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Rhodium-Catalyzed Ring-Opening Reactions of *N*-Boc-Azabenzonorbornadienes with Amine Nucleophiles

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Abstract: In the presence of a rhodium catalyst (5 mol %) generated in situ from $[Rh(cod)Cl]_2$ and (*S,S*′)−(*R,R*′)-C_2-ferriphos (**4a**), the asymmetric ring-opening reaction of azabenzonorbornadienes (**1a**−**m**) with various aliphatic and aromatic amines (**2a**−**l**) proceeded with high enantioselectivity (up to >99% ee) to give the corresponding 1,2-diamine derivatives **3** in high yields. In the specific case of pyrrolidine as nucleophile, Et_3NHCl was necessary as an additive for good reactivity and enantioselectivity. Additionally, a practical protocol was developed for the ring-opening of **1a** with volatile amines at elevated temperatures and standard pressure, using R_2NH_2I and *i*-Pr_2NEt. The experimental results showed that the nature of the chiral ligand has the significant impact on the reactivity of the catalyst and the use of excess amount (2.2 eq to Rh) of the chiral ligand plays an important role to improve the enantioselectivity in the present asymmetric reaction.

Introduction

Transition metal-catalyzed asymmetric reactions are powerful tools in modern organic synthesis.[1] In particular, catalytic asymmetric carbon−carbon bond and carbon-heteroatom bond forming reactions have attracted a great deal of attention. Although there are several other methods of providing optically active compounds, for example optical resolution, catalytic asymmetric synthesis is an ideal and practical method as far as high enantioselectivity is obtained, because a large amount of chiral product can be produced with a catalytic amount of chiral material.[2]

The transition metal-catalyzed allylic substitution[3] with various nucleophiles represents a fundamentally important reaction for the construction of useful chiral building blocks, and many methods have been developed which enable a wide range of allylic leaving groups to be used along with a variety of carbon- and heteroatom nucleophiles.[4] Ring-opening reactions of heterobicyclic alkenes formally represent a type of allylic substitution reaction. This class of reaction is particularly attractive because more than one stereocenter can be generated by the desymmetrization of a meso-bicyclic alkene in a single step.

We previously reported the rhodium-catalyzed asymmetric ring-opening of oxabenzonorbornadiene with alcohols and phenols, producing hydronaphthalenes in high yields and with excellent enantioselectivity.[5,6] Also, rhodium-catalyzed ring-opening of oxabicyclic alkenes with amines,[7] carboxylates,[8] 1,3-dicarbonyl nucleophiles[9] and sulfur nucleophiles[10] have extensively been studied.

We next focused our attention on expanding the scope of the asymmetric ring-opening of azabicyclic alkenes so as to have efficient access to the cyclohexyl-1,2-diamine moiety which has been found to be an important class of compounds, particularly for their utility as chiral ligands[11] and for their biological activity.[12] Recently, we reported the catalytic asymmetric ring-

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opening of azabenzonorbornadienes with aliphatic and cyclic amines in the presence of a rhodium catalyst coordinated with a chiral ferrocenyl phosphine ligand and the application of this methodology in the total synthesis of an analgesic compound.[13] In this type of reaction, the chiral 1,2-diamine is thought to be generated via the enantioselective cleavage of a bridgehead carbon−nitrogen bond in azanorbornadiene followed by S_N2' nucleophilic attack of amine.

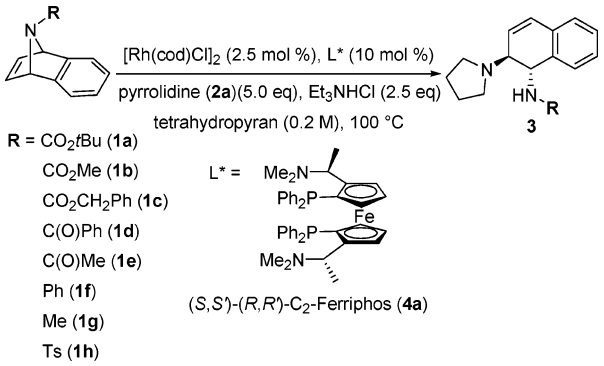
Here, we report a full description of the catalytic asymmetric ring-opening reaction of azabenzonorbornadienes with aliphatic and aromatic amines. The reaction proceeds under relatively mild conditions and generates a variety of 1,2-diamino compounds in high yield with excellent enantioselectivity.

Results and Discussion

The first example of the transition metal-catalyzed ring-opening reaction of azabicyclic alkenes is the palladium-catalyzed alkylative ring-opening of *N*-substituted azabenzonorbornadienes.[14] Palladium-catalyzed ring-opening addition of arylboronic acids to azabicyclic substrates has also been reported.[15] From our previous studies, azabicyclic alkenes, including azabenzonorbornadienes, were found to be less reactive than the corresponding oxabicyclic alkenes. For example, the catalytic ring-opening of oxabenzonorbornadiene with arylboronic acid proceeds at room temperature in the presence of Pd(dppf)Cl_2 whereas the reaction of *N*-Boc-azabenzonorbornadiene requires heating (60 °C) to ensure complete conversion under the same conditions.[5,15] As expected, the activating group on nitrogen has a strong effect on the reactivity of the substrate.

The results summarized in Table 1 show that the nature of the activating group strongly influences both the reaction yield and the enantioselectivity of the product. High enantioselectivity was observed in the reaction of *N*-Boc-**1a** (entry 1). In the presence of 2.5 mol % of $[Rh(cod)Cl]_2$[16] and 10 mol % of (*S*,*S*′)−(*R*,*R*′)-C_2-ferriphos (**4a**), **1a** with 2.5 equiv. of triethylamine hydrochloride and 5.0 equiv. of pyrrolidine in tetrahydropyran at 100 °C for 24 h gave the corresponding product **3aa** in 77% yield with 86% ee. While other carbamates such as methyl (**1b**) and benzyl (**1c**) showed good reactivity, the product was obtained in lower enantioselectivity (entries 2 and 3). The reactions using *N*-benzamide (**1d**) and *N*-acetamide (**1e**) also showed good reactivity (entries 4 and 5) and **1e** was found to be most enantioselective (99% ee). *N*-Phenyl (**1f**), the efficient substrate for the palladium-catalyzed ring-opening with dimethylzinc,[14] showed poor reactivity and enantioselectivity (entry 6) and the reaction using *N*-methyl (**1g**) did not give any ring-opening product (entry 7). The sulfonyl activating group showed the best reactivity but produced very poor enantioselectivity (entry 8), suggesting that electronic effects play a significant role in the reaction outcome. Since it is postulated that the rhodium-catalyzed ring-opening of strained allylic alkenes proceeds by an oxidative insertion pathway, use of a more electron-withdrawing tosyl group would be expected to facilitate this pathway. Although *N*-acetamide (**1e**) was found to be the most enantioselective substrate in the present reaction, **1a** was the more versatile substrate to find efficient conditions for ring-opening with amine nucleophiles since deprotection of the Boc group[17] is easy, high-yielding, and more amendable to scale-up with regards to starting material synthesis.

Table 1. Activating Group Effect on Enantioselectivity in Ring-Opening[a]



entry	azabicycle	time (h)	product	yield[b] (%)	% ee[c]
1	**1a**	24	**3aa**	77	86
2	**1b**	24	**3ba**	65	63
3	**1c**	24	**3ca**	73	68
4	**1d**	24	**3da**	71	96
5	**1e**	24	**3ea**	90	99
6	**1f**	24	**3fa**	40	25
7	**1g**	24		n. r.	
8	**1h**	8	**3ha**	96	10

[a] The reaction was carried out with azabicycle **1** (0.33 mmol) and 5.0 equiv. of pyrrolidine (**2a**) (1.64 mmol) in tetrahydropyran (1.6 mL) in the presence of $[Rh(cod)Cl]_2$ (2.5 mol %), **4a** (10 mol %), and Et_3NHCl (0.82 mmol). [b] Yield after silica gel chromatography. [c] Determined by HPLC analysis of the corresponding ring-opening product **3** with chiral stationary column (Chiralcel OD or Chiralcel OD-H).

We then examined the asymmetric ring-opening of *N*-Boc protected **1a** with pyrrolidine. It was found that (*S*,*S*′)−(*R*,*R*′)-C_2-ferriphos (**4a**)[18] gave the best enantioselectivity. We examined several chiral ligands such as BINAP, BPPFA,[19] DIPOF,[20] and PPF−P(*t*-Bu)$_2$,[21] all used successfully for other asymmetric ring-opening reactions of bicyclic alkenes, but these failed to give satisfactory results.[6b,9] For example, under the optimized conditions for the reaction of oxabenzonorbornadiene using (*S*,*R*)-PPF−P(*t*-Bu)$_2$ with NH_4I, the reaction of **1a** with pyrrolidine gave **3aa** in 65% yield and only 25% ee.

According to our preliminary study on the catalytic ring-opening reaction of oxabenzonorbornadiene with pyrrolidine, various additives, containing a proton and a halide, were tested to promote the reaction (Table 2).

The best overall results were obtained with Et_3NHCl.[7] Although the reaction of **1a** with pyrrolidine in THP at 100 °C gave the corresponding product **3aa** in 50% yield and 59% ee in the absence of an additive (entry 1), the use of Et_3NHCl gave 75% yield and 78% ee (entry 6). Slightly higher levels of

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(16) The use of 2.5 mol % of $[Rh(cod)Cl]_2$ is required to ensure high reaction yield and enantioselectivity. Lower catalyst loading (1∼2 mol %) brought lower enantioselectivity and slower reaction.
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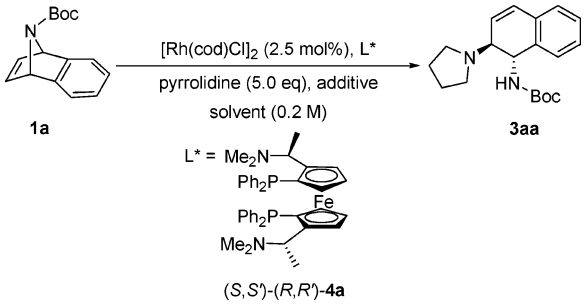
Table 2. Catalytic Asymmetric Ring-Opening of *N*-Boc-Azabenzonorbornadiene (**1A**) with Pyrrolidine (**2A**)[a]



entry	additive (equiv.)	ligand (equiv. to Rh)	solvent	*T* (°C)	time (h)	yield[b] (%)	% ee[c]
1		1.0	THP	100	24	50	59
2	NH_4Cl (2.5)	1.0	THP	100	24	31	80
3	NH_4Br (2.5)	1.0	THP	100	24	55	72
4	NH_4I (2.5)	1.0	THP	100	24	94	44
5	nBu$_4$NCl (2.5)	1.0	THP	100	24	16	57
6	Et_3NHCl (2.5)	1.0	THP	100	24	75	78
7	Et_3NHCl (2.5)	2.0	THP	100	24	77	86
8	Et_3NHCl (2.5)	2.0	DMF	100	24	75	80
9	Et_3NHCl (2.5)	2.0	CH_3CN	100	24	34	59
10	Et_3NHCl (2.5)	2.0	toluene	100	24	90	79
11	Et_3NHCl (2.5)	2.2	THP	100	24	80	90
12	Et_3NHCl (5.0)	2.2	THP	80	72	52	97
13	Et_3NHCl (2.5)	2.2	THP	80	72	65	98
14	Et_3NHCl (1.0)	2.2	THP	80	72	78	>99

[a] The reaction was carried out with **1a** (0.33 mmol) and 5.0 equiv. of pyrrolidine (**2a**) (1.64 mmol) in solvent (1.6 mL) in the presence of $[Rh(cod)Cl]_2$ (2.5 mol %), **4a**, and additive. [b] Yield after silica gel chromatography. [c] Determined by HPLC analysis of **3aa** with Chiralcel OD-H.

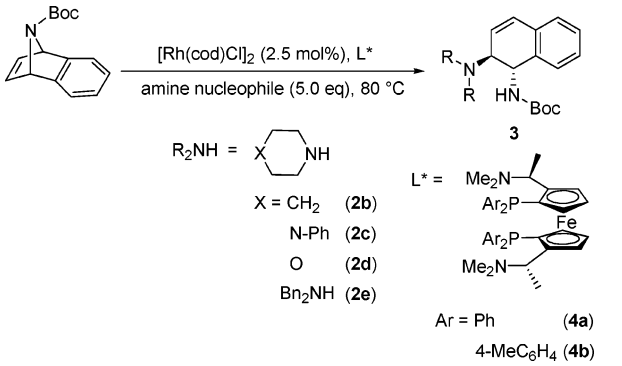
enantioselectivity (80% ee) were observed with NH_4Cl, but the reaction was sluggish and gave a low yield (entry 2). With a series of ammonium halides, an interesting trend was observed. The reaction yields increased in order Cl < Br < I, but enantioselectivities decreased (entries 2−4). This inverse relationship between reactivity and % ee is in contrast with the reaction of oxabicyclic alkenes using a rhodium catalyst prepared from $[Rh(cod)Cl]_2$ and (*S*,*R*)-PPF-P(*t*-Bu)$_2$, wherein the iodide additive gave enhanced reactivity and enantioselectivity.[9] Tetrabutylammonium chloride was also tested and showed low reactivity and enantioselectivity (entry 5). These results indicated that both a proton and chloride of the additive were required together to promote a faster reaction.[22]

The enantioselectivity of **3aa** was influenced by the amount of the chiral ligand. The reaction using 2.0 equiv. of (*S*,*S*′)−(*R*,*R*′)-C_2-ferriphos (**4a**) gave 77% yield of **3aa** with 86% ee (entry 7) whereas the use of 1.0 equiv. of chiral ligand gave the product in 78% ee (entry 6). Higher enantioselectivity was observed in the reaction using 2.2 equiv. of (*S*,*S*′)−(*R*,*R*′)-C_2-ferriphos which gave 80% yield of **3aa** in 90% ee (entry 11).

Among the solvents examined for the asymmetric ring-opening of azabenzonorbornadienes **1**, tetrahydropyran (THP) was found to be optimal to deliver the ring-opened product with high enantioselectivity. DMF and CH_3CN were tested and gave 80% ee and 59% ee, respectively (entries 8 and 9). The reaction

(22) In the presence of HCl, the regeneration of an active catalyst from the poisoned rhodium complex by tight binding with amine to the metal center was proposed. See: Vallarino, L. M.; Sheargold, S. W. *Inorg. Chim. Acta* **1979**, *36*, 243.

Table 3. Asymmetric Ring-Opening of **1A** with Various Aliphatic Amines (**2A-e**)[a]



entry	R_2NH	ligand (equiv. to Rh)	time (h)	product	yield[b] (%)	% ee[c]
1	**2b**	**4a** (2.2)	60	**3ab**	83	97
2	**2c**	**4a** (2.2)	24	**3ac**	92	93
3	**2d**	**4a** (2.2)	48	**3ad**	85	97
4	**2e**	**4b** (2.2)	48	**3ae**	98	97

[a] The reaction was carried out with **1a** (0.33 mmol) and 5.0 equiv. of amine **2** (1.64 mmol) in the presence of $[Rh(cod)Cl]_2$ (2.5 mol %) and chiral ligand (11.0 mol %). [b] Yield after silica gel chromatography. [c] Determined by HPLC analysis of the product **3** with chiral stationary column: (Chiralcel OD-H for **3aa** and **3ab**, Chiralcel AD for **3ac** and **3ad**, Chiralcel OD for **3ae**).

using toluene gave higher yield (90%) but lower ee (79%) (entry 10) than with THP (77%, 86% ee) (entry 7). The best results were obtained by decreasing the reaction temperature. In the presence of 2.5 mol % of $[Rh(cod)Cl]_2$ and 11 mol % of **4a**, the reaction of **1a** with 1.0 equiv. of Et_3NHCl and 5.0 equiv. of pyrrolidine in THP at 80 °C for 72 h gave 78% yield of pyrrolidine ring-opening product **3aa** in >99% ee (entry 14). The use of 1.0 equiv. of the additive was found to be most effective (entries 12, 13, and 14). We found that the ring-opening reaction works better with basic amines which have six-membered ring structures such as piperidine, morpholine, and piperazine, in the absence of additives and solvents. The use of additives was not beneficial in these cases and a significant reduction of reactivity was observed when Et_3NHCl was used.

As shown in Table 3, in the presence of 2.5 mol % of $[Rh(cod)Cl]_2$ and 11 mol % of **4a**, the asymmetric ring-opening of **1a** with piperidine (**2b**) proceeded at 80 °C for 60 h without additives and solvents to give 83% yield of the corresponding product **3ab** in 97% ee (entry 1). The reaction using morpholine (**2d**) also gave excellent yield and enantioselectivity (entry 3). Slightly lower enantioselectivity (93% ee) was observed in the reaction using 1-phenylpiperazine (**2c**) (entry 2). In the case of dibenzylamine (**2e**), the use of (*S*,*S*′)−(*R*,*R*′)-**4b**, which has *p*-tolyl groups on the phosphorus atom of the ligand instead of phenyl groups, was found to be more efficient than **4a**. The chiral ligand **4b** was prepared from (*S*,*S*)-1,1′-bis(α-*N*,*N*-dimethylaminoethyl)ferrocene[18] and di(4-methylphenyl)chlorophosphine. The reaction of **1a** with **2e** using a rhodium catalyst generated from $[Rh(cod)Cl]_2$ and (*S*,*S*′)−(*R*,*R*′)-**4b** gave 98% yield of **3ae** in 97% ee (entry 4).

The absolute configuration of the ring-opening product **3ac** was determined to be (*1S*, *2S*) by X-ray crystallography of a derivative, **6**. Crystals suitable for X-ray analysis were obtained by deprotection of the Boc group of **3ac** with TFA, followed

Scheme 1

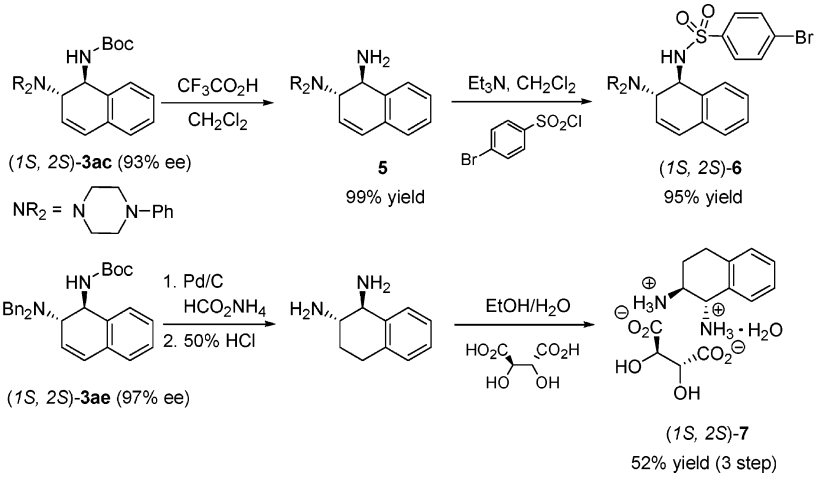
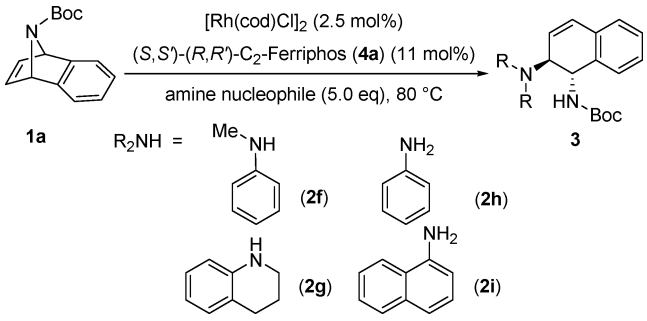


Table 4. Asymmetric Ring-Opening of **1A** with Various Aromatic Amines (**2f-i**)[a]



entry	R_2NH	time (h)	product	yield[b] (%)	% ee[c]
1	**2f**	48	**3af**	78	97
2	**2g**	48	**3ag**	92	97
3	**2h**	30	**3ah**	96	96
4	**2i**	30	**3ai**	88	97

[a] The reaction was carried out with azabicycle **1a** (0.33 mmol) and 5.0 equiv. of amine **2** (1.64 mmol) in the presence of $[Rh(cod)Cl]_2$ (2.5 mol %) and **4a** (11 mol %). [b] Yield after silica gel chromatography. [c] Determined by HPLC analysis of the product **3** with chiral stationary column: (Chiralcel AD for **3af** and **3ag**, Chiralcel OD for **3ah** and **3ai**).

by protection of **5** with 4-bromobenzenesulfonyl chloride (Scheme 1). Additionally, **3ae** was determined to be (*1S, 2S*) by correlation with **7** whose absolute configuration was confirmed by X-ray analysis. Tartrate salt **7** was prepared from **3ae** by removal of the dibenzyl groups via catalytic hydrogenation[23] and deprotection of the *N*-Boc group, followed by treatment of the free 1,2-diamine with L-tartaric acid.

Aromatic amines also showed high reactivity and excellent enantioselectivity in the asymmetric ring-opening under the new conditions (Table 4). The reactions of **1a** with *N*-methylaniline (**2f**) or tetrahydroquinoline (**2g**) proceeded to give high enantioselectivity of the corresponding products **3af** (97% ee) and **3ag** (97% ee), respectively (entries 1 and 2). Interestingly, the reactions using primary aromatic amines such as aniline (**2h**) (entry 3) and 1-aminonaphthalene (**2i**) (entry 4) proceeded at 80 °C in good yield and high enantioselectivity whereas the reaction with the primary aliphatic amines such as benzylamine did not produce the desired product.

Indole (**2j**) was also found to be a good nucleophile and to react exclusively at the C-3 position of the indole ring (Scheme 2), rather than through N-1. The structure of the indole ring-opening product **3aj** was assigned by ^1H-^{13}C coupled NMR experiments and identification of the *N*-H indole peak at 7.8 ppm. A similar pattern was also observed in the asymmetric ring-opening reaction of oxabenzonorbornadiene with indole.[7,9]

Scheme 2

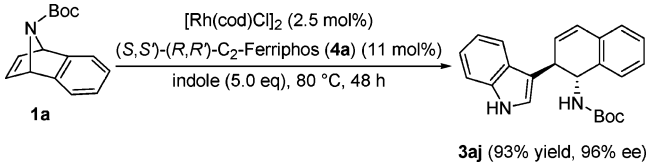
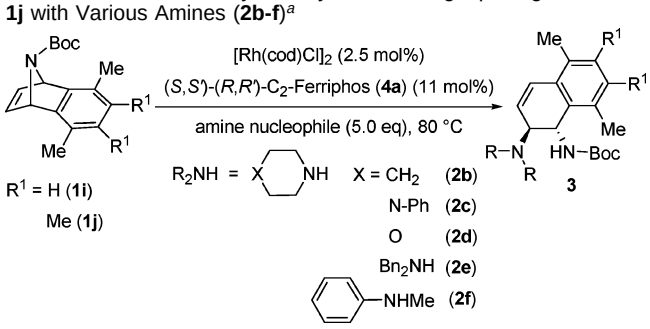


Table 5. Rhodium-Catalyzed Asymmetric Ring-Opening of **1i** and **1j** with Various Amines (**2b-f**)[a]



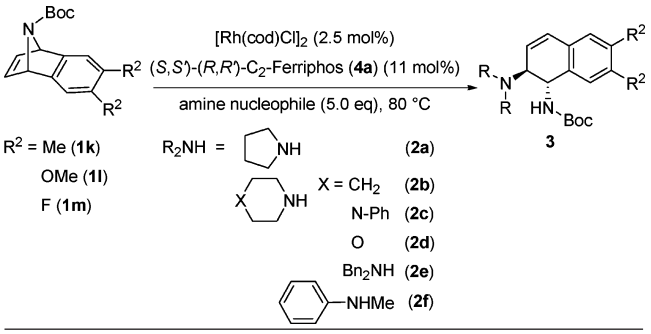
entry	R_2NH	R^1 (azabicycle)	time (h)	product	yield[b] (%)	% ee[c]
1	**2b**	H (**1i**)	120	**3ib**	84	94
2	**2c**	H (**1i**)	96	**3ic**	80	94
3	**2d**	H (**1i**)	96	**3id**	62	>99
4[d]	**2e**	H (**1i**)	96	**3ie**	91	99
5	**2f**	H (**1i**)	96	**3if**	76	96
6	**2c**	Me (**1j**)	96	**3jc**	57	89
7	**2d**	Me (**1j**)	96	**3jd**	50	94
8[d]	**2e**	Me (**1j**)	144	**3je**	70	99

[a] The reaction was carried out with **1** (0.33 mmol) and 5.0 equiv. of amine **2** (1.64 mmol) in the presence of $[Rh(cod)Cl]_2$ (2.5 mol %) and **4a** (11 mol %). [b] Yield after silica gel chromatography. [c] Determined by HPLC analysis of the product **3** with chiral stationary column: (Chiralcel OD-H for **3ib** and **3if**, Chiralcel AD for **3ic**, **3ie**, **3jc**, and **3je**, Chiralpak AS for **3jd**, Chiralcel OD for **3id**). [d] The reaction was performed with C_2-ferriphos-tolyl (**4b**) (11 mol %).

The asymmetric ring-opening of 5,8-dimethyl-*N*-Boc-azabenzonorbornadiene (**1i**) and 5,6,7,8-tetramethyl-*N*-Boc-**1j** with amine nucleophiles was investigated. The results are summarized in Table 5 and show that the introduction of methyl groups on the aromatic ring of azabenzonorbornadiene brought a decrease in the reactivity probably due to steric effects. Although a longer

(23) Lautens, M.; Schmid, G. A.; Chau, A. *J. Org. Chem.* **2002**, *67*, 8043.

Table 6. Asymmetric Ring-Opening of 6,7-Disubstituted-Azabicycles (**1k-m**) with Various Amines (**2b-f**)[a]



entry	R_2NH	R^2 (azabicycle)	time (h)	product	yield[b] (%)	% ee[c]
1	**2c**	Me (**1k**)	48	**3kc**	97	94
2	**2d**	Me (**1k**)	48	**3kd**	98	>99
3[d]	**2e**	Me (**1k**)	48	**3ke**	95	97
4[e]	**2a**	OMe (**1l**)	72	**3la**	80	>99
5	**2d**	OMe (**1l**)	48	**3ld**	86	94
6	**2f**	OMe (**1l**)	48	**3lf**	91	99
7[e]	**2a**	F (**1m**)	72	**3ma**	70	>99
8	**2b**	F (**1m**)	72	**3mb**	67	97
9	**2f**	F (**1m**)	60	**3mf**	95	98

[a] The reaction was carried out with **1** (0.33 mmol) and 5.0 equiv. of amine **2** (1.64 mmol) in the presence of $[Rh(cod)Cl]_2$ (2.5 mol %) and **4a** (11 mol %) at 80 °C (neat condition). [b] Yield after silica gel chromatography. [c] Determined by HPLC analysis of the product **3** with chiral stationary column: (Chiralcel AD for **3kc**, **3ld**, **3lf**, and **3mf**, Chiralcel OD for **3ke** and **3la**, Chiralcel OD-H for **3ma** and **3mb**, Chiralpak AS for **3kd**,). [d] The reaction was performed with C_2-ferriphos-tolyl (**4b**) (11 mol %). [e] The reaction was carried out with **1** (0.33 mmol) and **2a** (1.64 mmol) in THP (1.6 mL) in the presence of $[Rh(cod)Cl]_2$ (2.5 mol %), **4a** (11 mol %), and Et_3NHCl (0.33 mmol).

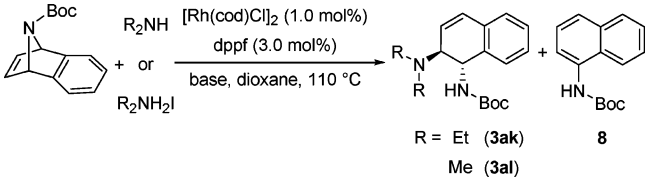
reaction time (over 96 h) was required, generally all substrates reacted in reasonable yields and high enantioselectivity. The bulkier substrate **1j** was found to be even less reactive than **1i**. The reactions of **1j** with 1-phenylpiperazine (**2c**) and morpholine (**2d**) at 80 °C for 96 h gave only 57% yield of **3jc** and 50% yield of **3jd**, respectively (entries 6 and 7). No obvious trend was observed in the relationship between substrate sterics and the enantioselectivity of products. Some substrates showed slight increases in enantioselectivity compared to **1a** (entries 2, 3, 4, and 8) but slight decreases were observed in other cases (entries 1, 5, 6, and 7).

The ring-opening of 6,7-disubstituted-*N*-Boc-azabenzonorbornadienes **1k**−**m** were also examined (Table 6).

Except for the reaction of **1l** with morpholine (**2d**) which showed slightly decreased enantioselectivity (entry 5), all nucleophiles gave the corresponding products in equal or better enantioselectivity compared to **1a**. A difference in reactivity between **1k** and the more electron-rich **1l** was not observed. However, 6,7-difluoro-*N*-Boc-**1m** was found to be a less reactive than **1k** and **1l** in this reaction. The reactions of **1f** with pyrrolidine (**2a**) and piperidine (**2b**) gave lower yields (entries 7 and 8), except for the reaction using *N*-methylaniline (**2f**) (entry 9).

We wanted to expand the scope of the reaction to include sterically small amines because the resulting compounds were highly desirable for ongoing medicinal chemistry studies. However, the rhodium-catalyzed ring-opening of azabicyclic alkenes with volatile amines such as diethylamine (bp 55 °C) and dimethylamine (bp 7 °C) was a significant challenge because of their poor reactivity. For example, in the presence of 1.0 mol % of $[Rh(cod)Cl]_2$ and 3.0 mol % of dppf, the reaction of

Table 7. Rhodium-Catalyzed Ring-Opening of **1A** with Volatile Amines (**2j-k**)[a]



entry	amine (equiv.)	base (eq)	T (°C)	time (h)	yield of **3** (%)[b]	yield of **8** (%)[b]
1[c]	Et_2NH (3.0)		65	26	4[d]	trace
2	Et_2NH_2I (5.0)[e]		110	6	n. r.	
3	Et_2NH_2I (5.0)	0.3	110	6	38	55
4	Et_2NH_2I (3.0)	0.3	110	6	59	30
5	Et_2NH_2I (2.0)	3.0	110	6	76	10
6	Et_2NH_2I (2.0)	3.0	110	14	90	<5
7	Me_2NH_2I (2.0)[e]	3.0	110	14	89	<5

[a] The reaction was carried out with **1a** (1.00 mmol), amine, *i*-Pr_2NEt, $[Rh(cod)Cl]_2$ (1.0 mol %), and dppf (3 mol %) in 1,4-dioxane (5.0 mL). [b] Yield after silica gel chromatography. [c] The reactions was carried out with 1.5 equiv. of NH_4I in THF instead of 1,4-dioxane. [d] 89% of **1a** was recovered. [e] Dialkylammonium iodide was prepared by the halide exchange of the commercial available corresponding ammonium chloride with NaI in ethanol.

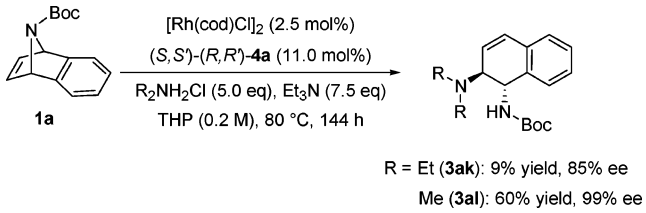
1a with diethylamine (**2k**) and 1.5 equiv. of NH_4I in THF at 65 °C for 24 h gave only 4% yield of the desired product **3ak** and 89% of starting material **1a** (Table 7, entry 1). It was previously reported that the catalytic ring-opening of azabenzonorbornadiene, which has a *p*-nitrobenzenesulfonyl group as the activating group instead of *N*-Boc group, proceeded with 10 equiv. of diethylamine and NH_4I as the additive in THP at 65 °C for 24 h to give the corresponding product in 91% yield.[13] Since the deprotection of the Boc group is easier and higher-yielding, **1a** was selected as the best substrate to find efficient conditions for ring-opening with volatile amines.

Fortunately, it was found that the use of dialkylammonium iodide dramatically increased the reactivity (Table 7). In the presence of 1.0 mol % of $[Rh(cod)Cl]_2$ and 3.0 mol % of dppf, reaction of **1a** with 2.0 equiv. of diethylammonium iodide and 3.0 equiv. of *N*,*N*-diisopropylethylamine (*i*-Pr_2NEt) in 1,4-dioxane at 110 °C for 14 h gave the corresponding product **3ak** in 90% yield (entry 6). The reaction using dimethylammonium iodide gave **3al** in 89% yield under the same conditions (entry 7). Addition of iodide led to an increase in the reactivity by halide exchange between $[Rh(cod)Cl]_2$ and iodide which generated the more reactive rhodium iodide species.[9] The use of *i*-Pr_2-NEt is required to ensure the high yield. Without base, the ring-opening reaction did not proceed using Et_2NH_2I (entry 2). The use of 0.3 equiv. of base gave 38% yield of **3ak** and a considerable amount (55% yield) of the side product **8** (entry 3). Increasing the amount of *i*-Pr_2NEt from 0.3 equiv. to 3.0 equiv. minimized the amount of **8** (entries 4 and 5). Dialkylammonium iodide was prepared from the commercially available dialkylammonium chloride by exchange of the halide with NaI at room temperature.[24]

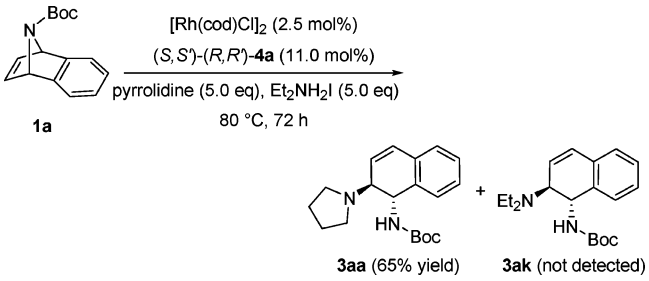
The asymmetric ring-opening reactions of **1a** with dialkylammonium iodides were also examined. Surprisingly, the reaction of **1a** with Et_2NH_2I using a rhodium catalyst generated from $[Rh(cod)Cl]_2$ and (*S*,*S*′)−(*R*,*R*′)-C_2-ferriphos (**4a**) instead of dppf did not give any desired product under the optimized conditions. We also tested the use of Et_2NH_2Cl instead of Et_2-

(24) See the Supporting Information.

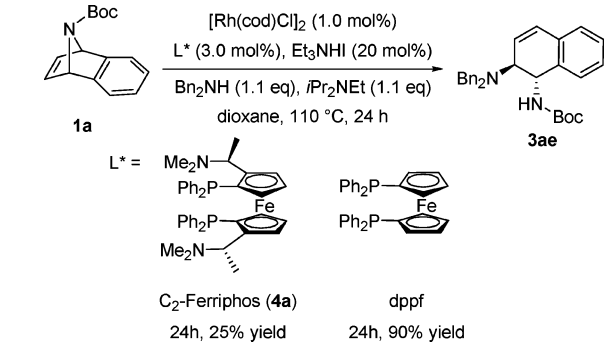
Scheme 3



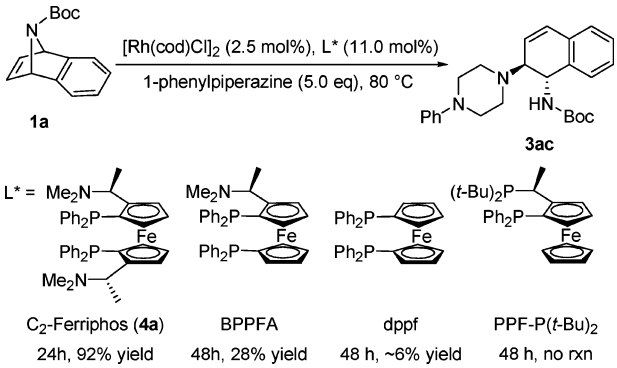
Scheme 4



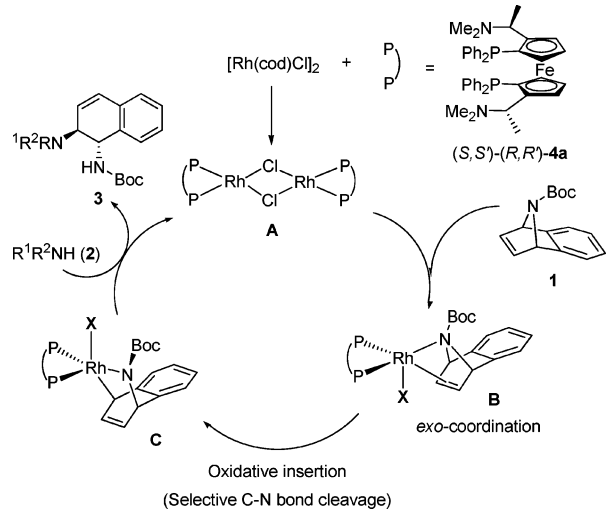
Scheme 5



Scheme 6



Scheme 7



NH_2I according to previous studies on halide effects in the asymmetric reaction of **1a** with other amines (see Table 2). In the presence of 2.5 mol % of $[Rh(cod)Cl]_2$ and 11.0 mol % of **4a**, the reaction of **1a** with 5.0 equiv. of Et_2NH_2Cl and 7.5 equiv. of Et_3N in THP proceeded at 80 °C for 144 h to give **3ak** with 85% ee but only in 9% yield (Scheme 3). Under the same conditions, the reaction of **1a** with Me_2NH_2Cl showed very slow reaction but gave excellent enantioselectivity. The ring-opened product **3al** was isolated in 60% yield with 99% ee.

A competition experiment revealed that the poor nucleophilicity of diethylamine was not due to poisoning of the rhodium catalyst (Scheme 4). For instance, pyrrolidine was added to the reaction mixture containing Et_2NH_2I, yet the reaction proceeded at 80 °C to give a 65% yield of the pyrrolidine ring-opening product **3aa**. The formation of **3al** was not observed.

The nature of the chiral phosphine ligand strongly influenced the reaction yield in the present reaction. As described above, in the reaction of **1a** with Et_2NH_2I and *i*-Pr_2NEt, the use of dppf gave 90% yield of the product while the reaction using **4a** did not proceed. Similar results were observed in the reaction of **1a** with Bn_2NH (**2e**) and Et_3NHI as the additive (Scheme 5). In the presence of 1.0 mol % of $[Rh(cod)Cl]_2$ and 3.0 mol % of dppf, the reaction of **1a** with 1.1 equiv. of Bn_2NH and 1.1 equiv. of *i*Pr_2NEt in 1,4-dioxane at 110 °C for 24 h gave the corresponding product **3ae** in 90% yield. However, the reaction using **4a** gave only 25% yield of **3ae** under the same condition.

The reactivity trends between dppf and **4a** were commonly observed in the ring-opening reaction of azabenzonorbornadiene with other amine nucleophiles. For example, the reaction of **1a** with 1-phenylpiperazine using a rhodium catalyst generated in situ from 2.5 mol % of $[Rh(cod)Cl]_2$ and 11.0 mol % of **4a**, which contains two dimethylamino groups in its structure, proceeded at 80 °C for 24 h to give 92% yield of **3ac** whereas the reaction using dppf gave only 6% yield after 48 h under the same conditions (Scheme 6).

The reaction using PPF-P(*t*-Bu)$_2$ did not produce the desired product, and BPPFA, which has a dimethylamino group in its structure provided a 28% yield of the product. Although a more detailed explanation of the relationship between the reactivity of the catalyst and the functionality present on the chiral ligand is not possible at this point, experimental evidence has shown that the two dimethylamino groups of **4a** somehow participate in the catalytic cycle and play an important role to promote the ring-opening reaction.

The proposed catalytic pathway for the rhodium-catalyzed ring-opening of azanorbornadienes follows closely that put forward regarding oxabicyclic alkenes[25] (Scheme 7). Beginning with the chiral rhodium complex **A**, *exo*-binding can occur to the nitrogen and the olefin on the substrate **1** to give the intermediate **B**, as proposed for the oxabenzonorbornadienes. Oxidative insertion of rhodium catalyst to C−N bond of **1** forms **C** and an S_N2' displacement of the rhodium catalyst by the nucleophile **2** gives product **3** and regenerates the catalyst.

(25) (a) Fagnou, K. In *Modern Rhodium-Catalyzed Organic Reactions*; Evans, P. A., Ed.; Wiley-VCH: Weinheim, 2005; Chapter 9, pp 173−190. (b) Lautens, M.; Fagnou, K. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5455.

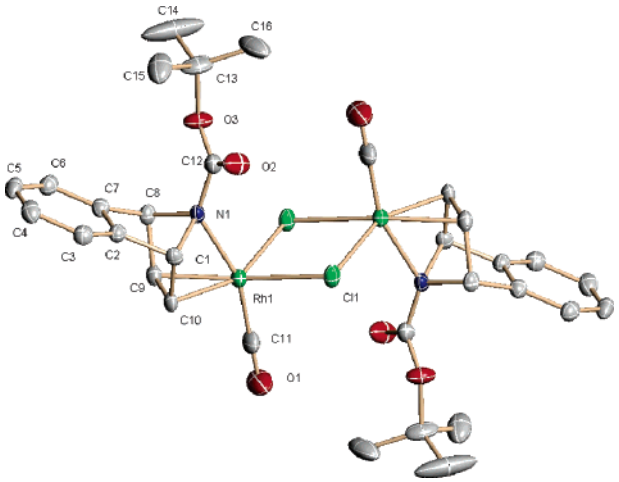
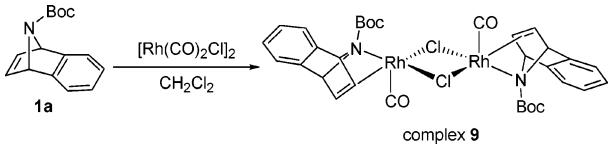


Figure 1. ORTEP drawing for **9**.

Scheme 8



Nucleophilic attack with inversion from the *endo*-direction provides the 1,2-*trans*-diamino product,[26] in an S_N2' fashion relative to the rhodium metal.

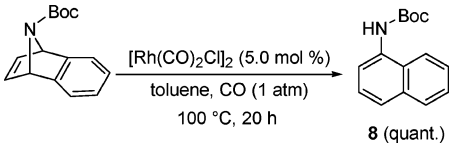
On the basis of steric arguments, the coordination of the rhodium catalyst to the azabenzonorbornadienes should be favored at the more accessible *exo* face.[27] The *exo*-coordination of the aryl rhodium (I) complex to the olefin can be explained by the stereochemical outcome in the ring-opening of oxabicyclic alkenes with arylboronic acid.[28] We were fortunate to obtain evidence that *exo*-coordination of the rhodium catalyst with azabenzonorbornadiene is a possible binding mode (Scheme 8) though we cannot say if this is an intermediate on the reaction pathway.

Treatment of *N*-Boc-azabenzonorbornadiene (**1a**) with $[Rh(CO)_2Cl]_2$ in CH_2Cl_2 at room temperature for 12 h produced the complex **9** whose structure was characterized by X-ray analysis[29] (Figure 1).

Interestingly, extrusion of one CO ligand is observed and the rhodium complex is isolated in its dimeric form. The lone pair on nitrogen of **1** facilitates this bidentate binding of the metal on the *exo* face of the substrate.

The oxidative insertion of the rhodium catalyst into the strained carbon−nitrogen bond has been studied in the rhodium-catalyzed carbonyl insertion of styrenyl aziridines and α-lactams.[30] Recently, Tam reported the ruthenium-catalyzed isomerization of 7-oxa/azabenzonorbornadienes to the corresponding vinyl epoxides and aziridines and a reaction pathway involving oxidative insertion of the ruthenium catalyst into the strained carbon−oxygen bond and carbon−nitrogen bond has also been proposed.[31] We attempted to insert carbon monoxide into the carbon−nitrogen bond of **1a** in order to support that an oxidative pathway to give **C** in the catalytic cycle (Scheme 9).

Scheme 9

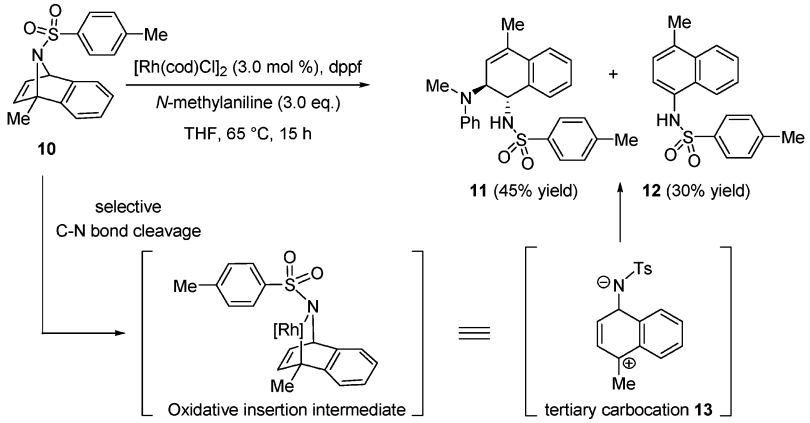


In the presence of 5.0 mol % of $[Rh(CO)_2Cl]_2$, the CO insertion into **1a** was examined in toluene at 100 °C for 20 h under a CO atmosphere (1 atm). The isolation of 1-aminonaphthalene (**8**) in quantitative yield suggests that insertion of rhodium occurs but β-elimination is much faster than CO insertion into the carbon−nitrogen bond.

The regioselective ring-opening of the unsymmetrical azabenzonorbornadiene (**10**) with *N*-methylaniline (**2f**) was also examined (Scheme 10). In the presence of 3.0 mol % $[Rh(cod)Cl]_2$ and 9.0 mol % of dppf, the reaction of **10** with 3.0 equiv. of **2f** proceeded in THF at 65 °C for 15 h to give the corresponding product **11** in 45% yield and aminonaphthalene **12** in 30% yield, respectively. In this reaction, the regioisomer **11** was the sole product arising for selective carbon−nitrogen bond cleavage at the more highly substituted position of **10**. The regioselective ring-opening of **10** suggests that ionization of the carbon−nitrogen bond is a key step in the catalytic cycle. If oxidative insertion were occurring, then ionization of the tertiary carbon−nitrogen bond should be preferred from an electronic point of view since the tertiary carbocation **13** will be more stabilized.

The oxidative insertion of the catalyst into a bridgehead carbon−nitrogen bond is considered as the enantiodiscriminating step in the catalytic cycle. As shown in the regioselective ring-opening of **10** (Scheme 10), the formation of **12** supports oxidative insertion occurs prior to nucleophilic attack.

Scheme 10



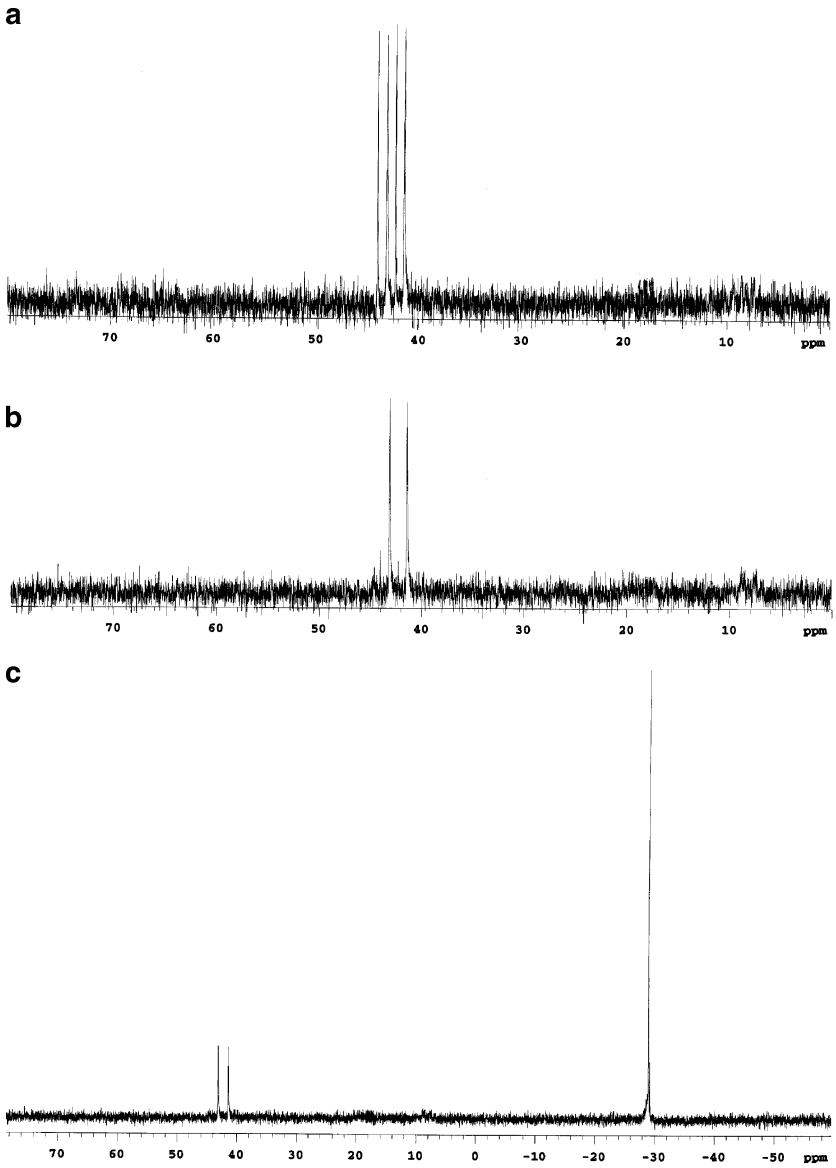
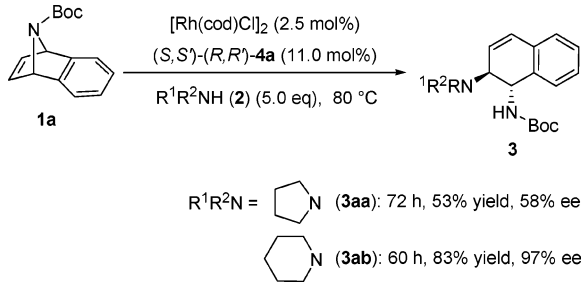


Figure 2. ^{31}P spectra (at 12×e2P MHz in toluene at 25 °C) of rhodium-phosphine complexes. (a) $[Rh(cod)Cl]_2$ and **4a** (1:2) in toluene at 80 °C for 1.5 h. Complexes **14** and **15** were observed. (b) $[Rh(cod)Cl]_2$ and **4a** (1:2) in toluene at 80 °C for 10 h. Complex **14** was observed. (c) $[Rh(cod)Cl]_2$ and **4a** (1:4) in toluene at 80 °C for 12 h. Complex **14** and free **4a** were observed.

If the ring-opening step was coincident with nucleophilic attack, then the side product **12** should have not been obtained. Thus, the nature of nucleophile should not influence the stereochemical outcome of the reaction. However, the stereoselectivity is influenced by the amine nucleophile in some cases. For example, of 2.5 mol % of $[Rh(cod)Cl]_2$ and 11.0 mol % of **4a**, the reaction of **1a** with piperidine (**2b**) proceeded at 80 °C for 60 h to give 83% yield of **3ab** in 97% ee while the reaction using pyrrolidine (**2a**) gave 53% yield of **3aa** in 58% ee under the same conditions (Scheme 11).

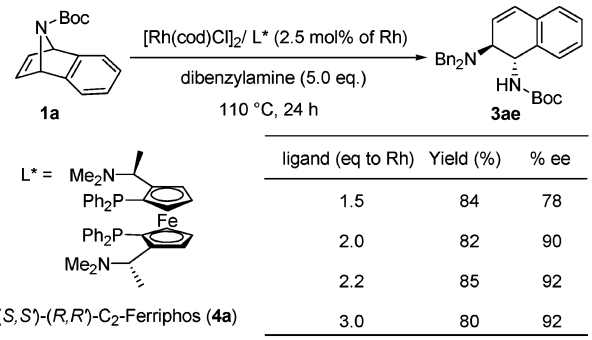
Scheme 11



The nucleophile obviously interacts[9] with the catalyst in a manner which affects the stereoselectivity of the reaction. The specifics of this interaction are unknown at this point. It is well-known that amines bind to the metal center of the catalyst and cause deactivation or poisoning.[32] However, pyrrolidine did not cause catalytic poisoning but rather influenced the catalytic efficiency resulting in low reactivity and enantioselectivity. As

(26) The *trans*-stereochemistry was also observed in the catalytic ring-opening reactions of oxabicyclic alkenes. See: refs 5 and 7.
(27) (a) Sun, C. H.; Chow, T. J. *J. Chem. Soc., Chem. Commun.* **1988**, 535. (b) Sun, C. H.; Chow, T. J.; Liu, L. K. *Organometallics* **1990**, *9*, 560. (c) Liu, L. K.; Sun, C. H.; Yang, C. Z.; Shih, S. Y.; Lin, K. S.; Wen, Y. S.; Wu, C. F. *Organometallics* **1992**, *11*, 972. (d) Chow, T.; Hwang, J. J.; Sun, C. H.; Ding, M. H. *Organometallics* **1993**, *12*, 3762.
(28) (a) Lautens, M.; Dockendorff, C.; Fagnou, K.; Malicki, A. *Org. Lett.* **2002**, *4*, 1311. (b) Fagnou, K.; Lautens, M. *Chem. Rev.* **2003**, *103*, 169.
(29) The crystals suitable for X-ray were obtained by the addition of hexanes to a solution of **9** in CH_2Cl_2 until the solution changed slightly cloudy, followed by slow evaporation of the solvent mixture.

Scheme 12



ligand (eq to Rh)	Yield (%)	% ee
1.5	84	78
2.0	82	90
2.2	85	92
3.0	80	92

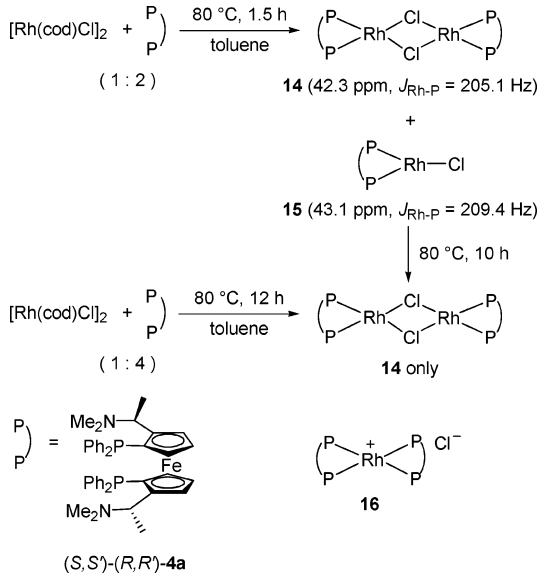
shown in Table 2, the use of Et_3NHCl prevents deactivation of the catalyst and leads to high yield and excellent enantioselectivity (see Table 2, entry 14). From the experimental evidence shown in Tables 3 and 4, the six-membered ring amines **2b**−**d**, dibenzylamine (**2e**), and the aromatic amines **2f**−**i** may bind to the catalyst less tightly than pyrrolidine and may be the reason these reactions showed the best results under the conditions without the additive and solvent.

In the present reaction, the experimental results revealed that the stereochemical outcome is also strongly dependent on the ratio of the chiral ligand **4a** to the Rh (Scheme 12).

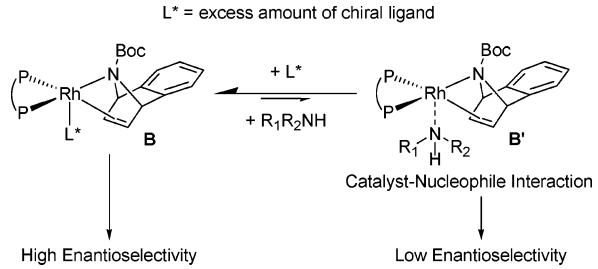
In the reaction of **1a** with dibenzylamine (**2e**) at 110 °C for 24 h, the use of 1.5 equiv. of **4a** to rhodium (7.5 mol %) gave 78% ee, whereas the use of 2.0 equiv. (10 mol %) gave 90% ee. Higher enantioselectivity was observed in the reaction using 3.0 equiv. of **4a** (15 mol %) which gave 92% ee. Finally, the use of 2.2 equiv. of **4a** (11 mol %) was found to be most effective (92% ee) for the present asymmetric reaction. Similar results were observed in the ring-opening of **1a** with pyrrolidine (**2a**) in Table 2 (entries 6, 7, and 11).

To try to learn more about the beneficial effort of the excess ligand on the enantioselectivity of the reaction, we undertook some simple ^{31}P NMR studies to characterize the rhodium-phosphine complexes in solution (Figure 2 and Scheme 13). The reaction of $[Rh(cod)Cl]_2$ and **4a** (1.0 equiv. to Rh) in toluene at 80 °C for 1.5 h showed two doublets, 42.3 ppm (J_{Rh-P} = 205.1 Hz) for the complex **14** and 43.1 ppm (J_{Rh-P} = 209.4 Hz) for the complex **15** in a ratio of 1:1. After heating the mixture of **14** and **15** at 80 °C for 10 h, the peak of attributed to complex **15** disappeared and only the doublet of **14** was observed. According to previous reports,[33] $[RhL_2Cl]_2$ type of dimers showed a large coupling constant of 197 Hz. For example, $[Rh(binap)Cl]_2$[33a] and $[Rh(dppe)Cl]_2$[33b] have J_{Rh-P} = 197.0 and 198.5 Hz, respectively. On the basis of the analogy of the coupling constant with other rhodium complexes already reported and the stoichiometry, complex **14** should be [Rh(C_2-ferriphos)Cl]$_2$. Also, complex **15** is proposed to be a 14-electron

Scheme 13



Scheme 14



monomer complex based on the larger J_{Rh-P} value. The trends in the coupling constants between monomer and dimer of the $[RhL_2Cl]_2$ type complexes have been investigated by Van Gaal.[34] A mixture of $[Rh(cod)Cl]_2$ and **4a** (2.0 equiv to Rh) was also reacted at 80 °C for 12 h and showed only the doublets of **14** at 42.3 ppm (J_{Rh-P} = 205.1 Hz) and a peak for free **4a**. Monomeric $[RhL_2]^+X^-$ complexes **16**, known to have a smaller coupling constant of ca. 132 Hz, were not observed.[35] For example, $[Rh(dppe)_2]^+Cl^-$ and $[Rh(dppf)_2]^+BF_4^-$ have J_{Rh-P} = 132 and 139 Hz, respectively. Thus, the rhodium catalyst **14** is generated from $[Rh(cod)Cl]_2$ and **4a** in a ratio 1 to 2.

The results indicate that after the formation of the dimer **14** consumed 2.0 equiv. of ligand **4a**, 2.0 equiv. of free **4a** still remained. It was shown by ^{31}P NMR that excess ligand does not lead to a detectable amount of a new complex such as **16**, however excess ligand is still envisioned to play an important role by interacting with the catalytic intermediates to minimize catalyst-nucleophile interactions which presumably cause lower enantioselectivity at the enantiodiscriminating step (Scheme 14).

Conclusion

We have developed rhodium-catalyzed asymmetric ring-opening reaction of azabenzonorbornadienes **1** with various

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aliphatic, aromatic, and volatile amines and an efficient route to the optically active 1,2-diamine derivatives **3** that can be obtained in high yields and with excellent enantioselectivities (up to >99% ee). The nature of the activating group on nitrogen influenced the reactivity of azabicyclic alkenes and the stereochemical outcome of the ring-opening. Good reactivity and enantioselectivity was generally observed with a variety of substituted azabenzonorbornadienes. The asymmetric ring-opening with small amines such as pyrrolidine and dimethylamine give the best results with ammonium hydrochloride additives, but generally no additives are needed when **4a** is used as the ligand. Also, the combination of R_2NH_2I and *i*-Pr_2NEt (optimal ratio 2:3) led to ring-opening reaction of **1a** with volatile amines such as Et_2NH and Me_2NH, with relatively low catalyst loadings (1.0 mol % of $[Rh(cod)Cl]_2$. Experiments revealed that the nature of the chiral ligand has the significant impact on the reactivity of the catalyst and the use of an excess amount (2.2 equiv. to Rh) of the chiral ligand plays an important role to increase the enantioselectivity in the ring-opening reactions of azabenzonorbornadienes with amine nucleophiles.

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Supporting Information Available: Experimental procedures and spectral, analytical data for all reaction products (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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