Pd-Catalyzed Asymmetric Allylic Amination with BOP Ligands and Its Applications to the Synthesis of Fused polycyclic Alkaloids

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Dedicated to late Professor Harry H. Wasserman for his outstanding achievements and fond memories

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ABSTRACT

Pd-catalyzed asymmetric allylic amination reaction of piperonylamides and a 2-siloxymethylcyclohexenyl carbonate, using chiral biphenol-based diphosphinite (BOP) ligands gave the corresponding cyclohexenylpiperonylamides in excellent yield and enantiopurity (93–95% ee). These amides were applied to the synthesis of fused polycyclic alkaloids in a short sequence of steps.

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Amaryllidaceae family consists of about 85 genera and 1,100 species.¹ To date, nearly 500 structurally diverse alkaloids have been isolated from these plants.¹ Some representative alkaloids are shown in Figure 1. Most of them exhibit various biological activities.^{2–12} Crinine-type alkaloids have been shown to be active against rat hepatoma cells.⁴ A preliminary structure-activity study revealed that a free secondary hydroxyl group at C11 and an α -5,10b-ethano bridge were essential for their biological activity.^{2,3} Lycorine was found to be a potential therapeutic agent against acute promyelocytic leukemia.⁴ Montanine and pancratistatin exhibited antiviral, anxiolytic, antidepressive, and anticonvulsive activities.^{5–12}

Because of their diverse biological activities and intriguing structures, many chemical syntheses of these alkaloids have been reported.^{13–24} The first total synthesis of racemic pancracine was accomplished by Overman (Scheme 1A).¹³ The Overman's intermediate **3** bearing a 5,11-methanomorphanthridine skeleton was constructed through a tandem aza-Cope rearrangement/Mannich cyclization of **1**, followed by a Pictet-Spengler cyclization of **2**.¹³ This intermediate **3** was also used in the asymmetric total synthesis of (-)-pancracine by Anada.¹⁴ Weinreb reported the first enantioselective total synthesis of (-)-montanine employing an intramolecular concerted allenylsilane imino ene cyclization of **4** and the subsequent intramolecular Heck reaction of **5** in the pivotal steps (Scheme 1B).¹⁵ Since certain polycyclic alkaloids, such as **2**, **3**, **5** and **6**, serve as key intermediates for the total synthesis of amaryllidaceae alkaloids, we envisioned potential

utilities of similar polycyclic alkaloids bearing piperonylamine skeleton with excellent enantiopurity (Scheme 2).

Figure 1. Amaryllidaceae alkaloids

We have been developing a library of novel chiral biphenol-based monodentate phosphite and phosphoramidite ligands,^{25–34} as well as bidentate diphosphinite ligands (BOP ligands) for a variety of catalytic asymmetric reactions.^{31,32,24} These ligands are easy to prepare and fine-tunable through modification of the groups at the 3,3'-positions and the substituents attached to the phosphorous atoms. Our BOP ligands have exhibited excellent efficiency in Pd-catalyzed asymmetric allylic amination^{31,32} (AAA) and

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etherification³⁴ (AAE) reactions (up to 97% ee). Accordingly, we examined the efficiency of our BOP ligands in the AAA reaction of piperonylamides **8** and cyclohexenylcarbonates **7** to give cyclohexenylpiperonylamides **10** (Scheme 2). We describe here excellent efficiency of the optimized BOP ligand for this AAA

reaction and versatility of **10** with high enantiopurity for the synthesis of fused polycyclic alkaloids, which would serve as advanced intermediates for the total synthesis of complex amaryllidaceae alkaloids and their analogs.

Scheme 1. The syntheses of montanine-type alkaloids

Scheme 2. Pd-catalyzed AAA reactions for the syntheses of fused polycyclic alkaloids

First, the evaluation of allylic substrates **7a-c** was performed using BOP ligand (*S*)-**L1c** and nucleophile **8a** (1.1 equiv.) under conditions similar to those used for the successful intermolecular Pd-catalyzed AAE reaction recently reported.³² Thus, the reactions were carried out in DMF at 0.1 M substrate concentration with a Pd(II)/(*S*)-**L1c** ratio of 1:1.5. The results are shown in Table 1. The AAA reaction proceeded as anticipated for **7a** and **7b** to give the corresponding cyclohexenylamides (*S*)-**10x** and (*S*)-**10a** in good yields and enantiopurity (entries 1 and 2). However, no AAA reaction took place when **7c** was used as the substrate under the same conditions (Table 1, entry 3). The result indicates that the TBDPS group is too bulky for the π -allylic-Pd species generated to accept a nucleophilic attack of piperonylamides **8a**. It is worthy of note that **7c** gave the best result in the AAE reaction.³² Thus, the results have revealed that the nature of nucleophiles plays a critical role in asymmetric allylic substitution reactions. The reactions also yielded cyclohexadiene side products **11x** and **11a** (entries 1 and 2). Since it is easy to separate non-polar side product **11** by flash chromatography, it is not important for this AAA process, especially when **8** is used as the limiting reactant. Nevertheless, this side reaction can be used for selection of reaction variables for optimization. Based on the results, allylic carbonate **7b** was naturally selected for further study.

Table 1. Evaluation of **7a-c** in the reaction with **8a**

entry	substrate	conversion ^a (%)	(<i>S</i>)- 10 ^b (% ee)	10 : 11
1	7a	>95%	82	72:28
2	7b	>95%	85	85:15
3	7c	— ^c	— ^c	—

^aDetermined by ¹H NMR. ^bDetermined by HPLC using Chiralcel ODH. ^c**7c** was consumed, but no reaction with **8a**.

Next, several BOP ligands (Scheme 2) were evaluated for the reaction of **7b** with **8a** using DMF as the solvent at room temperature for 24 h. The results are summarized in Table 2. All reactions completed in 24 h. The entry 0 shows the result using (*S*)-**L1c** from Table 1 for comparison. BOP ligand (*S*)-**L1a** bearing a benzyl group at the 3,3'-positions gave (*S*)-**10a** with 80% ee (entry 1). The introduction of a bulky substituent at the *meta* position, i.e., 3,5-di-*tert*-butylbenzyl groups at the 3,3'-positions of the biphenyl moiety, i.e., (*S*)-**L1b**, slightly improved the

enantioselectivity (entry 2). The use of 2,4,6-trimethylbenzyl groups at the 3,3'-positions and 3,5-dimethylphenyl groups on phosphorus, i.e., (S)-**L2c**, substantially increased the enantioselectivity to 93% ee (entry 3). Although (S)-**L1a** gave the best product selectivity, we selected (S)-**L2c** for further study, simply because it gave the best enantioselectivity.

Table 2. Evaluation of BOP ligands for the reaction of 7b with 8a^a

entry	ligand	conversion ^b (%)	(S)- 10a ^c (% ee)	10a:11a
0	(S)- L1c	>95%	85	85:15
1	(S)- L1a	>95%	80	91:9
2	(S)- L1b	>95%	83	85:15
3	(S)- L2c	>95%	93	73:27

^aReactions were run using **7b** (0.1 M), **8a** (1.1 equiv.), [Pd(allyl)Cl]₂ (2.5 mol %) with a BOP ligand (7.5 mol %) in DMF at room temperature (25 °C) for 24 h. ^{b,c}See footnotes of Table 1.

Next, we examined the effects of Pd catalyst precursors, reaction temperature and the concentration of reactants. Results are summarized in Table 3. We examined the efficiency of Pd(0) catalyst precursor, i.e., Pd₂(dba)₃, as compared to Pd(II) complex, [Pd(allyl)Cl]₂. The reaction using the Pd(0) complex gave the same enantioselectivity as that with the Pd(II) complex, but the product selectivity was higher (entry 1). The same reaction run at 0 °C increased the enantioselectivity to 95% ee with further improved product selectivity, but the reaction was slowed as anticipated (entry 2). The reduction in the catalyst loading from 2.5 mol% to 1.0 mol% in the reaction at 25 °C did not affect the enantioselectivity, but the product selectivity was somewhat lowered (entry 3). Increase in the substrate concentration from 0.1 M to 0.2 M significantly accelerated the reaction by keeping excellent enantioselectivity (95% ee) (entry 4). Although Pd₂(dba)₃ appeared to serve as excellent Pd catalyst precursor, dibenzylideneacetone (dba) released to the reaction mixture happened to have almost the same R_f value as that of the product **10a**, and thus rather difficult to separate by chromatography. Accordingly, we switched back to [Pd(allyl)Cl]₂ under the optimized conditions, i.e., 0.2 M substrate concentration with 1.0 mole % of the Pd catalyst precursor. Then, it was found that the Pd(II) precursor gave essentially the same results, i.e. full conversion and 95% ee, as those for the Pd(0) precursor (entry 5). Thus, [Pd(allyl)Cl]₂ was used as the Pd catalyst precursor for further study.

Table 3. Effect of Pd catalyst precursors and reaction variables

entry	catalyst (mol %)	temp. (°C)	conversion ^a (%)	10a ^b (% ee)	10a:11a
1 ^c	Pd ₂ (dba) ₃ (2.5)	25	>95	93	79:21
2 ^c	Pd ₂ (dba) ₃ (2.5)	0	66	95	86:14
3 ^d	Pd ₂ (dba) ₃ (1.0)	25	68	95	75:25
4 ^{d,e}	Pd ₂ (dba) ₃ (1.0)	25	>95	95	75:25
5 ^{d,e}	[Pd(allyl)Cl] ₂ (1.0)	25	>95	95	73:27

^{a,b}See the footnotes of Table 1. ^cAt 0.1 M concentration. ^d1 mol% of Pd complex and 3 mol% of BOP ligands. ^eAt 0.2 M concentration.

Finally, we examined the effects of *N*-protecting groups of piperonylamides **8** on the enantioselectivity and reactivity in this AAA reaction under the optimized conditions described above. We used tosyl, 2-nosyl, mesyl, trifluoroacetyl and *t*-Boc as the *N*-protecting groups. Results are summarized in Table 4. The reactions with **8** bearing *N*-sulfonyl groups, i.e., **8a**, **8b** and **8c**, exhibited high reactivity and enantioselectivity (entries 1-3), although the use of mesyl, a smaller sulfonyl group, somewhat lowered enantioselectivity to 90% ee (entry 3). In contrast, attempted reactions with **8d** bearing a trifluoroacetyl group and **8e** bearing a *t*-Boc group did not yield the corresponding AAA products at all (entries 4 and 5).

In addition to 2-bromopiperonylsulfonamides **8a-c**, piperonylsulfonamide **8f** was also employed as a nucleophile in this AAA reaction (entry 6). The reaction gave the corresponding product **10f** with 93% ee.

Table 4. Effects of *N*-protecting groups of 8 on the AAA reaction

entry	nucleophile	conversion ^a (%)	Product	(S)- 10 ^b (% ee)	10:11a
1	8a	>95%	10a	95	73:27
2	8b	>95%	10b	94	70:30
3	8c	>95%	10c	90	78:22
4	8d	-- ^c	--	--	--
5	8e	-- ^c	--	--	--
6	8f	>95%	10f	93	78:22

^{a,b}See footnotes of Table 1. ^c**7b** was consumed, but no reaction with **8d** or **8e**.

Although both **8a** and **8b** were found to be excellent nucleophiles in this AAA reaction, yielding **10a** and **10b**, respectively, with excellent enantiopurity, a nosyl *N*-protecting group has an advantage for certain functional group manipulations, due to its easier removal than an *N*-tosyl group.³³ Accordingly, we decided to prepare (S)-**10b** in a multi-gram scale and use it for the synthesis of a couple of fused polycyclic alkaloids.

The asymmetric synthesis of (S)-**10b** was carried out using 1.4 equivalents of **7b** with **8b** in the presence of [Pd(allyl)Cl]₂ (1.0 mol%) and (S)-**L2c** (3 mol%) at 25 °C in DMF for 24 h. The reaction gave (S)-**10b** in 96% isolated yield (based on **8b**) and 94% ee (Scheme 3). The removal of **11a** was very easy as mentioned above. In the same manner, (S)-**10f** was obtained in 94% yield and 93% ee.

Cyclohexenylpiperonylamide (S)-**10b** (94% ee), thus obtained, was converted to a fused tetracyclic alkaloid **18** and an indoline alkaloid **19**, as illustrated in Scheme 3. Nitrile (S)-**14** was obtained in excellent yield for 2 steps from (S)-**10b** via (S)-**13b** alcohol using a Mitsunobu reaction. The attempted Pd-catalyzed intramolecular Heck reaction of (S)-**14** under the standard conditions did not proceed at all. We reasoned that this would be due to the bulkiness of the nosyl group. Thus, nitrile (S)-**16**, bearing a smaller trifluoroacetyl group, was prepared by the simple deprotection and protection of (S)-**14** and subjected to an intramolecular Heck reaction. Indeed the reaction gave tetracyclic (-)-**17** in 58% yield, which was deprotected to afford fused tetracyclic alkaloid (-)-**18** in excellent yield. The relative stereochemistry of (-)-**18** was determined by NOESY.

Indoline alkaloid (*S*)-**19** with a 2-bromopiperonyl group was synthesized from (*S*)-**15** via reduction of nitrile, followed by reductive amination in fairly good yield for two steps (Scheme 3).

Another fused tetracyclic alkaloid (*S*)-**21** bearing a benzazepine skeleton was synthesized starting from (*S*)-**10f** (93% ee). This synthesis features Zn(II)-promoted intramolecular Friedel-Crafts reaction of bromide (*S*)-**20**, which was prepared from (*S*)-**10f** in two steps (Scheme 3). It is noteworthy that common Lewis acids for Friedel-Craft reactions, such as AlCl₃, InBr₃, SnCl₄, TiCl₄, etc. only yielded messy reactions.

In summary, cyclohexenylpiperonylamides **10** with excellent enantiopurity (93–95% ee) were obtained in high yields through the AAA reaction of piperonylamides **8** with **7b** using BOP ligand (*S*)-**L2c**. These amides (*S*)-**10b** (94% ee) and (*S*)-**10f** (93% ee) were converted to fused polycyclic alkaloids, (–)-**18**, (*S*)-**19** and (*S*)-**21**, in a short sequence of steps. Further transformations of these fused polycyclic alkaloids to amaryllidaceae alkaloids are currently underway in our laboratory.

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Scheme 3. Syntheses of polycyclic alkaloids **18**, **19** and **21**

Supplementary data

Supplementary data (experimental procedures and analytical data for all the new compounds with ¹H and ¹³C NMR spectra) associated with this article can be found, in the online version, xxxxxxxxxxxxxxxxxxxx.

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