ H ₄	3d	97	97
5	Et	2-MeOC ₆ H ₄	3e	90	97
6	Et		3f	96	98
7	Et	4-ClC ₆ H ₄	3g	97	95
8 ^d	Et	4-BrC ₆ H ₄	3h	99	96
9	Et	4-FC ₆ H ₄	3i	99	96
10	Et	2-FC ₆ H ₄	3j	94	95
11	Et	2-furyl	3k	96	98
12	Et	2-thienyl	3l	98	98
13	Et	1-naphthyl	3m	90	94
14	Et	2-naphthyl	3n	99	95
15	Et	PhCH ₂ CH ₂	3o	99	98
16	Et	<i>i</i> Pr	3p	96	98
17	Et	<i>i</i> Bu	3q	91	>99
18	Et	<i>n</i> Hex	3r	90	98
19	<i>n</i> Pr	Ph	3s	96	98
20	<i>n</i> Bu	Ph	3t	99	>99
21		Ph	3u	99	96

^a Unless otherwise noted, reactions were carried out with **1** (0.375 mmol, 1.5 equiv) and **2** (0.25 mmol) in 4.0 mL toluene at rt for 12 h. ^b Yield of isolated product. ^c Enantiomeric excess was determined by HPLC analysis. ^d Absolute configuration of **3h** was determined to be S by X-ray analysis.

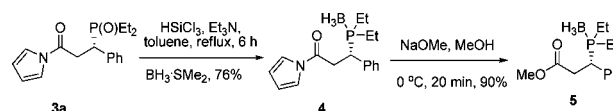
acids, Lewis acids, Ph₃PO/S, amines, and pyridines (entries 6–17), we were pleased to find pyridine gave the best result (86% *ee*, entry 17). The enantioselectivity increased favorably with the amount of pyridine increased and the best result was attained when 10 equivalents of pyridine was employed (95% *ee*, entry 20). The enantioselectivity further increased to 97% *ee* when the concentration of reaction was changed from 0.1 to 0.0625 M and Me₂Zn instead of Et₂Zn was used to form the zinc catalyst (97% *ee*, entry 21).

With the optimal conditions established above, we then examined the scope of the phospha-Michael reaction of **1** and **2**. In general, all reactions proceeded smoothly to give the desired product in high chemical yields and excellent enantioselectivities. The scope of *N*-acylpyrroles was tested using **1a** as a nucleophile. As shown in Table 2, aromatic

(11) For an excellent review on additives and cocatalysts in asymmetric catalysis, see: Vogl, E. M.; Gröger, H.; Shibasaki, M. *Angew. Chem., Int. Ed.* **1999**, 38, 1570–1577.

N-acylpyrroles, regardless of the electronic nature or positions of the substituents on the phenyl ring, heteroaromatic and aliphatic *N*-acylpyrroles were all applicable to the present catalysis with excellent enantioselectivities (94–99% *ee*, entries 1–18). Other phosphine oxides were also examined under the same conditions.¹² We found that dipropyl and dibutyl phosphine oxides were also excellent substrates for the reaction (entries 19, 20). Interestingly, diallyl phosphine oxide also provided the desired adducts in 96% *ee* (entry 21). The versatility of the allyl group facilitates further transformations of the phosphorus adducts.

Finally, the synthetic utility of the products can be demonstrated by the following transformations. Phosphine oxide **3a** can be reduced to phosphine by HSiCl₃, and the phosphine can be transformed in situ to air-stable borane phosphine **4**. Then **4** can be readily converted into the corresponding methyl ester **5** in the presence of MeONa.

Scheme 1. Transformations of the Products

In conclusion, we report for the first time the application of dialkyl phosphine oxides in catalytic asymmetric reactions. An unprecedented phospha-Michael reaction of dialkyl phosphine oxide with α,β -unsaturated *N*-acylpyrroles was disclosed. Excellent enantioselectivities (94–99% *ee*) and chemical yields (up to 99%) were achieved with a broad substrate scope of the *N*-acylpyrroles. Importantly, the products can be readily reduced to chiral phosphines by HSiCl₃. We believe this study will greatly facilitate the asymmetric synthesis of tertiary phosphine oxide or phosphines and arouse a new interest of dialkyl phosphine oxides.

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Supporting Information Available: Experimental details, characterization data for new compounds, and a CIF. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(12) Diaryl phosphine oxides are not applicable to the present catalysis, only racemic products were obtained.