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Amination of *N*-Aryl Prolinol via Ring Expansion and Contraction: Application to the Chiral Ligand for the Catalytic Asymmetric Reaction

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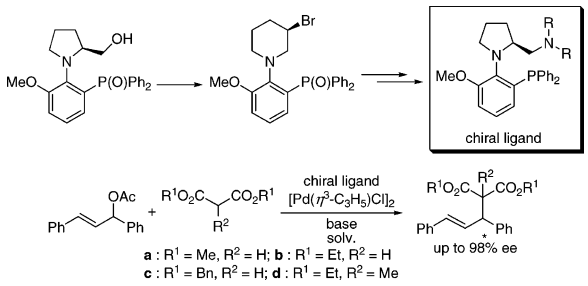
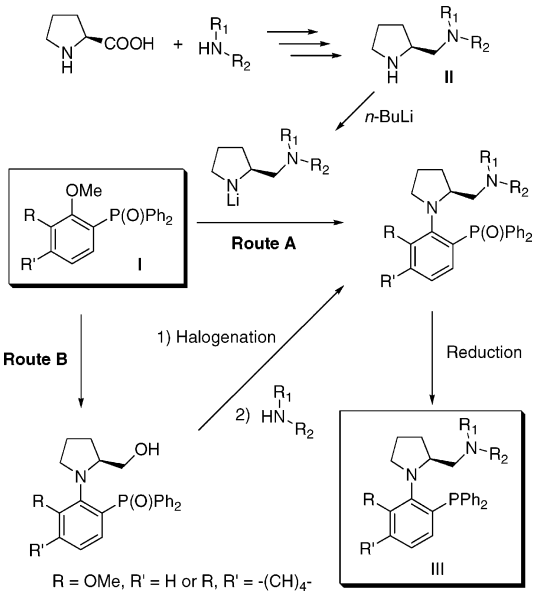


Chiral diaminophosphines **4** were prepared from (*S*)-prolinol-derived aminophosphine oxide **5** by bromination with ring expansion followed by amination with ring contraction and reduction, using trichlorosilane. In the presence of **4** as a ligand, palladium-catalyzed asymmetric allylic alkylation of 1,3-diphenyl-2-propenyl acetate (**11**) with a dialkyl malonate−BSA−LiOAc system was successfully carried out with good enantioselectivities (up to 98% ee).

Palladium-catalyzed allylic alkylation is a widely used process in organic synthesis,[1] and the development of efficient enantioselective catalysis for this reaction is awaited.[2] It has been found that chiral 2-(phosphinoaryl)-oxazoline can induce high enantiomeric excesses in this reaction.[3] Following this pioneering study, aminophosphines have been used as ligands for this reaction. Especially, pyrrolidinyl-containing aminophosphines were found to be efficient chiral sources.[4] Previously, we reported the preparation of chiral aminophosphines **1**[5]

SCHEME 1. Preparation of Diaminophosphine



and **2**,[6] and investigated the effect of the terminal groups of the side chain on the ligand in palladium-catalyzed asymmetric allylic alkylation. Recently, Kondo reported on the preparation of chiral diaminophosphine **3**[7] and investigation of its application to asymmetric[7b,d] or regioselective[7c] reactions. In this case, **3** (**III**: R, R′ = −(CH)$_4$−) was prepared from the corresponding diamine **II**, such as (*S*)-1-(2-pyrrolidinylmethyl)pyrrolidine with phosphine oxide **I**, by using the nucleophilic aromatic substitution (S_NAr) reaction as a key step. This route (Route A in Scheme 1) did not provide a convenient way of tuning on the terminal groups of the side chain on the diaminophosphine unlike the case of tuning on the phosphine site and benzene backbone,[5,6] and necessitated the preparation of various corresponding diamines **II** from proline over several steps.[8] Here, we report the more straightforward preparation of various chiral diaminophosphines **4**[9] (**III**: R = OMe, R′ = H) by bromination

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(7) (a) Horibe, H.; Fukuda, Y.; Kondo, K.; Okuno, H.; Murakanmi, Y.; Aoyama, T. *Tetrahedron* **2004**, *60*, 10701. (b) Sakamoto, Y.; Kondo, K.; Tokunaga, M.; Kazuta, K.; Fujita, H.; Murakami, Y.; Aoyama, T. *Heterocycles* **2004**, *63*, 1345. (c) Horibe, H.; Kazuta, K.; Kotoku, K.; Kondo, K.; Okuno, H.; Murakami, Y.; Aoyama, T. *Synlett* **2003**, 2047. (d) Kondo, K.; Kazuta, K.; Saitoh, A.; Murakami, Y. *Heterocycles* **2003**, *59*, 97. (e) Kondo, K.; Kazuta, K.; Fujita, H.; Sakamoto, Y.; Murakami, Y. *Tetrahedron* **2002**, *58*, 5209.

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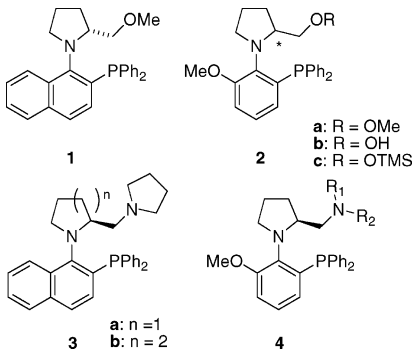
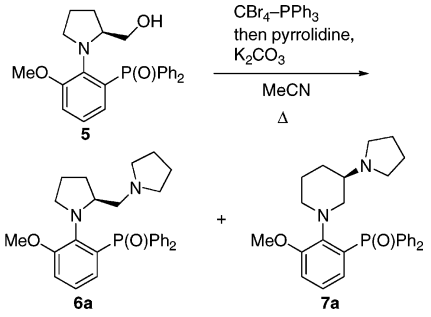
with ring expansion and amination using the corresponding amines with ring contraction on the pyrrolidine ring (Route B).



Initially, we tried the Mitsunobu-type reaction with pyrrolidine using DEAD for direct amination of the hydroxyl group[10] at the terminal side chain of prolinol-derived aminophosphine oxide **5**.[6] We could not isolated a desired product. The desired product was trace under this reaction checked by TLC, because the diphenyl phosphinoyl group of **5** was sterically hindered. Under the condition using carbon tetrabromide-triphenylphosphine with pyrrolidine, 1-(2-pyrrolidinylmethyl)pyrrolidine type diaminophosphine oxide **6a** was directly obtained from **5** in a 47% yield accompanied by 3-(1-pyrrolidinyl)piperidine type diaminophosphine oxide **7a** as a byproduct in a 23% yield.

This reaction mechanism was investigated step by step. In the bromination of aminophosphine oxide **5** with carbon tetrabromide-triphenylphosphine[11] at room temperature, chiral 3-bromopiperidine derivative **8a** (see Figure S1 in Supporting Information) was obtained with ring expansion in a 92% yield (Scheme 3).

SCHEME 2. Amination of *N*-Aryl Prolinol 5



We tried halogenation of **5** under various conditions. Iodination of **5** with the iodine−triphenylphosphine−imidazole method[12] gave chiral 3-iodopiperidine derivative **8b** in a good yield similar to that achieved by the bromination (entry 1 in Table 1). Although chlorination of **5** proceeded slowly, this reaction gave 3-chloropiperidine derivative **8c** (see Figure S2 in Supporting Information) with 2-chloromethylpyrrolidine **9c** as a byproduct under various methods (entries 2−4). 2-Chloromethylpyrrolidine **9c** was easily converted to **8c** in chloroform at 50 °C (Scheme 4).

SCHEME 3. Bromination of *N*-Aryl Prolinol 5 with Ring Expansion

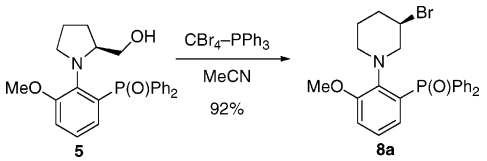
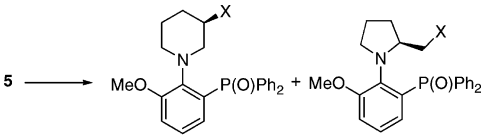


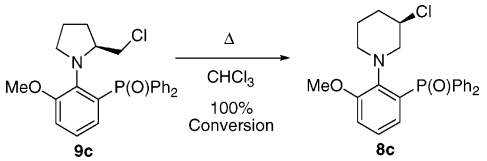
TABLE 1. Halogenation of 5 with Ring Expansion under Various Conditions



entry	X	conditions	yield of **8** (%)[a]	yield of **9** (%)[a]
1	I	I_2, PPh_3, imidazole, THF, rt, 3 h	95	
2	Cl	CCl_4, PPh_3,[b] MeCN, rt, 24 h	30	15
3	Cl	MsCl, Et_3N,[c] THF, Δ, 3 h	56	21
4	Cl	$SOCl_2$, Et_3N,[d] $CHCl_3$, rt, 2 h	51	31

[a] Isolated yields. [b] Reference 13. [c] Reference 14. [d] Reference 15.

SCHEME 4. Ring Expansion Rearrangement of 9c



A plausible mechanism for this halogenation with ring expansion is given below.[15,16] Treatment of **5** with halogenated reagents led to 2-halomethylpyrrolidine **A** (Scheme 5). This intermediate **A** was easily rearranged to 2-halomethylpyrrolidine derivative **C** via aziridine **B**, followed by ring opening by a concerted attack of halogenated anion without racemization (see Supporting Information) similar to ring expansion reactions reported by Ori[13] and Cossy.[14]

The amination of 3-bromopiperidine derivative compound **8a** via aziridinium ion intermediate **A**[17] was employed in the preparation of **6** (Route A in Scheme 6). Using pyrrolidine as an amine, diaminophosphine oxide

(9) Preliminary communication: Mino, T.; Tanaka, Y.; Sato, Y.; Saito, A.; Sakamoto, M.; Fujita, T. *Tetrahedron Lett*. **2003**, *44*, 4677; *Tetrahedron Lett*. **2003**, *44*, 5759.

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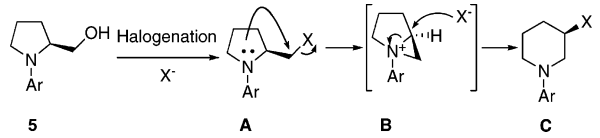
SCHEME 5. A Plausible Mechanism for Halogenation with Ring Expansion



SCHEME 6. A Plausible Mechanism for Amination with Ring Contraction

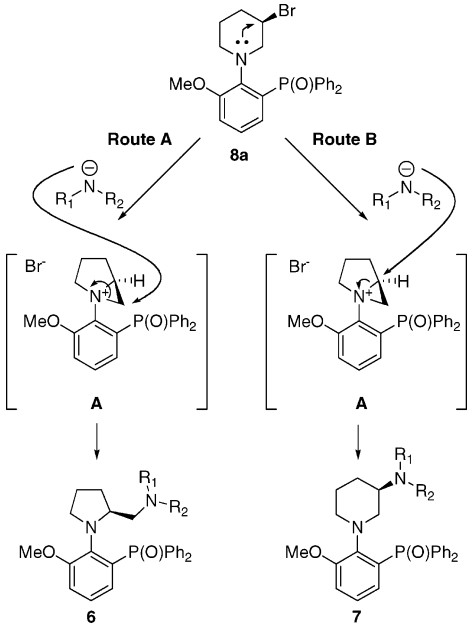
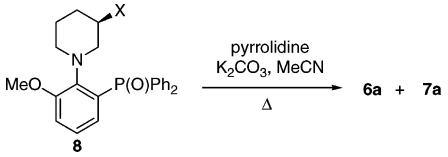


TABLE 2. Amination of 8 with Pyrrolidine



entry	X	reaction time (h)	ratio of **6a**:**7a**[a]	yield of **6a** and **7a** (%)[b]
1	Br (**8a**)	7	60:40	95
2	I (**8b**)	5.5	60:40	93
3	Cl (**8c**)	30	63:37	68

[a] Determined by ^{1}H NMR analysis. [b] Isolated yields.

6a was obtained with 3-(1-pyrrolidinyl)piperidine type diaminophosphine oxide **7a** as a byproduct (Route B). The ratio of **6a** and **7a** was estimated to be about 60:40 by ^{1}H NMR analysis (entry 1 in Table 2). Although the reaction rate was different, this ratio was similar to that for the reaction of 3-iodopiperidine **8b** or 3-chloropiperidine **8c** instead of **8a** (entries 2 and 3). Both isomers were stable under the reaction conditions without rearrangement.

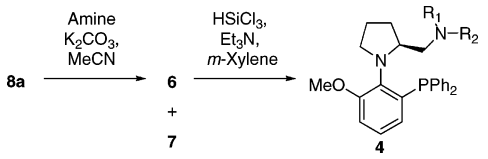
The diaminophosphine oxide **6a** was separated from 3-(1-pyrrolidinyl)piperidine type phosphine oxide **7a** by silica gel column chromatography. As shown in entry 1 in Table 3, the phosphine oxide **6a** was converted into the desired chiral diaminophosphine **4a**[18] by using trichlorosilane-triethylamine in a good yield without racemization (see Supporting Information). The diaminophosphines **4b**−**g** were prepared in the same manner with the various corresponding diamines (entries 2−7). Unfortunately, the mixture of products from indoline and *N*-ethylbenzylamine could not easily be separated by silica gel column chromatography. However, the mixture of isomers was directly converted into the desired chiral diaminophosphines **4h**,**i** and **10h**,**i** by using trichlorosilane-triethylamine and separated in good yields (Table 4). We also prepared piperidine type diaminophosphines **10a** (77% yield) and **10b** (58% yield) by the reduction of **7a** and **7b** using the trichlorosilane-triethylamine method.

We successfully conducted X-ray crystallographic analysis of **4b** and **10b**. The ORTEP drawings are shown in Figures S3 and S4 (see Supporting Information). Although we previously reported the compound **10b** was an atorpisomeric diastereomer of **4b** on the C−N bond in a preliminary communication,[9] the correct structure of **10b** was 3-(1-piperidinyl)piperidine type phosphine.

Acetylation of diaminophosphines **4e** and **4f** with acetyl chloride and triethylamine gave the corresponding diaminophosphines **4j** (86%) and **4k** (94%).

The chiral diaminophosphines **4**, **10a**, and **10b** were applied to the chiral ligands for the palladium-catalyzed asymmetric allylic alkylation of 1,3-diphenyl-2-propenyl

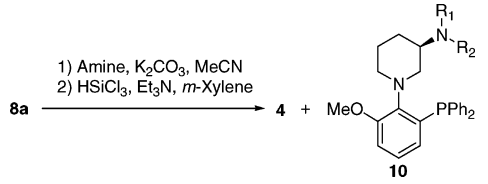
TABLE 3. Preparation of Diaminophosphine 4a−h



entry	amine	yield of **6** (%)[a]	yield of **7** (%)[a]	yield of **4** (%)[a]
1	pyrrolidine	59 (**6a**)	39 (**7a**)	84 (**4a**)
2	piperidine	54 (**6b**)	40 (**7b**)	88 (**4b**)
3	morpholine	55 (**6c**)	34 (**7c**)	87 (**4c**)
4	dicyclohexylamine	82 (**6d**)	nd[b] (**7d**)	87 (**4d**)
5	*N*-ethylethanol amine	54 (**6e**)	43 (**7e**)	77 (**4e**)
6	diethanol amine	61 (**6f**)	26 (**7f**)	79 (**4f**)
7	diethyl iminoacetate	32 (**6g**)	6 (**7g**)	23 (**4g**)

[a] Isolated yields. [b] Not detected.

TABLE 4. Preparation of Diaminophosphine 4h and 4i

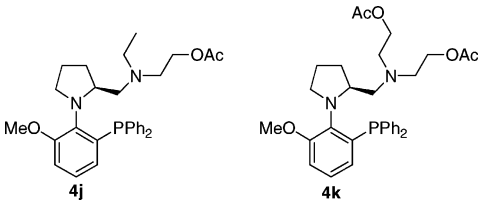


entry	amine	yield of **4** from **8a** (%)[a]	yield of **10** from **8a** (%)[a]
1	indoline	41 (**4h**)	42 (**10h**)
2	*N*-ethylbenzylamine	54 (**4i**)	26 (**10i**)

[a] Isolated yields.

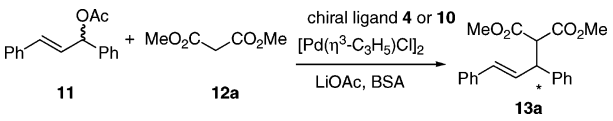
(17) (a) Graham, M. A.; Wadsworth, A. H.; Thornton-Pett, M.; Rayner, C. M. *Chem. Commun.* **2001**, 966. (b) Connor, D. T.; Unangst, P. C.; Schwender, C. F.; Sorenson, R. J.; Carethers, M. E.; Puchalski, C.; Brown, R. E.; Finkel, M. P. *J. Med. Chem.* **1989**, *32*, 683.

(18) Recently Kondo independently reported the preparation of **4a** via Route A in Scheme 1 and the application to the asymmetric Kumada cross coupling reaction: see refs 7a and 7b.



acetate (**11**) with dimethyl malonate (**12a**) as a model reaction. This reaction was carried out in the presence of 2 mol % of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$, 4 mol % of diaminophosphine, and a mixture of *N*,*O*-bis(trimethylsilyl)acetamide (BSA) and 2 mol % of metal acetate (Table 5).[19]

TABLE 5. Palladium-Catalyzed Asymmetric Allylic Alkylation with Diaminophosphine[a]

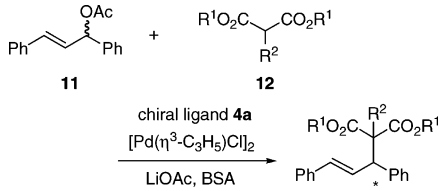


entry	ligand	solv	temp (°C)	yield (%)[b]	ee (%)[c]	config[c]
1	**4a**	PhMe	rt	93	82	*S*
2	**4a**	PhMe	−10	15	91	*S*
3	**4a**	$PhCF_3$	−10	95	91	*S*
4[d]	**4a**	$PhCF_3$	−10	89	86	*S*
5	**4a**	THF	−10	97	93	*S*
6	**4a**	ether	−10	99	95	*S*
7[e]	**4a**	$PhCF_3$	−20	93	93	*S*
8[e]	**4a**	THF	−20	99	95	*S*
9	**10a**	PhMe	rt	65	15	*R*
10	**10a**	$PhCF_3$	−10	nr[f]		
11	**10a**	ether	−10	nr[f]		
12	**10b**	$PhCF_3$	−10	nr[f]		
13	**4b**	ether	−10	99	92	*S*
14	**4c**	ether	−10	98	92	*S*
15	**4d**	ether	−10	97	95	*S*
16	**4e**	ether	−10	98	95	*S*
17	**4f**	ether	−10	86	92	*S*
18	**4g**	ether	−10	84	94	*S*
19	**4h**	ether	−10	91	86	*S*
20	**4i**	ether	−10	99	92	*S*
21	**4j**	ether	−10	98	95	*S*
22	**4k**	ether	−10	77	95	*S*

[a] All reactions were carried out for 24 h. [b] Isolated yields. [c] Determined by HPLC analysis, using a chiral column (Chiralcel OD-H). [d] KOAc was used instead of LiOAc. [e] This reaction was carried out for 48 h. [f] No reaction.

With use of ligand **4a** at room temperature in toluene, (*S*)-**13a** was obtained in a good chemical yield, but the enantiomeric excess was moderate (entry 1). Although the enantioselectivity was improved to 91% ee, the reaction rate became slow with a decrease of the reaction temperature to −10 °C (entry 2). When the reaction was carried out in α,α,α-trifluorotoluene at −10 °C, the reactivity was dramatically increased without decrease of the enantioselectivity (entry 2 vs entry 3). To improve the enantioselectivity of **13a**, we further examined the effect of the metal of the base, the solvent, and the reaction temperature (entries 4−8). With use of ether as a solvent at −10 °C for 24 h, (*S*)-**13a** was obtained in a good yield (99%) with 95% ee (entry 6). On the other hand, when the reaction was carried out with **10a** at room temperature in toluene, the reactivity and enantioselectivity of **13a** were decreased and the configuration of **13a** was inverted (entry 9). When we decreased the reaction temperature to −10 °C, the reaction did not occur after 24 h (entries 10 and 11). This occurred in the case of ligand **10b** (entry 12). Next, we examined AAA reactions of various diaminophosphines **4b**−**k** as a ligand in ether at −10 °C (entries 13−22). Each reaction provided a similar level of chemical yield and enantioselectivity to the reaction with use of **4a**, except **4h** and **4k**. When the reaction was carried out with **4h**, the enantioselectivity of **13a** was slightly decreased (entry 19). In the case of **4k**, (*S*)-**13a** was obtained with a similar level of enantioselectivity, but the reaction rate became slow (entry 22).

TABLE 6. Palladium-Catalyzed Asymmetric Allylic Alkylation with 4a[a]



entry	malonate	yield (%)[b]	ee (%)[c]	config[c]
1	**12a**	99	95	*S*
2	**12b**	96	95	*S*
3	**12c**	84	91	
4	**12d**	91	95	*R*
5[d]	**12b**	93	96	*S*
6[d,e]	**12b**	71	98	*S*

[a] All reactions were carried out for 24 h. [b] Isolated yields. [c] Determined by chiral HPLC analysis. [d] This reaction was carried out with 10 mol % catalyst at −40 °C for 72 h. [e] This reaction was carried out with **4j** instead of ligand **4a**.

In addition, we examined the AAA reactions of various dialkyl malonates using **4a** as a ligand. As shown in Table 6, each reaction provided a similar level of chemical yield and enantioselectivity, except dibenzyl malonate **12c**. When the reaction was carried out with **12c**, the enantioselectivity of **13c** was slightly decreased (entry 3).

In summary, we successfully obtained various chiral diaminophosphines **4** from (*S*)-prolinol-derived aminophosphine oxide **5** by bromination with ring expansion followed by amination with ring contraction, and demonstrated palladium-catalyzed asymmetric allylic alkylation of 1,3-diphenyl-2-propenyl acetate (**11**) with malonates using them with good enantiomeric excesses. Further studies on optimization of the ligand and application to other asymmetric reactions are underway.

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Supporting Information Available: Figures S1−S4 showing X-ray crystal structures of **8a**, **8c**, **4b**, and **10b**, full experimental procedures and characterization data, NMR spectra of new compounds, copies of HPLC charts of **8a**, **8c**, **4a**, **4b**, and **13a**−**d**, and X-ray crystallographic files (CIF) for **4b**, **8a**, **8c**, and **10b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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