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Pd-Catalyzed Asymmetric Allylic Amination Using Aspartic Acid Derived P-Chirogenic Diaminophosphine Oxides: DIAPHOXs

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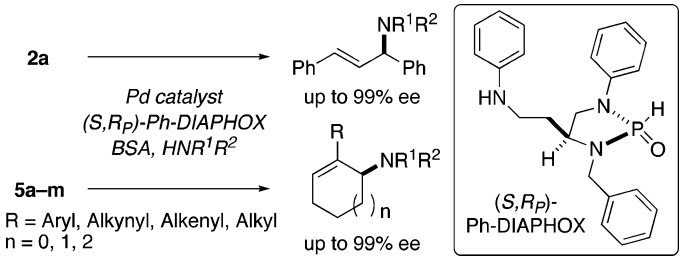
ABSTRACT



A Pd-catalyzed asymmetric allylic amination using aspartic acid derived P-chirogenic diaminophosphine oxides (DIAPHOXs) is described. Asymmetric allylic amination of both linear and cyclic substrates proceeded at room temperature to give the chiral allylic amines in 72–99% ee.

Considerable effort has been directed toward the catalytic asymmetric synthesis of α-chiral amines because of the ubiquity of the chiral amine unit in biologically active compounds. Various approaches, involving asymmetric hydrogenation,[1] as well as asymmetric addition of carbon nucleophiles[2] and nitrogen nucleophiles,[3] have been investigated. Among them, a transition-metal-catalyzed asymmetric allylic amination reaction is a powerful method for the synthesis of chiral allylic amines.[4] Several reactions of this type using Pd,[5] Ir,[6] or other transition metal catalysts[7] have been reported.

(1) For a review, see: Ohkuma, T.; Kitamura, M.; Noyori, R. *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2000; pp 1−110.

(2) For recent representative examples, see: (a) Strecker reaction: Vachal, P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 10012−10014 and references cited therein. (b) Reissert reaction: Ichikawa, E.; Suzuki, M.; Yabu, K.; Albert, M.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126*, 11808−11809 and references therein. (c) Mannich-type reaction: Yoshida, T.; Morimoto, H.; Kumagai, N.; Matsunaga, S.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 3470−3474 and references therein. (d) Boezio, A. A.; Charette, A. B. *J. Am. Chem. Soc.* **2003**, *125*, 14260−14261. (e) Taylor, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 10558−10559. (f) Ogawa, C.; Sugiura, M.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2004**, *43*, 6491−6493. (g) Ooi, T.; Kameda, M.; Taniguchi, M.; Maruoka, K. *J. Am. Chem. Soc.* **2004**, *126*, 9685−9694. (h) Momiyama, N.; Yamamoto, H. *J. Am. Chem. Soc.* **2004**, *126*, 5360−5361.

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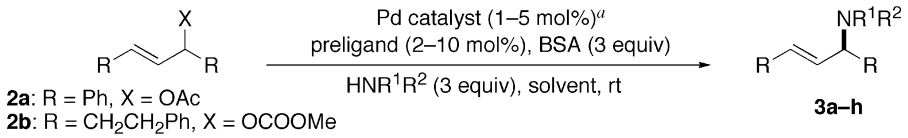
Table 1. Pd-Catalyzed Asymmetric Allylic Amination



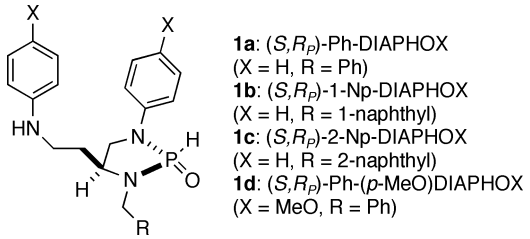
2a: R = Ph, X = OAc
2b: R = CH_2CH_2Ph, X = OCOOMe

3a–h

entry	substrate	HNR^1R^2	Pd catalyst (mol %)	solvent	preligand	product	time (h)	yield[b] (%)	ee[c] (%)
1	**2a**	$BnNH_2$	2	CH_2Cl_2	**1a**	**3a**	24	91	98 (*R*)
2	**2a**	furfurylamine	2	CH_2Cl_2	**1a**	**3b**	24	92	96
3	**2a**	*n*-$BuNH_2$	2	CH_2Cl_2	**1a**	**3c**	60	79	99
4	**2a**	cyclohexylamine	2	CH_2Cl_2	**1a**	**3d**	24	87	98
5	**2a**	*i*-$PrNH_2$	2	CH_2Cl_2	**1a**	**3e**	12	99	94
6	**2a**	morpholine	2	CH_2Cl_2	**1a**	**3f**	7	92	95
7	**2a**	morpholine	1	CH_2Cl_2	**1a**	**3f**	12	90	97
8	**2a**	*N*-methylaniline	2	CH_2Cl_2	**1a**	**3g**	24	nr[d]	
9	**2b**	$BnNH_2$	5	CH_3CN	**1a**	**3h**	23	63	35
10	**2b**	$BnNH_2$	5	CH_3CN	**1b**	**3h**	23	72	52
11	**2b**	$BnNH_2$	5	CH_3CN	**1c**	**3h**	23	75	48
12	**2b**	$BnNH_2$	5	CH_3CN	**1d**	**3h**	23	76	29

[a] $(\eta^3\text{-}C_3H_5PdCl)_2$ was used. [b] Isolated yield. [c] Determined by HPLC analysis. [d] No reaction.

We recently developed aspartic acid derived air- and moisture-stable pentavalent phosphorus preligands: P-chirogenic diaminophospine oxides **1a**−**d** (Figure 1).[8] These



1a: (S,R_P)-Ph-DIAPHOX
(X = H, R = Ph)
1b: (S,R_P)-1-Np-DIAPHOX
(X = H, R = 1-naphthyl)
1c: (S,R_P)-2-Np-DIAPHOX
(X = H, R = 2-naphthyl)
1d: (S,R_P)-Ph-(*p*-MeO)DIAPHOX
(X = MeO, R = Ph)

Figure 1. Aspartic acid derived P-chirogenic diaminophosphine oxides: (S,R_P)-DIAPHOXs.

preligands were activated in situ by *N*,*O*-bis(trimethylsilyl)-acetamide (BSA) induced P(V) to P(III) transformation to afford trivalent phosphorus ligands and were successfully applied to stereoselective construction of tertiary and quaternary stereocenters through Pd-catalyzed asymmetric allylic alkylation. These results led us to expect that the present catalyst system could be extended to carbon−nitrogen bond-forming reactions. Herein, we report Pd-catalyzed asymmetric allylic amination reactions using P-chirogenic diaminophosphine oxides.[9]

We first examined asymmetric allylic amination of 1,3-diphenylallyl acetate **2a** with benzylamine using (S,R_P)-Ph-DIAPHOX **1a**. The reaction was performed under conditions similar to the case of asymmetric allylic alkylation of **2a** with dimethyl malonate,[8b] and the best reactivity and enantioselectivity were obtained when CH_2Cl_2 was used as the solvent (Table 1). Various amine nucleophiles were applied to this type of asymmetric allylic amination. Using 1−2 mol % of Pd catalyst and 2−4 mol % of **1a**, asymmetric allylic amination of **2a** with both primary and secondary amines proceeded at room temperature to give the corresponding products **3a**−**f** in good yield with high stereoselectivity. No reaction, however, occurred when aniline derivatives were utilized as the nucleophiles.[10] This catalyst system was also applied to asymmetric allylic amination of 1,3-dialkyl-substituted allyl carbonate **2b**. The reaction was performed using **1a** in CH_3CN, affording the corresponding product in moderate yield with low enantiomeric

(6) (a) Ohmura, T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 15164−15165. (b) Kiener, C. A.; Shu, C.; Incarvito, C.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 14272−14273. (c) Shu, C.; Leiner, A.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2004**, *43*, 4797−4800. (d) Tissot-Croset, K.; Polet, D.; Alexakis, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 2426−2428. (e) Lipowsky, G.; Helmchen, G. *Chem. Commun.* **2004**, 116−117. (f) Welter, C.; Dahnz, A.; Bruner, B.; Steiff, S.; Dübon, P.; Helmchen, G. *Org. Lett.* **2005**, *7*, 1239−1242. (g) Polet, D.; Alexakis, A. *Org. Lett.* **2005**, *7*, 1621−1624.

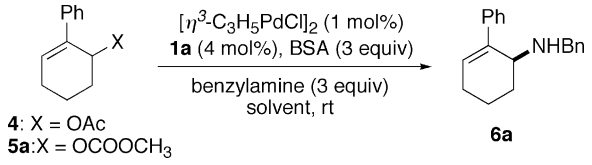
(7) (a) Ru catalyst: Matsushima, Y.; Onitsuka, K.; Kondo, T.; Mitsudo, T.; Takahashi, S. *J. Am. Chem. Soc.* **2001**, *123*, 10405−10406. (b) Ni catalyst: Bekowitz, D. B.; Maiti, G. *Org. Lett.* **2004**, *6*, 2661−2664. (c) Enantiospecific allylic amination using Rh catalyst: Evans, P. A.; Robinson, J. E.; Nelson, J. D. *J. Am. Chem. Soc.* **1999**, *121*, 6761−6762.

(8) (a) Nemoto, T.; Matsumoto, T.; Masuda, T.; Hitomi, T.; Hatano, K.; Hamada, Y. *J. Am. Chem. Soc.* **2004**, *126*, 3690−3691. (b) Nemoto, T.; Masuda, T.; Matsumoto, T.; Hamada, Y. *J. Org. Chem.* **2005**, *70*, 7172−7178. (c) Nemoto, T.; Fukuda, T.; Matsumoto, T.; Hitomi, T.; Hamada, Y. *Adv. Synth. Catal.* In press.

(9) For representative examples of transition metal catalysis with pentavalent phosphorus preligands, see: (a) Li, G. Y. *Angew. Chem., Int. Ed.* **2001**, *40*, 1513−1516. (b) Jiang, X.-B.; Minnaard, A. J.; Hessen, B.; Feringa, B. L.; Duchateau, A. L. L.; Andrien, J. G. O.; Boogers, J. A. F.; de Vries, J. G. *Org. Lett.* **2003**, *5*, 1503−1506. (c) Ackermann, L.; Born, R. *Angew. Chem., Int. Ed.* **2005**, *44*, 2444−2447. (d) Bigeault, J.; Giordano, L.; Buono, G. *Angew. Chem., Int. Ed.* **2005**, *44*, 4753−4757 and references therein.

(10) When benzylamine and morpholine were treated with 1 equiv of BSA in $CDCl_3$, *N*-trimethylsilylation was observed in each case by ^1H NMR. This fact indicates that *N*-trimethylsilylated amines would be the actual nucleophiles in this reaction system. In contrast, no trimethylsilylation occurred in the case of *N*-methylaniline. These results appear to suggest that *N*-trimethylsilylation might be important for the reaction.

Table 2. Effect of Solvent in Pd-Catalyzed Asymmetric Allylic Amination of **5a** with Benzylamine



entry	substrate	solvent	time (h)	yield[a] (%)	ee[b] (%)
1	**4**	CH_2Cl_2	24	nr[c]	
2	**5a**	CH_2Cl_2	48	75	93
3	**5a**	THF	48	33	92
4	**5a**	DMF	48	71	92
5	**5a**	toluene	48	39	90
6	**5a**	CH_3CN	17	93	96

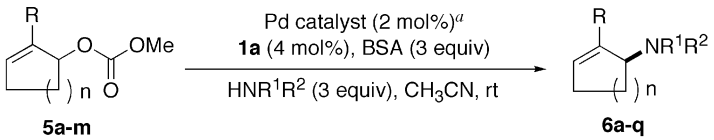
[a] Isolated yield. [b] Determined by HPLC analysis. [c] No reaction.

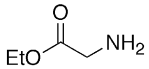
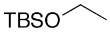
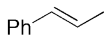
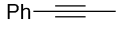
excess.[11] There was a slight improvement in the enantioselectivity when (*S*,R_P)-1-Np-DIAPHOX **1b** was used as the preligand.

The satisfactory results in the conventional reaction system led us to turn our attention to asymmetric allylic amination of cyclic substrates. Asymmetric allylic amination of 2-substituted cycloalkenyl alcohol derivatives affords versatile adducts for the synthesis of nitrogen-containing natural products. Despite its usefulness, the success of this type of reaction is limited.[12] Therefore, we examined asymmetric allylic amination of 2-phenylcyclohexenyl alcohol derivatives with benzylamine (Table 2). Although no reaction occurred when 2-phenylcyclohexenyl acetate **4** was used as the substrate, allylic amination reaction of 2-phenylcyclohexenyl carbonate **5a** proceeded in the presence of 2 mol % of the catalyst at room temperature, affording the corresponding product **6a** in 75% yield and 93% ee. Examination of the solvent effect revealed that the reaction medium dramatically affected reactivity rather than enantioselectivity, and the best results were obtained when CH_3CN was used as the solvent.[13]

The scope and limitation of different substrates were further examined under optimized conditions (Table 3). When 2 mol % of Pd catalyst and 4 mol % of **1a** were used, asymmetric allylic amination of 2-phenyl cyclohexenyl carbonates using primary and secondary amines proceeded at room temperature to provide the corresponding products in good yield with high enantioselectivity (95−97% ee). Other cyclic substrates with a five-membered ring and a seven-membered ring were also applicable to this reaction,

Table 3. Pd-Catalyzed Asymmetric Allylic Amination of 2-Substituted Cycloalkenyl Carbonates



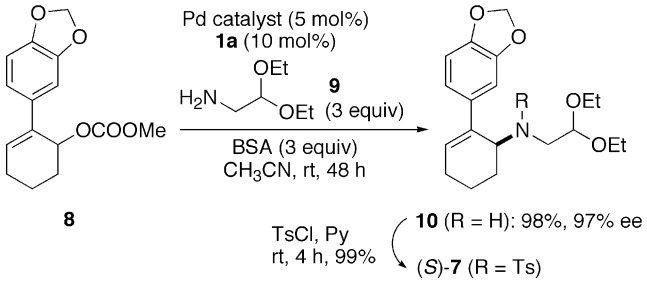
entry	R	n	substrate	HNR^1R^2	product	time	yield[b]	ee[c]
1	Ph	2	**5a**	$BnNH_2$	**6a**	17 h	93%	96% ee
2	Ph	2	**5a**	*n*-$BuNH_2$	**6b**	50 h	85%	95% ee
3	Ph	2	**5a**		**6c**	48 h	88%	96% ee (*S*)
4	Ph	2	**5a**	morpholine	**6d**	7 h	90%	97% ee
5	Ph	1	**5b**	$BnNH_2$	**6e**	8 h	99%	93% ee
6	Ph	1	**5b**	morpholine	**6f**	12 h	75%	99% ee
7[d]	Ph	3	**5c**	$BnNH_2$	**6g**	3 h	84%	83% ee
8	2-naphthyl	2	**5d**	$BnNH_2$	**6h**	18 h	90%	94% ee
9	4-CF_3-C_6H_4	2	**5e**	$BnNH_2$	**6i**	5 h	95%	93% ee
10	4-F-C_6H_4	2	**5f**	$BnNH_2$	**6j**	26 h	81%	91% ee
11	3-F-C_6H_4	2	**5g**	$BnNH_2$	**6k**	7 h	95%	93% ee
12	2-F-C_6H_4	2	**5h**	$BnNH_2$	**6l**	7 h	83%	98% ee
13[d]	4-MeO-C_6H_4	2	**5i**	$BnNH_2$	**6m**	24 h	92%	91% ee
14[d]	3-MeO-C_6H_4	2	**5j**	$BnNH_2$	**6n**	4 h	93%	93% ee
15[d]		2	**5k**	$BnNH_2$	**6o**	4 h	95%	72% ee
16		2	**5l**	$BnNH_2$	**6p**	24 h	55% (36%)[e]	94% ee
17		2	**5m**	$BnNH_2$	**6q**	24 h	75%	80% ee

[a] (η^3-$C_3H_5PdCl)_2$ was used. [b] Isolated yield. [c] Determined by HPLC analysis. [d] 5 mol % of Pd catalyst and 10 mol % of **1a** were used. [e] The number in parentheses indicates recovered starting material.

affording the chiral allylic amines with good to excellent enantioselectivity (83−99% ee). Furthermore, asymmetric allylic amination of cyclohexenyl carbonates with various substituents at the 2-position were examined using benzylamine as the nucleophile. Aryl groups with an electron-withdrawing functionality, as well as an electron-donating functionality, were tolerant to this reaction, giving the products with high enantioselectivity (91−98% ee). Substrates with alkyl, alkenyl, and alkynyl substituents were also applicable to this reaction, and the corresponding products were obtained in moderate to good enantiomeric excess (72−94% ee).[14]

Thus, the present catalytic asymmetric system had broad generality for both electrophiles and amine nucleophiles, affording α-chiral allylic amines in up to 99% ee for both linear and cyclic substrates.[15] To demonstrate the synthetic utility, we applied this catalyst system to the catalytic asymmetric synthesis of (*S*)-**7**, which is the key intermediate for Mori's total synthesis of crinine-type alkaloids (Scheme 1).[12e] Using 5 mol % of Pd catalyst and 10 mol % of **1a**, asymmetric allylic amination of **8** with amine **9** proceeded at room temperature, affording the chiral allylic amine **10** in 98% yield and 97% ee, which could be converted to the key intermediate (*S*)-**7**.[16]

Scheme 1. Catalytic Asymmetric Synthesis of (*S*)-**7**



In conclusion, we succeeded in Pd-catalyzed asymmetric allylic amination using aspartic acid derived P-chirogenic diaminophosphine oxides, which afforded the chiral allylic amines in up to 99% ee. The broad substrate generality of the developed system resulted in a highly enantioselective synthesis of the key intermediate for crinine-type alkaloid synthesis.

Acknowledgment. This work was supported by a Grant-in Aid for Encouragement of Young Scientist (B) from the Ministry of Education, Culture, Sport, Science, and Technology, Japan, and the Banyu Award in Synthetic Organic Chemistry, Japan.

Supporting Information Available: General procedure for Pd-catalyzed asymmetric allylic amination, compound characterization of new compounds, and NMR charts. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) The reaction proceeded very sluggishly in other solvents such as CH_2Cl_2.

(12) (a) Mori, M.; Kuroda, S.; Zhang, C.-S.; Sato, Y. *J. Org. Chem.* **1997**, *62*, 3263−3270. (b) Trost, B. M.; Oslob, J. D. *J. Am. Chem. Soc.* **1999**, *121*, 3057−3064. (c) Hamada, Y.; Sakaguchi, K.; Hatano, K.; Hara, O. *Tetrahedron Lett.* **2001**, *42*, 1297−1299. (d) Mori, M.; Nakanishi, M.; Kajishima, D.; Sato, Y. *J. Am. Chem. Soc.* **2003**, *125*, 9801−9807. (e) Nishimata, T.; Sato, Y.; Mori, M. *J. Org. Chem.* **2004**, *69*, 1837−1843.

(13) We speculate that coordination of CH_3CN to palladium metal might prevent catalyst deactivation by competitive coordination of the product, resulting in the higher reactivity compared with the cases of other solvents.

(14) Asymmetric allylic amination of cyclohexenyl methyl carbonate with benzylamine gave less satisfactory result under the same reation conditions [Pd catalyst (2 mol %), **1a** (4 mol %), $BnNH_2$ (3 equiv), BSA (3 equiv), CH_3CN, rt, 36 h: 57%, 35% ee]. This result indicates the importance of the 2-substituent on the asymmetric induction.

(15) For the experimental procedure of asymmetric allylic amination reactions; see Supporting Information.

(16) In Mori's optimized conditions (5 mol % of Pd catalyst, 5 mol % of (*S*)-BINAPO, THF, −20 °C), (*S*)-**7** was obtained from the corresponding vinyl carbonate in 82% yield and in 74% ee.[12e]