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Pd-Catalyzed Asymmetric Allylic Amination of Morita–Baylis–Hillman Adduct Derivatives Using Chiral Diaminophosphine Oxides: DIAPHOXs

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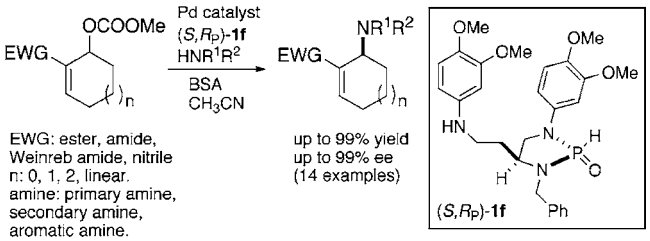
ABSTRACT



Asymmetric allylic amination of allylic carbonates prepared from racemic Morita–Baylis–Hillman adducts proceeded in the presence of Pd catalyst, chiral diaminophosphine oxide (DIAPHOX), and BSA, affording the corresponding chiral aza-Morita–Baylis–Hillman adduct derivatives in excellent yield with up to 99% ee. The cyclic reaction products could be converted into various synthetically useful compounds such as chiral cyclic β-amino acids.

Considerable efforts have been devoted to designing asymmetric catalysts for the Morita−Baylis−Hillman reaction, due to the versatile property of chiral Morita−Baylis−Hillman adducts.[1] The Trost group, on the other hand, developed an alternative strategy to synthesize chiral Morita−Baylis−Hillman adducts based on a conceptually distinct strategy: deracemization of racemic Morita−Baylis−Hillman adduct derivatives using Pd-catalyzed asymmetric allylic substitution.[2,3] Various oxygen nucleophiles are competent for this deracemization process, and several enantioselective total syntheses of natural products have been achieved using the present strategy.[2b−e] In contrast, there are limited applications of nitrogen nucleophiles to this deracemization process.[4] This type of transformation provides easy access to various chiral aza-Morita−Baylis−Hillman adduct derivatives. An efficient method to prepare this versatile class of compounds can be a useful tool in asymmetric synthesis of nitrogen-containing natural products. We describe herein a general and highly enantioselective allylic amination of Morita−Baylis−Hillman adduct derivatives using Pd−chiral diaminophosphine oxide catalyst systems.

We recently reported that aspartic acid-derived P-chirogenic diaminophosphine oxides (DIAPHOXs) **1** (Figure 1)

(1) For a review, see: Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811.

(2) (a) Trost, B. M.; Tsui, H.-C.; Toste, F. D. *J. Am. Chem. Soc.* **2000**, *122*, *3534*. (b) Trost, B. M.; Thiel, O. R.; Tsui, H.-C. *J. Am. Chem. Soc.* **2002**, *124*, 11616. (c) Trost, B. M.; Thiel, O. R.; Tsui, H.-C. *J. Am. Chem. Soc.* **2003**, *125*, 13155. (d) Trost, B. M.; Machacek, M. R.; Tsui, H.-C. *J. Am. Chem. Soc.* **2005**, *127*, 7014. (e) Trost, B. M.; Tang, W.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 14785.

(3) For a review on the Pd-catalyzed asymmetric allylic substitution reaction, see: Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921.

(4) (a) Trost, B. M.; Oslob, J. D. *J. Am. Chem. Soc.* **1999**, *121*, 3057. (b) Mori, M.; Nakanishi, D.; Kajishima, D.; Sato, Y. *J. Am. Chem. Soc.* **2003**, *125*, 9801.

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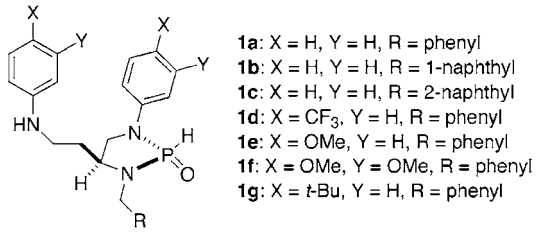
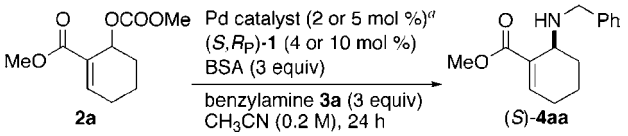


Figure 1. (S,R_P)-DIAPHOXs.

are useful chiral ligands for Pd-catalyzed asymmetric allylic substitution reactions.[5−7] We first selected asymmetric allylic amination of 2-methoxycarbonyl 2-cyclohexenyl alcohol derivatives with benzylamine **3a** as the model reaction because the cyclic products such as **4aa** are not readily accessible using the asymmetric aza-Morita−Baylis−Hillman reaction (Table 1).[8] Although cyclic adduct **4aa** with low enantiomeric excess was obtained when an acetate derivative (26% ee) and a pentafluorobenzoate derivative (31% ee) were used as substrates, allylic amination of carbonate derivative **2a** proceeded in the presence of 5 mol % of Pd catalyst and 10 mol % of (S,R_P)-**1a** at 4 °C, affording (S)-**4aa** in 91% yield and 87% ee. The effect of the ligand structure revealed that the introduction of electron-donating groups onto the aromatic rings attached to the nitrogen atoms increases the enantioselectivity, and the 3,4-dimethoxy-type ligand (S,R_P)-**1f** was best for asymmetric induction. Moreover, enantioselectivity was increased when the reaction was performed at a lower temperature. Using 2 mol % of Pd catalyst and 4 mol % of (S,R_P)-**1f**, cyclic product (S)-**4aa** was obtained in 99% yield with 99% ee (entry 9).[9]

Table 1. Optimization of the Reaction Conditions



entry	DIAPHOX	T (°C)	yield[b] (%)	ee[c] (% ee)
1[d]	**1a**	4	91	87
2[d]	**1b**	4	92	69
3[d]	**1c**	4	97	83
4[d]	**1d**	4	99	71
5[d]	**1e**	4	96	90
6[d]	**1f**	4	99	94
7[d]	**1g**	4	99	89
8[e]	**1f**	4	99	94
9[e]	**1f**	−30	99	99

[a] [η^3-C_3H_5PdCl]$_2$ (1 or 2.5 mol %) was used. [b] Isolated yield. [c] Determined by HPLC analysis. [d] 5 mol % of Pd catalyst and 10 mol % of DIAPHOX were used. [e] 2 mol % of Pd catalyst and 4 mol % of DIAPHOX were used.

Having developed efficient conditions, we next examined the scope and limitation of different substrates (Table 2).[10] When 2 mol % of Pd catalyst and 4 mol % of (S,R_P)-**1f** were used, asymmetric allylic amination of **2a** using primary amines (entries 1−7), a secondary amine (entry 8), and an aromatic amine[11] (entry 9) proceeded efficiently to provide the corresponding products in excellent yield and enantiomeric excess. It is noteworthy that the present catalysis could be performed on a gram scale using 1 mol % of the catalyst, and (S)-**4aa** was obtained in excellent yield without any decrease in the enantiomeric excess (entry 2).[10] Other cyclic substrates with a five-membered ring and a seven-membered ring were also applicable to this reaction, affording the corresponding chiral allylic amines in 91% ee and 84% ee, respectively (entries 10 and 11). Furthermore, asymmetric allylic amination of cyclic substrates with other electron-withdrawing groups was examined using benzylamine as the nucleophile (entries 12−15). A substrate with a simple secondary amide, as well as the Weinreb amide-type substrate, could be utilized for this reaction system, giving the corresponding products in excellent yield and enantiomeric excess. Similarly, a reaction using a cyclic substrate with a nitrile group proceeded at −40 °C to provide the corresponding product in high enantiomeric excess. In addition, linear substrates with a nitrile group were examined (entries 15 and 16). Asymmetric allylic amination of 1,3-diphenylallyl carbonate derivative **2g** proceeded at 4 °C to provide the corresponding product in 89% ee.[12] Monosubstituted-type substrates such as **2h** are applicable to the Trost's catalyst system, giving branched products with high regio and enantioselectivity.[2a−d] In our catalyst system,

(5) (a) Nemoto, T.; Matsumoto, T.; Masuda, T.; Hitomi, T.; Hatano, K.; Hamada, Y. *J. Am. Chem. Soc.* **2004**, *126*, 3690. (b) Nemoto, T.; Masuda, T.; Matsumoto, T.; Hamada, Y. *J. Org. Chem.* **2005**, *70*, 7172. (c) Nemoto, T.; Fukuda, T.; Matsumoto, T.; Hitomi, T.; Hamada, Y. *Adv. Synth. Catal.* **2005**, *347*, 1504. (d) Nemoto, T.; Masuda, T.; Akimoto, Y.; Fukuyama, T.; Hamada, Y. *Org. Lett.* **2005**, *7*, 4447. (e) Nemoto, T.; Jin, L.; Nakamura, H.; Hamada, Y. *Tetrahedron Lett.* **2006**, *47*, 6577. (f) Nemoto, T.; Sakamoto, T.; Matsumoto, T.; Hamada, Y. *Tetrahedron Lett.* **2006**, *47*, 8737.

(6) For other examples of transition metal catalysis using diaminophosphine oxides, see: (a) Ackermann, L.; Born, R. *Angew. Chem., Int. Ed.* **2005**, *44*, 2444. (b) Ackermann, L.; Born, R.; Spatz, J. H.; Meyer, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 7216. (c) Ackermann, L.; Althammer, A.; Born, R. *Angew. Chem., Int. Ed.* **2006**, *45*, 2619. (d) For a review, see: Ackermann, L. *Synthesis* **2006**, 1557.

(7) For other examples of transition metal-catalyzed asymmetric reactions using chiral phosphine oxides, see: (a) 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. (b) Dai, W.-M.; Yeung, K. K. Y.; Leung, W. H.; Haynes, R. K. *Tetrahedron: Asymmetry* **2003**, *14*, 2821. (c) Bigeault, J.; Giordano, L.; Buono, G. *Angew. Chem., Int. Ed.* **2005**, *44*, 4753.

(8) As far as we know, there are no reports of an intramolecular asymmetric aza-Morita−Baylis−Hillman reaction. For intermolecular catalytic asymmetric aza-Morita−Baylis−Hillman reactions, see: (a) Shi, M.; Xu, Y.-M. *Angew. Chem., Int. Ed.* **2002**, *41*, 4507. (b) Shi, M.; Chen, L.-H. *Chem. Commun.* **2003**, 1310. (c) Kawahara, S.; Nakano, A.; Esumi, T.; Iwabuchi, Y.; Hatakeyama, S. *Org. Lett.* **2003**, *5*, 3103. (d) Balan, D.; Adolfsson, H. *Tetrahedron Lett.* **2003**, *44*, 2521. (e) Raheen, I. T.; Jacobsen, E. N. *Adv. Synth. Catal.* **2005**, *347*, 1701. (f) Matsui, K.; Takizawa, S.; Sasai, H. *J. Am. Chem. Soc.* **2005**, *127*, 3680. (g) See also: Krawczyk, E.; Owsianik, K.; Skowronska, A. *Tetrahedron* **2005**, *61*, 1449.

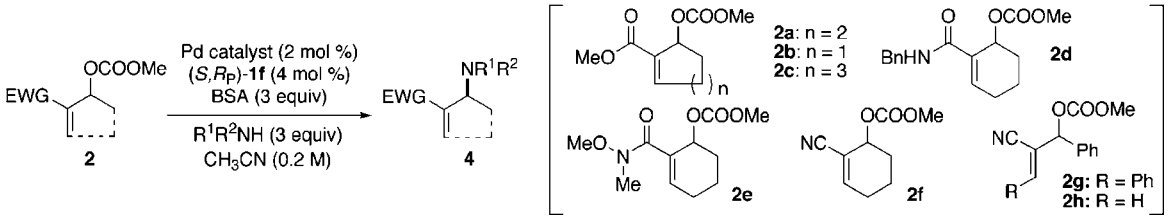
(9) Although this reaction was examined under several catalyst conditions with representative chiral ligands, no satisfactory results were obtained. See the Supporting Information for details.

(10) For the experimental procedure, see the Supporting Information.

(11) No reaction occurred when 4-methoxyphenol was used as a nucleophile.

(12) Although asymmetric allylic amination of a linear substrate with an ester group proceeded under the same reaction conditions, the product was obtained as the mixture of geometrical isomers of the olefin.

Table 2. Substrate Scope



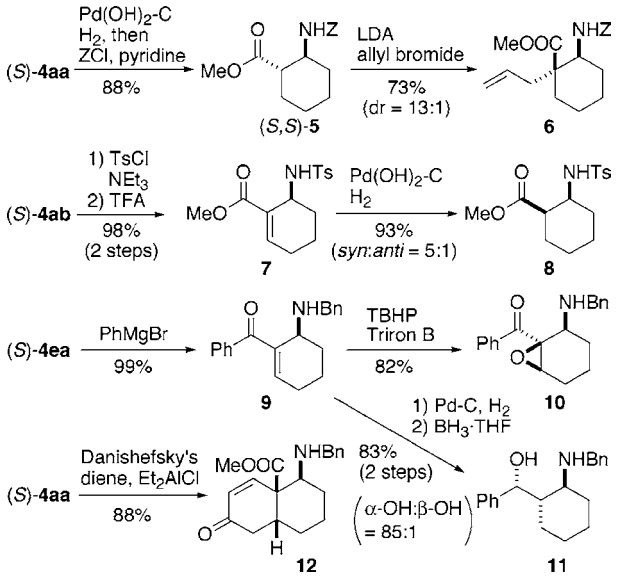
entry	substrate	R^1R^2NH	product	T (°C)	time[a] (h)	yield[b] (%)	ee[c] (% ee)
1	**2a**	benzylamine (**3a**)	**4aa**	−30	24	99	99 (*S*)
2[d]	**2a**	benzylamine (**3a**)	**4aa**	−30	24	98	99 (*S*)
3	**2a**	4-methoxybenzylamine (**3b**)	**4ab**	−30	24	99	97 (*S*)
4	**2a**	furfurylamine (**3c**)	**4ac**	−30	24	99	98
5	**2a**	allylamine (**3d**)	**4ad**	−40	24	99	98
6	**2a**	isopropylamine (**3e**)	**4ae**	−30	24	92	99
7	**2a**	N^{in}-Boc-tryptamine (**3f**)	**4af**	−30	24	97	96
8	**2a**	morpholine (**3g**)	**4ag**	−10	15	98	99
9[e]	**2a**	4-methoxyaniline (**3h**)	**4ah**	−30	48	99	94
10[e,f]	**2b**	benzylamine (**3a**)	**4ba**	−40	18	81	91 (*S*)
11[e]	**2c**	benzylamine (**3a**)	**4ca**	−40	18	99	84
12	**2d**	benzylamine (**3a**)	**4da**	−30	48	94	98
13[e]	**2e**	benzylamine (**3a**)	**4ea**	−30	32	98	99 (*S*)
14	**2f**	benzylamine (**3a**)	**4fa**	−40	18	99	95
15[g]	**2g**	benzylamine (**3a**)	**4ga**	4	24	96	89
16	**2h**	benzylamine (**3a**)	**4ha**	4	24	0 (99)[h]	

[a] Reaction times have not been optimized. [b] Isolated yield. [c] Determined by HPLC analysis. For the determination of the absolute configuration, see the Supporting Information. [d] 1 mol % of Pd catalyst and 2 mol % of (*S*,*R*P)-**1f** were used. Reaction scale: 1.07 g of **2a** was used. [e] (*S*,*R*P)-**1a** was used as the chiral ligand. Results for the use of other DIAPHOXs are summarized in the Supporting Information. [f] Dichloroethane was used as the solvent. [g] (*S*,*R*P)-**1e** was used as the chiral ligand. Results for the use of other DIAPHOXs are summarized in the Supporting Information. [h] Yield of the linear product (geometry of olefin: *Z*).

however, the corresponding linear product was obtained exclusively.

Thus, the present deracemization reaction of allylic carbonates prepared from racemic Morita−Baylis−Hillman adducts through asymmetric allylic amination had broad generality for both electrophiles and amine nucleophiles, affording chiral allylic amines, so-called aza-Morita−Baylis−Hillman adducts, in up to 99% ee. To demonstrate the usefulness of these chiral allylic amines, several diastereoselective modifications were performed (Scheme 1).[10] Chiral cyclic β-amino acids have gained much attention due to their increasing importance for the synthesis of β-peptides.[13] There are, however, few catalytic asymmetric synthetic methods.[14] Our synthesis started with (*S*)-**4aa** and (*S*)-**4ab**. Both olefin hydrogenation and debenzylation of (*S*)-**4aa** using $Pd(OH)_2$−C, followed by protection of the resulting free amine with a carbobenzyloxy (Z) group, afforded the cyclic *anti*-β-amino acid derivative (*S*,*S*)-**5** in 88% yield as a nearly optically pure compound (99% ee).[15] In this hydrogenation, the reaction proceeded with complete diastereoselection, giving the anti product exclusively. On the other hand, protection of (*S*)-**4ab** with a tosyl group, followed by treatment with trifluoroacetic acid, gave α,β-unsaturated ester **7** in 98% yield without any noticeable loss of optical purity (97% ee).[15] This product could be transformed into the cyclic *syn*-β-amino acid derivative **8** with good diastereoselectivity (syn/anti = 5:1).[16] The usefulness of these compounds was further

Scheme 1



(13) For a review, see: Cheng, R. P.; Gellman, S. H.; DeGrado, W. F. *Chem. Rev.* **2001**, *101*, 3219.

(14) (a) Tang, W.; Wu, S.; Zhang, X. *J. Am. Chem. Soc.* **2003**, *125*, 9570. (b) Mita, T.; Fujimori, I.; Wada, R.; Wen, J.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 11252.

(15) Enantiomeric excess was determined by HPLC analysis.

demonstrated. After the formation of lithium enolate of **5**, diastereoselective alkylation was performed using allyl bromide as an electrophile,[17] affording the product with an all-carbon quaternary stereocenter in 73% yield with high diastereoselectivity (dr = 13:1).[16] Weinreb amide-type adduct (*S*)-**4ea** (99% ee) reacted with a Grignard reagent at −40 °C to provide the corresponding enone **9** in 99% yield (99% ee).[15,18] This enone could be converted into α,*β*-epoxy ketone **10** (82% yield) and 1,3-amino alcohol **11** (83% yield) in a highly diastereoselective manner.[16] Moreover, Diels−Alder reaction of **4aa** with the Danishefsky's diene proceeded in the presence of Et_2AlCl, giving the bicyclic product **12** in 88% yield as a single diastereomer.[16]

(16) Diastereoselectivity was determined by ^{1}H-NMR analysis. For the epoxidation and the Diels−Alder reaction, no peaks corresponding to the diastereomer could be detected. The relative configuration was determined by the NOE experiment. See the Supporting Information for details.

(17) Seebach, D.; Estermann, H. *Tetrahedron Lett.* **1987**, *28*, 3103.

(18) Asymmetric allylic amination of cyclohexenyl carbonate with phenyl ketone using benzylamine gave **9** with low enantiomeric excess (37% ee). This was due to the competitive racemic pathway through a conjugate addition of benzylamine. See the Supporting Information for details.

In conclusion, we succeeded in the general and highly enantioselective allylic amination of Morita−Baylis−Hillman adduct derivatives using Pd-DIAPHOX catalyst systems. The versatile property of the reaction products was demonstrated. Application to asymmetric synthesis of nitrogen-containing natural products is ongoing.

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Supporting Information Available: Experimental procedures and supplementary data, compound characterization, and NMR charts. This material is available free of charge via the Internet at http://pubs.acs.org.

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