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P-Chirogenic Diaminophosphine Oxide: A New Class of Chiral Phosphorus Ligands for Asymmetric Catalysis

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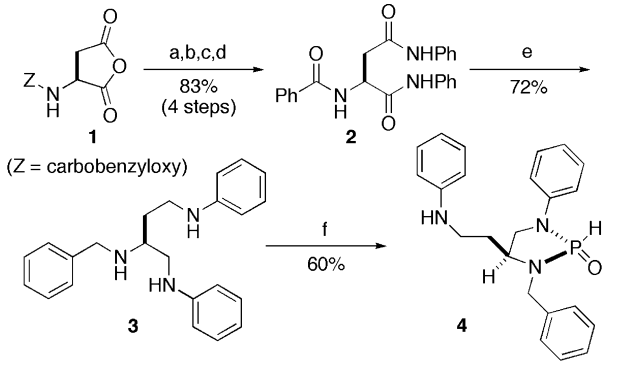
Considerable effort has been devoted to the design and synthesis of various types of chiral ligands.[1] From a practical point of view, stable, inexpensive, and easily accessible ligands are desirable. Secondary phosphine oxides and phosphonic acid derivatives exist in equilibrium between the pentavalent forms (RR′P(═O)H) and trivalent tautomeric forms (RR′POH).[2,3] Secondary phosphine oxides have been utilized as air- and moisture-stable ligand precursors in Pt- and Pd-catalyzed reactions, wherein the tautomeric phosphinous acids coordinate to the metal center through a phosphorus atom.[4] The first application of P-chirogenic secondary phosphine oxide to iridium-catalyzed asymmetric hydrogenation was recently reported.[5] Intensive examination of the ligand structure, however, might be hampered by the difficult optical resolution by preparative chiral HPLC. These aspects prompted us to develop a new class of chiral phosphorus ligands. We report a novel P-chirogenic diaminophosphine oxide that can be utilized for catalytic asymmetric carbon−carbon bond forming reactions to construct quaternary carbon centers.

Cyclic diaminophosphine oxides (diazaphosphole oxides) prepared from asymmetric diamines possess a stereogenic center on the phosphorus atom.[6] Triaminophosphines are reactive under aqueous acidic conditions, giving the corresponding diaminophosphine oxides via an S_N2 type process.[2] Thus, we expected that optically active triamines derived from aspartic acid would be ideal precursors of the desired asymmetric diamine. Our ligand synthesis started with the known acid anhydride **1** (Scheme 1).[7] Nucleophilic opening of **1**, followed by condensation with aniline, yielded the corresponding dianilide, which was transformed into triamide **2** in 83% overall yield. After reduction of all of the amide groups, the obtained triamine **3** was reacted with phosphorus trichloride to afford the corresponding triaminophosphine, which was converted into diaminophosphine oxide **4** by treatment with SiO_2 in wet AcOEt.[8] The absolute structure of **4** was unequivocally determined by X-ray crystal structure analysis.

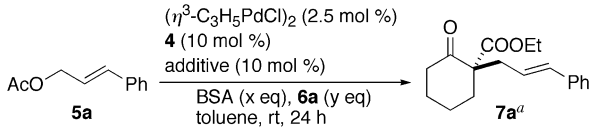
With an optically pure P-chirogenic diaminophosphine oxide **4** in hand, we attempted to use **4** as a chiral phosphorus ligand. Catalytic enantioselective synthesis of a quaternary carbon center is a formidable challenge in organic synthesis.[9] Pd-catalyzed asymmetric allylic substitution using prochiral nucleophiles is one of the most straightforward approaches toward this end.[10] We first examined asymmetric allylic substitution of cinnamyl acetate **5a** with ethyl 2-oxo cyclohexane carboxylate **6a** (Table 1). With the use of 2.5 mol % of $(\eta^3\text{-}C_3H_5PdCl)_2$ and 10 mol % of **4**, the reaction proceeded in the presence of *N*,*O*-bis(trimethylsilyl)acetamide (BSA)[11] to afford **7a** in 53% ee, even though the yield was only 10%. Encouraged by this result, we investigated the effect of the additive and the amount of BSA and **6a** in detail. $Zn(OAc)_2$ was the best additive for asymmetric induction, and 4 equiv of BSA and 1.5 equiv of **6a** to **5a** gave the best reactivity.

Scheme 1. Synthesis of Diaminophosphine Oxide **4**[a]



[a] Reagents and conditions: (a) aniline, DMSO, room temperature, 1 h; (b) aniline, WSCI, DMF, room temperature, 24 h; (c) Pd−C (2 mol %), H_2, 2-propanol−DMF, room temperature, 6 h; (d) benzoyl chloride, NEt_3, THF, room temperature, 1 h; (e) $LiAlH_4$, THF, reflux, 13 h; (f) PCl_3, NEt_3, toluene, −78 °C to room temperature, 16 h, then SiO_2, H_2O, AcOEt, room temperature, 18 h.

Table 1. Asymmetric Allylic Substitution of **5a** with **6a**



run	additive	*x* (equiv)	*y* (equiv)	yield[b]	ee[c]
1		3.0	1.25	10%	53% ee
2	LiOAc	3.0	1.25	53%	8% ee
3	$Mg(OAc)_2{\cdot}4H_2O$	3.0	1.25	99%	66% ee
4	$Zn(OAc)_2{\cdot}2H_2O$	3.0	1.25	81%	89% ee
5	$Zn(OAc)_2$	3.0	1.25	80%	91% ee
6	$Zn(OAc)_2$	3.0	1.5	86%	91% ee
7	$Zn(OAc)_2$	4.0	1.5	99%	92% ee

[a] The absolute configuration was determined to be *S*; see the Supporting Information for details. [b] Isolated yield. [c] Determined by HPLC analysis.

Having developed efficient conditions, we further examined the scope and limitation of different substrates (Table 2). When 0.5−5 mol % of the catalyst was employed, asymmetric substitution of both γ-aryl and γ-alkyl substituted-allyl acetates **5a**−**f** using prochiral nucleophiles with a six-membered ring (runs 1−5, 9−15) proceeded smoothly at room temperature to provide the corresponding products in good yield with good to high enantioselectivity (80−94% ee).[12] In addition, this reaction system was also effective for nucleophiles with five-, seven-, and eight-membered rings (runs 6−8), resulting in the formation of quaternary carbon centers with modest to good enantioselectivity (72−85% ee). To the best of our

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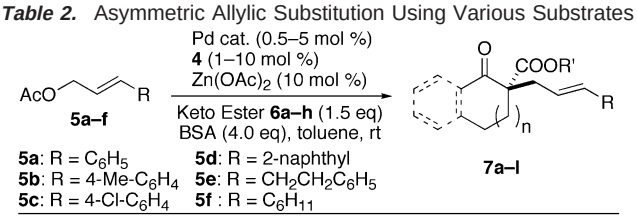
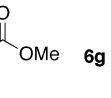
Table 2. Asymmetric Allylic Substitution Using Various Substrates



run	acetates	keto esters	products	time (h)	yield[a] (%)	ee[b] (%)
1[c]	**5a**	**6a** (n = 2, R' = Et)	**7a**	16	99	93(*S*)[i]
2[d]	**5a**	**6a** (n = 2, R' = Et)	**7a**	20	98	92
3[e]	**5a**	**6a** (n = 2, R' = Et)	**7a**	32	85	93
4[c]	**5a**	**6b** (n = 2, R' = Bn)	**7b**	15	99	91(*S*)[i]
5[c]	**5a**	**6c** (n = 2, R' = Me)	**7c**	20	93	94
6[f]	**5a**	**6d** (n = 1, R' = Me)	**7d**	24	75	85(*S*)[i]
7[c,g]	**5a**	**6e** (n = 3, R' = Me)	**7e**	24	85	78
8[c,g]	**5a**	**6f** (n = 4, R' = Me)	**7f**	20	97	72
9[c]	**5a**	**6g**	**7g**	8	99	93(*S*)[i]
10[d]	**5a**	**6g**	**7g**	12	96	93
11[c]	**5b**	**6g**	**7h**	10	98	92
12[c]	**5c**	**6g**	**7i**	7	99	91
13[c]	**5d**	**6g**	**7j**	6	91	91
14[f]	**5e**	**6g**	**7k**	24	74	82
15[f,h]	**5f**	**6g**	**7l**	20	83	80



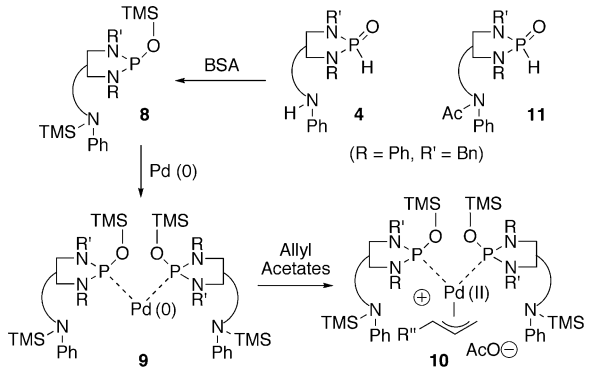
[a] Isolated yield. [b] Determined by HPLC analysis. [c] 2 mol % of the Pd catalyst was used. [d] 1 mol % of the Pd catalyst was used. [e] 0.5 mol % of the Pd catalyst was used. [f] 5 mol % of the Pd catalyst was used. [g] Xylenes was used as a solvent. [h] 12.5 mol % of **4** was used. [i] See the Supporting Information for details.

knowledge, this is the first asymmetric catalysis using diaminophosphine oxide as a chiral ligand.

Typical bases other than BSA did not promote the reaction. ^{31}P NMR studies revealed that pentavalent **4** (chemical shift: 10.9 ppm) first reacts with BSA to provide trivalent **8** (chemical shift: 109.0 ppm). To gain preliminary insight into the catalyst structure and reaction mechanism, we performed several mechanistic studies.[13] When the catalyst was prepared in different Pd−ligand ratios [Pd:**4** = 1:1 and 1:1.5 (Pd, 2 mol %; substrate, **5a** and **6a**)], there was a remarkable decrease in the reactivity without any loss of enantioselectivity (2 h, no reaction; and 2 h, 34%, 93% ee, respectively), as compared to the case of the best ratio (2 h, 89%, 93% ee). Kinetic studies were performed, and the reaction rate had a first-order dependency on the catalyst. Moreover, there was a positive nonlinear effect in this reaction. From these observations, Pd complex **9** (Pd:**8** = 1:2) is proposed to be the active species, where two molecules of **8** coordinate to the Pd metal in a monodentate fashion (Scheme 2).[14] On the other hand, there was a significant decrease in both the reactivity and the selectivity with the use of *N*-acetylated ligand **11** [2h, 37%, 79% ee (Pd, 2 mol %; substrate, **5a** and **6a**)], indicating that nitrogen atoms on the sidearms should have an important role in the catalytic activity, as well as the enantiofacial discrimination of prochiral nucleophiles.[15]

In conclusion, we developed a novel chiral ligand precursor, P-chirogenic diaminophosphine oxide, which is activated to trivalent phosphorus ligand in situ by BSA-induced tautomerization. This unique property was successfully applied to catalytic asymmetric synthesis of quaternary carbon centers. Further studies using a structurally optimized ligand are in progress.

Scheme 2. Proposed Structure of the Active Species



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Supporting Information Available: Experimental procedures, characterization of the products, other data, and discussions (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) Reaction using simple allyl acetate gave less satisfactory results [cat. 5 mol %, keto ester **6g**, 48 h, 24%, 63% ee, absolute configuration *S*].
(13) See the Supporting Information for details.
(14) No signal was observed in the ^{31}P NMR measurement of the reaction mixture, which might indicate that several complexes exist in a fast equilibrium.
(15) At the present stage, we speculate that the nitrogen atoms might fix the nucleophiles in the appropriate position through secondary ligand substrate interaction mediated by Zn metal. For the secondary ligand substrate interaction, see ref 10a−c.

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