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Enantioselective Iridium-Catalyzed Ring Opening of Low-Activity Azabenzonorbornadienes with Amines

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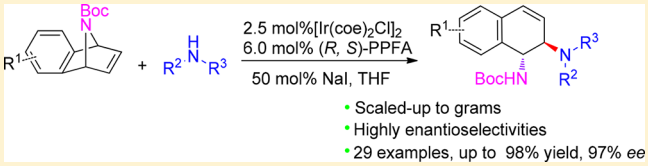
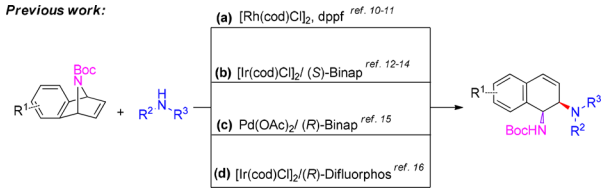
Supporting Information

ABSTRACT: An iridium catalyst (2.5 mol %) generated in situ from $[Ir(coe)_2Cl]_2$ and a nitrogen phosphorus ligand was efficient in the asymmetric ring-opening reactions of low-activity azabenzonorbornadiene with various aliphatic and aromatic amines, providing the corresponding chiral vicinal 1,2-diamine scaffolds in high yields (up to 98%) and excellent enantioselectivities (up to 97% ee). The synthetic utility of the transformation was demonstrated by performing a gram-scale reaction.



Chiral vicinal 1,2-diamines have attracted much attention, owing to their importance in a large number of bioactive natural compounds and medicinal products.[1−7] Due to their importance, various synthesis methods have been developed to construct the chiral 1,2-diamine frameworks.[8,9] Notably, the transition-metal-catalyzed asymmetric ring-opening reaction of azabenzonorbornadienes with amines is an attractive and useful synthetic strategy (Scheme 1). Initially, Lautens and co-workers

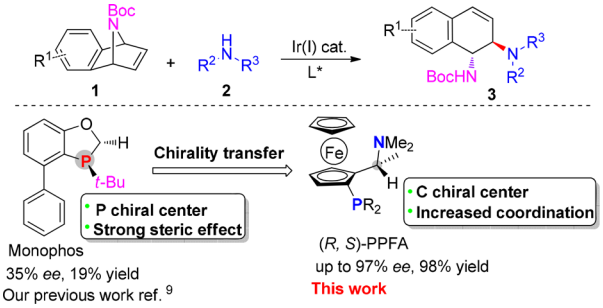
Scheme 1. Transition-Metal-Catalyzed Asymmetric Ring-Opening Reactions of Azabenzonorbornadienes with Amines



reported the first example of rhodium-catalyzed asymmetric ring opening of azabenzonorbornadienes with amines (Scheme 1a).[10,11] Subsequently, iridium/Binap-catalyzed asymmetric ring opening of azabenzonorbornadienes with primary and secondary amines proceeding with moderate to good yields and enantioselectivities was developed by Yang and co-workers (Scheme 1b).[12−14] In addition, Fan and co-workers have employed palladium-catalyzed and iridium/copper-catalyzed asymmetric ring opening of azabenzonorbornadienes with aromatic amines, respectively (Scheme 1c,d).[15,16]

Recently, we also have studied a chiral monophosphine ligand in the iridium-catalyzed asymmetric ring opening of both oxabenzonorbornadienes and azabenzonorbornadienes with amines (Scheme 2).[17] Unfortunately, the result was not as good as that for the reaction with oxabenzonorbornadienes, owing to the low activities of azabenzonorbornadienes.

Scheme 2. Chirality Transfer Effect on Enantioselectivity in Ring Opening of Azabenzonorbornadienes



Additionally, it was quite possible that the lower enantioselectivity and yield were due to the strong steric hindrance effect caused by the *tert*-butyl substituent backbone and the lower coordination of the phosphorus chiral center. Thus, we envisioned that the high tunability of these nitrogen phosphorus ligands ((*R*,*S*)-PPFA) with a carbon chiral center may be able to increase the activity and enantioselectivity of iridium-catalyzed asymmetric ring opening of azabenzonorbornadienes via the increased coordination of the substrate to the catalyst (Scheme 2). On the basis of our previous work with oxabenzonorbornadienes and our continuous interest in iridium-catalyzed asymmetric ring opening of azabenzonorbornadienes, we herein report the asymmetric ring-opening reaction of azabenzonorbornadienes with amines catalyzed by the iridium nitrogen phosphorus ligand **L1** (Scheme 3).

At the outset of this project, a series of ligands **L1**−**L5** were used, considering that the carbon chiral center would increase the activity of the asymmetric ring-opening reaction (Scheme

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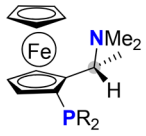
Scheme 3. Tunable Chiral Nitrogen Phosphorus Ligands

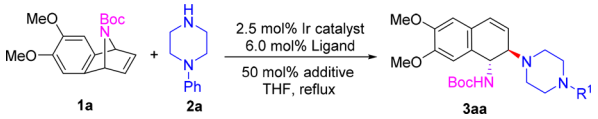


L1: R = Ph;
L2: R = 3,5-(*t*-Bu)$_2$C$_6$H$_3$;
L3: R = 3,5-(CH$_3$)$_2$C$_6$H$_3$;
L4: R = C$_{10}$H$_{21}$;
L5: R = Cy;

3). The ligands **L1**−**L5** can be easily prepared by the method in a previous report.[18]

We have subsequently studied the asymmetric ring opening of low-activity **1a** with *N*-phenylpiperazine **2a** in the presence of 2.5 mol % of [Ir(coe)$_2$Cl]$_2$. Not surprisingly, the desired ring-opening product **3a** was not obtained; instead, there was complete recovery of the starting material (Table 1, entry 1).

Table 1. Optimization of Asymmetric Iridium-Catalyzed Ring Opening of Azabenzonorbornadiene with *N*-Phenylpiperazine



1a **2a** **3aa**

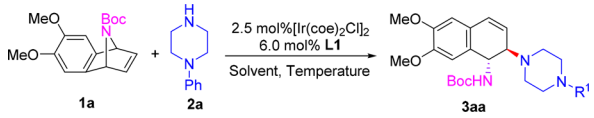
entry	catalyst	additive	L*	yield/%[a]	ee/%[b]
1	[Ir(coe)$_2$Cl]$_2$			<5	
2	[Ir(coe)$_2$Cl]$_2$	NaI		<5	
3	[Ir(coe)$_2$Cl]$_2$		**L1**	<5	
4	[Ir(coe)$_2$Cl]$_2$	NaI	BINAP	<5	ND
5	**[Ir(coe)$_2$Cl]$_2$**	**NaI**	**L1**	**95**	**93**
6	[Ir(coe)$_2$Cl]$_2$	NaI	**L2**	92	77
7	[Ir(coe)$_2$Cl]$_2$	NaI	**L3**	93	68
8	[Ir(coe)$_2$Cl]$_2$	NaI	**L4**	90	21
9	[Ir(coe)$_2$Cl]$_2$	NaI	**L5**	91	20
10	[Ir(coe)$_2$Cl]$_2$	Bu$_4$NI	**L1**	98	60
11	[Ir(coe)$_2$Cl]$_2$	KI	**L1**	96	39
12	[Ir(coe)$_2$Cl]$_2$	LiI	**L1**	95	92
13[c]	[Ir(coe)$_2$Cl]$_2$	NaI	**L1**	70	85
14	[Ir(cod)Cl]$_2$	NaI	**L1**	95	79
15	Ir(NBD)BF$_4$	NaI	**L1**	93	55
16	[IrCp*Cl]$_2$	NaI	**L1**	<5	ND

[a]Yield of isolated product. [b]The ee value was determined by HPLC analysis on a chiral phase (Chiralcel OD-H). [c]1.0 mol % of [Ir(coe)$_2$Cl]$_2$ and 2.4 mol % of **L1** were used.

Initial control experiments of the reaction conditions showed that the ligands and additives played key roles in both reactivity and enantioselectivity, which was in accordance with the results obtained by Fagnou and Lautens[19] (Table 1, entries 2 and 3). A variety of ligands and additives were then screened. Surprisingly, excellent yields were obtained when the nitrogen phosphorus ligands **L1**−**L5** were employed in contrast to the previous BINAP ligand which was routinely used in ring-opening reactions of azabenzonorbornadienes[12−14] (Table 1, entries 4−9). Notably, the introduction of a bulky group at the R position resulted in significantly reduced enantioselectivities. Meanwhile, NaI, which was found to be an important additive in many asymmetric reactions,[19] was proved to be optimal with an isolated yield of 95% and 93% ee (Table 1, entries 10−12). Additionally, further investigations were examined which revealed 2.5 mol % of the iridium precursor [Ir(coe)$_2$Cl]$_2$ furnished product **3a** with an optimal yield and ee (Table 1, entries 13−16).

To further employ these reaction conditions, a range of solvents, reaction temperatures, and reaction times were systematically explored (Table 2). As a result, the asymmetric

Table 2. Effects of Solvents in Ring-Opening Reactions of Azabenzonorbornadiene with *N*-Phenylpiperazine



1a **2a** **3aa**

entry	solvent	*T*/°C	*t*/h	yield/%[a]	ee/%[b]
1	**THF**	**80**	**15**	**95**	**93**
2	Et$_2$O	40	15	93	90
3	MTBE[c]	60	15	90	50
4	DMF	60	24	87	25
5	CH$_3$CN	80	15	93	92
6	DCE	80	15	93	91
7	dioxane	90	24	60	81
8	DME	80	15	87	88
9	hexane	80	24	90	92
10	toluene	90	24	90	91

[a]Isolated product. [b]Determined by HPLC (Chiralcel OD-H column). [c]MTBE = methyl *tert*-butyl ether.

products proceeded with excellent yields and enantioselectivitives in the solvents THF, Et$_2$O, CH$_3$CN, DCE, hexane, and toluene while modest enantioselectivitives were obtained in the solvents methyl *tert*-butyl ether (MTBE, 50% ee) and DMF (only 25% ee) (Table 2, entries 1−10). Thus, THF was employed as the terminal solvent. In addition, the reaction time affected the reactivity but not the enantioselectivity.

With the optimal conditions in hand, the scope of *N*-Boc-protected azabenzonorbornadienes and various *N*-phenylpiperazine was evaluated (Table 3). In all cases, a wide variety of electron-rich and -poor substituted dihydronaphthalenes were synthesized in excellent yields and high enantioselectivities. Of particular interest was the low-activity dimethoxy-substituted **2a**, which furnished the desired dihydronaphthalene products in high yields and good enantioselectivities (Table 3, enties 1−13). For example, a series of ortho-substituted phenyl rings with electron-donating and electron-withdrawing groups afforded high yields and ee values with low-activity 6,7-dimethoxy-substituted **1a** (**3ab**−**ad**). Notably, the reactions of phenyl-substituted piperazines with both electron-rich and -poor groups in the para and meta positions proceeded efficiently in good to excellent yields and ee values (**3ae**−**ak**). *N*-Bn piperazine and *N*-Boc piperazine provided the corresponding products **3al**,**am** in excellent yields of 90% and 92% with 76% and 96% ee values, respectively (Table 3, entries 12 and 13).

Similarly, phenyl-substituted piperazines with both electron-rich and -poor groups in ortho and para positions also worked well to complete the ring-opening transformation with the simple *N*-Boc protected azabenzonorbornadiene **1b** (**3ba**−**bg**). Interestingly, 2-methoxyphenyl-substituted piperazine was subjected to this reaction with **1b** to give a high yield of 91% and up to 97% ee (**3bc**). To our delight, various *N*-phenylpiperazine substrates were also compatible with the electron-withdrawing group of **1c** under the optimal reaction conditions (**3ca**−**cd**).

To further demonstrate the generality of this transformation, we explored the scope of other amines for dihydronaphthalene

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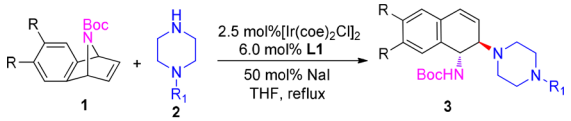
Table 3. Substrate Scope of Iridium-Catalyzed Ring-Opening Reactions of Azabenzonorbornadiene with Piperazines



1 2 3

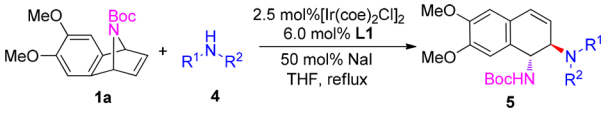
1a: R = OMe; **1b**: R = H; **1c**: R = F

entry	R	R^1	*t*/h	yield/%[a]	.ee/%[b]
1	**1a**	C_6H_5	24	95 (**3aa**)	93
2	**1a**	2-$OMeC_6H_4$	16	98 (**3ab**)	92
3	**1a**	2-$CH_3C_6H_3$	16	98 (**3ac**)	91
4	**1a**	2-FC_6H_4	24	93 (**3ad**)	86
5	**1a**	3-ClC_6H_4	24	93 (**3ae**)	90
6	**1a**	4-$CH_3C_6H_4$	16	96 (**3af**)	95
7	**1a**	4-$OCH_3C_6H_3$	16	98 (**3ag**)	94
8	**1a**	4-ClC_6H_4	24	92 (**3ah**)	92
9	**1a**	2,4-di-$CH_3C_6H_3$	14	96 (**3ai**)	84
10	**1a**	3,4-di-ClC_6H_3	36	78 (**3aj**)	85
11	**1a**	4-FC_6H_4	24	93 (**3ak**)	92
12	**1a**	3-Cl-Bn	18	90 (**3al**)	75
13	**1a**	Boc	14	92 (**3am**)	96
14	**1b**	C_6H_5	16	95 (**3ba**)	93
15	**1b**	2-FC_6H_4	16	90 (**3bb**)	94
16	**1b**	2-$OCH_3C_6H_4$	16	91 (**3bc**)	97
17	**1b**	4-$CH_3C_6H_4$	14	93 (**3bd**)	93
18	**1b**	4-$OCH_3C_6H_4$	14	93 (**3be**)	90
19	**1b**	3,4-di-ClC_6H_3	16	88 (**3bf**)	96
20	**1b**	2,4-di-$CH_3C_6H_3$	14	93 (**3bg**)	90
21	**1c**	C_6H_5	12	93 (**3ca**)	96
22	**1c**	2-$OMeC_6H_4$	12	91 (**3cb**)	89
23	**1c**	4-ClC_6H_4	12	90 (**3cc**)	96
24	**1c**	4-$OCH_3C_6H_4$	12	95 (**3 cd**)	96

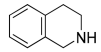
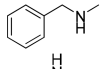
[a]Yield of isolated product. [b]The ee value was determined by HPLC analysis on a chiral phase (Chiralcel OD-H, AD-H, Chiralcel AS-H, or Chiralcel IC-H column).

synthesis (Table 4). As can be seen from Table 4, a series of aliphatic amines were also found to give excellent yields but moderate enantioselectivities (Table 4, entries 3 and 4).

Table 4. Substrate Scope of Iridium-Catalyzed Ring-Opening Reactions of Azabenzonorbornadiene with Amines



1a 4 5

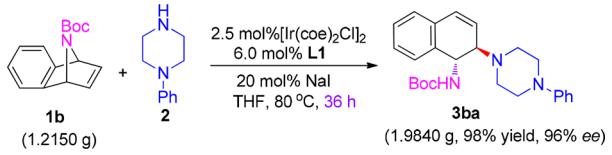
Entry	NHR^1R^2	Yield /% [a]	*ee* /% [b]
1		<5 (**5aa**)	ND
2		<5 (**5ab**)	ND
3		93 (**5ac**)	88
4		90 (**5ad**)	77
5		<5 (**5ae**)	ND

[a]Yield of isolated product. [b]The ee value was determined by HPLC analysis on a chiral phase (Chiralcel OD-H or AD-H).

Disappointingly, no desired products were observed when aromatic amines and 1*H*-pyrrole were employed in the reaction, which may be attributed to the weak nucleophilicities (Table 4, entries 1, 2, and 5). In addition, 2-chloro-*N*-methylaniline failed to give the desired products also probably owing to the hindered ortho-substituted group in the reaction (Table 4, entry 2).

As a demonstration of the scalability of this protocol, the iridium-catalyzed ring opening of azabenzonorbornadiene **1b** with *N*-phenylpiperazine **2a** was performed on a gram scale (Scheme 4). The corresponding dihydronaphthalene product **3ba** was isolated with 98% yield (1.9840 g) and 96% ee through a pad of silica gel after 36 h.

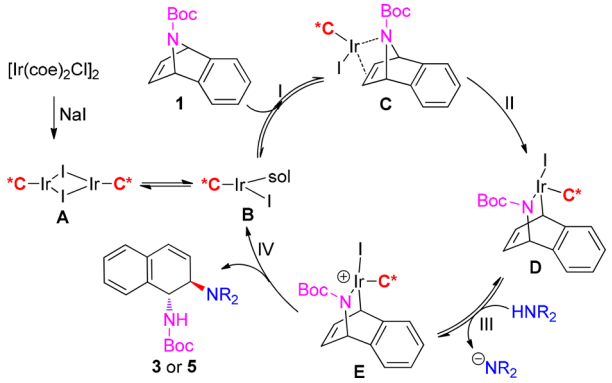
Scheme 4. Gram-Scale Iridium-Catalyzed Ring-Opening of Azabenzonorbornadiene 1b with *N*-Phenylpiperazine 2a



1b (1.2150 g) **2** **3ba** (1.9840 g, 98% yield, 96% *ee*)

On the basis of the above results and previous reports,[17,20] the proposed mechanistic details of the current reaction are depicted in Scheme 5. The dimeric complex **A** was initially

Scheme 5. Proposed Mechanism of Iridium-Catalyzed Ring Opening of Azabenzonorbornadienes with Amines



generated from the iridium precursor $[Ir(coe)_2Cl]_2$ and NaI. Subsequently, the intermediate **A** was dissociated by solvent to afford the corresponding monomer. Then the monomer iridium catalyst **B** complexed with azabenzonorbornadienes **1** to give the intermediate **C**, followed by oxidative insertion to form the iridium alkoxide species **D**. Protonation of **D** and then nucleophilic attack by amine **2** or **3** afforded the desired product **3** or **5**. Finally, the monomeric iridium(I) species **B** were regenerated, thereby initiating the new catalytic cycle. This trans stereochemical model is in accordance with the absolute configuration obtained for the ring-opening product **3ae**.[12]

In summary, an efficient and convenient protocol for the synthesis of a variety of substituted dihydronaphthalenes with excellent yields and high enantioselectivities by Ir-**L1**-catalyzed ring opening of azabenzonorbornadienes with amines has been developed. The new nitrogen phosphorus ligand **L1** with a carbon chiral center with strong coordination contributed to the success of this reaction.

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■ ASSOCIATED CONTENT

Supporting Information

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Experimental details and characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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