ORGANIC LETTERS

2008
Vol. 10, No. 21
4723−4726

Iridium-Catalyzed Asymmetric Ring-Opening Reactions of *N*-Boc-azabenzonorbornadiene with Secondary Amine Nucleophiles

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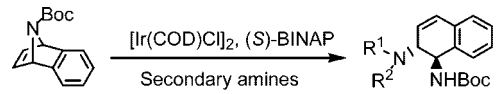
Received June 17, 2008

ABSTRACT



1 **2a-y** **3a-h**

Iridium-catalyzed asymmetric ring-opening reactions of *N*-Boc-azabenzonorbornadiene with a number of secondary amines has been developed for the first time. The reaction gave 1,2-*trans*-diamine derivatives in moderate to good yields with high enantioselectivity in the presence of 2.5 mol % of $[Ir(COD)Cl]_2$ and 5 mol % of (*S*)-BINAP. The *trans*-configuration of the 1,2-diamino products was confirmed by X-ray crystallography.

Transition-metal-catalyzed asymmetric ring-opening of heterobicyclic alkenes is one of the most powerful tools for the synthesis of optically active compounds. Iridium-catalyzed allylic substitution reaction is an efficient protocol; it has emerged as an effective approach to the construction of carbon−carbon bonds and carbon−heteroatom bonds, which provides a feasible way to generate useful multifunctional chiral building blocks.[1] As a result, two new chiral centers can be established by desymmetrization of a meso-bicyclic alkene in a single step.[2]

Recently, Cu-catalyzed, highly enantioselective conjugate addition and allylic alkylation reactions with Grignard reagents were developed by Feringa[3] and Alexakis,[4] respectively.

To the best of our knowledge, asymmetric ring-opening of *N*-substituted azabenzonorbornadienes is currently focused on Rh and Pd catalysts. For example, Lautens and co-workers[5] and Carretero and co-workers[6] have extensively investigated the Pd-catalyzed asymmetric ring-opening of *N*-substituted azabenzonorbornadienes with organozinc reagents.

In addition, Lautens and co-workers[7] also explored the Rh-catalyzed asymmetric ring-opening of *N*-Boc-azabenzonorbornadienes with amine nucleophiles.

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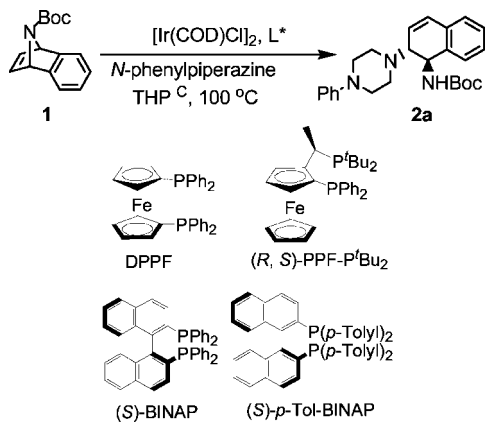
10.1021/ol801768e CCC: $40.75
Published on Web 10/04/2008

However, the ring-opening of *N*-substituted azabenzonorbornadiene using other transition-metal catalysts remains unknown. Herein, we report the first iridium-catalyzed asymmetric ring-opening of *N*-Boc-aza-benzonorbornadiene with *N*-substituted piperazine nucleophiles. Compared with previous methods, this method has several advantages: the catalyst $[Ir(COD)Cl]_2$ is easy to make and the BINAP ligand is commercially available at low cost. Both catalyst and ligand are air-stable, which would remarkably simplify the synthetic procedure. This new method also offers potentially useful synthetic routes to *trans*-1,2-diamines which are the scaffolds for chiral ligands[8] and valuable intermediates for total synthesis of bioactive compounds.[9]

N-Boc-azabenzonorbornadiene **1** and $[Ir(COD)Cl]_2$ were prepared according to the reported procedure.[10,11] We first chose an achiral 1,1′-bis(diphenylphosphino)ferrocene (DPPF) ligand to validate the catalytic activity of the iridium complex.

In the initial attempts, *N*-phenylpiperazine was used as a nucleophile. When it reacted with *N*-Boc-azabenzonorbornadiene **1** (0.21 mmol) in THP (2 mL) at 100 °C in the presense of 2.5 mol % of $[Ir(COD)Cl]_2$ and 5 mol % of DPPF, the corresponding product **2a** was obtained in a high yield of 78% after 6 h (Table 1, entry 1). This result

Table 1. Identification of Optimal Chiral Ligand for Iridium-Catalyzed Asymmetric Ring-Opening of *N*-Boc-azabenzonorbornadiene **1** with *N*-Phenylpiperazine



entry	ligand	time (h)	yield[a] (%)	ee[b] (%)
1	DPPF	6	78	0
2	(*R*,*S*)-PPF-P^t-Bu_2	24	23	58
3	(*S*)-BINAP	8	76	79
4	(*S*)-*p*-Tol-BINAP	8	75	70

[a] Isolated yield after silica gel column chromatography. [b] Determined by HPLC with a Chiralcel AD column. [c] Solvent is tetrahydropyran.

encouraged us to screen other chiral phosphine ligands so as to optimize the reaction conditions. Ferrocenyl diphosphine ligand, (*R*,*S*)-PPF-P^tBu_2,[12] was first attempted.

Unfortunately, the desired product, **2a**, was obtained in low yield (23%) with reasonable enantioselectivity (58% ee) after 24 h (Table 1, entry 2). This result suggested (*R*,*S*)-PPF-P^tBu_2 was not an ideal ligand, which prompted us to screen other ligands. Among several chiral ligands we had tested, (*S*)-BINAP[13] and (*S*)-*p*-Tol-BINAP were found to give better yields and reasonable enantioselectivity (Table 1, entries 3 and 4). Moreover, in the case of (*S*)-BINAP, the enantioselectivity is slightly higher (79% vs 70% ee); therefore, we decided to use (*S*)-BINAP as a ligand.

We further found that the use of 2.5 mol % of $[Ir(COD)Cl]_2$ and 5 mol % of (*S*)-BINAP was needed to ensure both high yield and enantioselectivity (Table 2, entry 1).

Table 2. Condition Screening for Iridium-Catalyzed Asymmetric Ring-Opening Reactions of *N*-Boc-Azabenzonorbornadiene **1** with *N*-Phenylpiperazine[a]

entry	solvent	*T* (°C)	additive	time (h)	yield[b] (%)	ee[c] (%)
1	THP[g]	100		8	76	79
2[d]	THF[h]	100		24	36	72
3[e]	THP	100		8	77	72
4[f]	THP	100		8	78	70
5	toluene	100		24	35	45
6	CH_3CN	100		24	31	68
7	DME	100		24	21	10
8	DMF	100		24	26	50
9	dioxane	100		8	70	75
10	THP	25		12	n.r	
11	THP	80		48	18	70
12	THP	120		8	79	67
13	THP	100	NH_4F	24	nr	
14	THP	100	NH_4Cl	24	10	21
15	THP	100	NH_4Br	24	24	43
16	THP	100	NH_4I	24	48	68

[a] The reaction was carried out with **1** (0.21 mmol) and 3.0 equiv of *N*-phenylpiperazine (0.63 mmol) in solvent (2.0 mL) in the presence of $[Ir(COD)Cl]_2$ (2.5 mol %) and (*S*)-BINAP (5.0 mol %). [b] Isolated yield after silica gel column chromatography. [c] Determined by HPLC with a Chiralcel AD column. [d] $[Ir(COD)Cl]_2$: 1.0 mol %, (*S*)-BINAP: 2.0 mol %. [e] $[Ir(COD)Cl]_2$: 3.5 mol %, (*S*)-BINAP: 7.0 mol %. [f] $[Ir(COD)Cl]_2$: 5.0 mol %, (*S*)-BINAP: 10.0 mol %. [g] THP is tetrahydropyran. [h] THF is tetrahydrofuran.

Slightly higher yields but lower enantioselectivities were observed when more catalyst was loaded (Table 2, entries 3 and 4), and lower catalyst loading (1.0 mol %) resulted in a considerable decrease in yield (Table 2, entry 2).

Next, we screened the impact of solvents (Table 2, entries 5−9). Among the solvent systems tested, tetrahydropyran (THP) was found to be optimal to give the best yield and enantioselectivity for **2a**. Temperature was found to play an important role in the reaction. At room temperature, there was no reaction (Table 2, entry 10). The best results were obtained at 100 °C (Table 2, entry 1). At 80 °C, a sluggish reaction was observed with poor yield (Table 2, entry 11). At higher temperature, such as 120 °C, it was found that the reaction gave a better yield but with worse enantioselectivity (Table 2, entry 12).

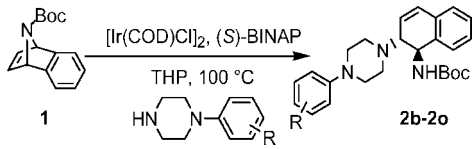
Lautens and Fagnou[14] found that the halide ions might play an important role in transition-metal catalysis, in which the reactivity and enantioselectivity could be significantly improved by choosing a suitable halide ion. Inspired by those

findings, we attempted to use ammonium halides (NH_4X, X = F, Cl, Br, I) as additives[15] (1 equiv to **1**) (Table 2, entries 13−16).

However, in our hands, we found that the halide ions were not necessary and that the reaction worked even better without them.

Based on those observations, we decided to expand the reaction to a number of substituted *N*-phenylpiperazines (Table 3), which consistently showed satisfactory yields and enantioselectivities.

Table 3. Scope of Ring-Opening Reactions of *N*-Boc-azabenzonorbornadiene **1** with Substituted *N*-Phenylpiperazines[a]



entry	R	time (h)	product	yield[b] (%)	ee[c] (%)
1	*p*-OMe	6	**2b**	86	87
2	*p*-Me	8	**2c**	77	83
3	*p*-F	8	**2d**	79	77
4	*p*-Cl	8	**2e**	82	79
5	*p*-COMe	24	**2f**	67	75
6	*p*-CF_3	24	**2g**	73	80
7	*p*-NO_2	24	**2h**	61	65
8	*o*-OMe	12	**2i**	72	81
9	*o*-Me	24	**2j**	59	82
10	*o*-F	18	**2k**	65	81
11	*o*-Cl	18	**2l**	69	76
12	*o*-CN	48	**2m**	55	78
13	*m*-Me	12	**2n**	75	78
14	*m*- CF_3	12	**2o**	70	82

[a] The reaction was carried out with **1** (0.21 mmol) and 3.0 equiv of substituted *N*-phenylpiperazine (0.63 mmol) in THP (2 mL) at 100 °C in the presence of $[Ir(COD)Cl]_2$ (2.5 mol %) and (*S*)-BINAP (5.0 mol %). [b] Isolated yield after silica gel column chromatography. [c] Determined by HPLC with a Chiralcel AD column.

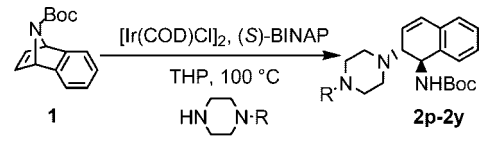
The results (Table 3) also demonstrated that the functional groups on the phenyl ring of nucleophiles had less impact on both yields and enantioselectivies. However, it was observed that electron-rich functional groups on the phenylpiperazines are more reactive than those of electron-deficient ones. For example, the reaction of *N*-Boc-azabenzonorbornadiene **1** with 4-methoxyphenylpiperazine offered much higher yield in a shorter time compared to that of 4-nitrophenylpiperazine (Table 4, entries 1 and 7).

Moreover, we observed that substituted groups at the ortho-position of the phenyl ring gave poorer yields (Table 4, entries 8−12) than those of meta- and para-substituted *N*-phenylpiperazines, probably due to steric hindrance.

We further extended our reactions to the phenylpiperazines with two substituents on the phenyl ring as well as other types of substituted piperazines (Table 4).

These ring-opening reactions all proceeded smoothly with high yields and enantioselectivities.

Table 4. Scope of Ring-Opening Reactions of *N*-Boc-azabenzonorbornadiene **1** with Disubstituted *N*-Phenylpiperazines and Other Types of Substituted Piperazines[a]



entry	R	time (h)	product	yield[b] (%)	ee[c] (%)
1	3,4-$Cl_2C_6H_3$	8	**2p**	84	79
2	2,4-$F_2C_6H_3$	10	**2q**	78	73
3	3,4-$Me_2C_6H_3$	12	**2r**	76	73
4	2,5-$Me_2C_6H_3$	12	**2s**	68	74
5	2,4-$Me_2C_6H_3$	12	**2t**	72	75
6	2,3-$Me_2C_6H_3$	18	**2u**	65	84
7	$CHPh_2$	12	**2v**	83	77
8	CH_2Ph	48	**2w**	61	84
9	CO_2Et	24	**2x**	73	73
10	furoyl	48	**2y**	67	61

[a] The reaction was carried out with **1** (0.21 mmol) and 3.0 equiv of substituted piperazine (0.63 mmol) in THP (2 mL) at 100 °C in the presence of $[Ir(COD)Cl]_2$ (2.5 mol %) and (*S*)-BINAP (5.0 mol %). [b] Isolated yield after silica gel column chromatography. [c] Determined by HPLC with a Chiralcel AD column.

The crystal structure of **2w**, obtained by solvent-evaporation from its solution in dichloromethane and petroleum ether, confirmed its 1,2-trans configuration, i.e, (1*R*,2*R*)[16] as shown in Figure 1. It is obvious that the reaction favors the formation of *trans*-1,2-diamino products.

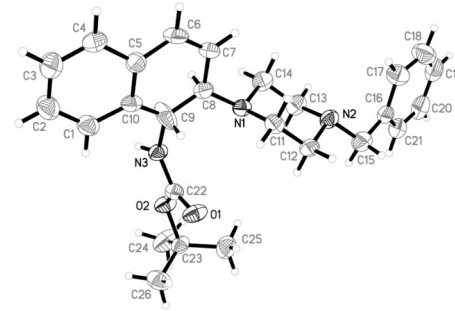
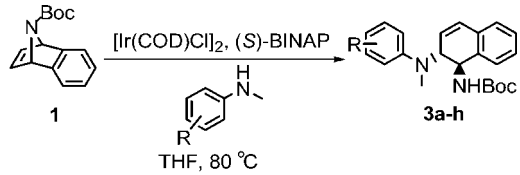


Figure 1. ORTEP plot for **2w**.

To further investigate the scope of this new catalyst system, ring-opening reactions of *N*-Boc-azabenzonorbornadienes with compounds such as substituted *N*-methylaniline as nucleophiles were investigated. The optimized conditions in this reaction were used to study the catalytic asymmetric ring-opening of **1** in the presence of 1.5 mol % of $[Ir(COD)Cl]_2$ and 3.0 mol % of (*S*)-BINAP in THF with the results summarized in Table 5. Remarkably, it was found that the reactivity and enantioselectivity are both lower than that of *N*-substituted piperazines nucleophiles. This happens because of the *p*-π conjugation of the nitrogen lone pair with

Table 5. Asymmetric Ring-Opening Reactions of *N*-Boc-azabenzonorbornadiene **1** with Substituted *N*-Methylanilines



1 3a-h

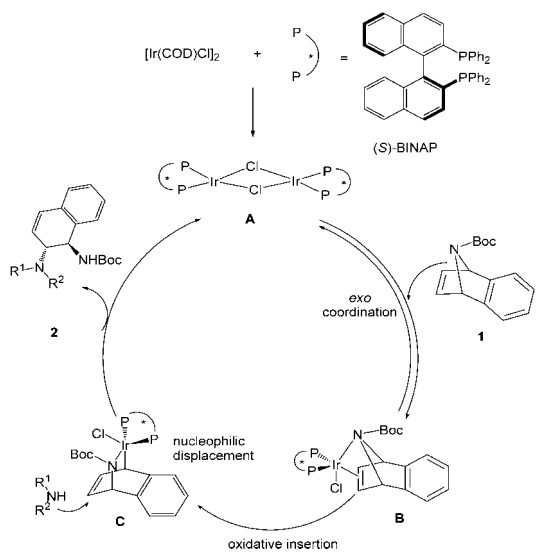
entry	R	time (h)	product	yield[b] (%)	ee[c] (%)
1	H	48	**3a**	56	80
2	3-Cl	48	**3b**	48	49
3	3-Me	48	**3c**	56	85
4	4-Cl	48	**3d**	59	55
5	4-F	48	**3e**	24	51
6	4-Br	48	**3f**	29	65
7	4-OMe	48	**3g**	48	42
8	4-NO_2	48	**3h**	nr	

[a] The reaction was carried out with **1** (0.21 mmol) and 3.0−5.0 equiv of *N*-methylanilines in THF (2.0 mL) at 80 °C in the presence of $[Ir(COD)Cl]_2$ (1.5 mol %) and (*S*)-BINAP (3.0 mol %). [b] Isolated yield after silica gel column chromatography. [c] Determined by HPLC with a Chiralcel AD column.

the electron cloud of the benzene ring for substituted *N*-methylaniline and decreases the ability of nucleophiles. For example, electron-withdrawing substituted groups on the benzene ring of *N*-methylanilines decreased the ability of nucleophiles and gave low yields and enantioselectivities (Table 5, entries 2, 4−6, and 8).

Based on our studies, a working hypothesis is shown in Scheme 1.[17] The chiral dimeric iridium complex **A** is first formed. The nitrogen atom and the double bond of *N*-Boc-azabenzonorbornadiene **1** are then reversibly coordinated to the iridium center of the catalyst to give the intermediate **B**.

Scheme 1. Working Hypothesis for the Asymmetric Ring-Opening of *N*-Boc-azabenzonorbornadiene **1** with Secondary Amine Nucleophiles



Insertion of the iridium into the C−N bond of **B** forms **C**.

Nucleophilic attack with configuration inversion is proposed to occur in an S_N2' displacement of the iridium catalyst. The *trans*-1,2-diamino product **2** was subsequently released, and the iridium complex **A** was regenerated.

In summary, we have successfully developed the first enantioselective iridium-catalyzed ring-opening reactions of *N*-Boc-azabenzonorbornadiene with a number of secondary amine nucleophiles. It provides an efficient and practical access to the optically active 1,2-diimine derivatives in moderate to good yields with high enantioselectivities. The new method is significant in terms of the low cost for the ligands and facile manipulation compared to literature close precedents. An investigation on the biological and pharmaceutical activities of the products is in progress. Studies on further expansion of the scope and synthetic utility of this Ir-catalyzed method are also being pursued in our laboratory.

Acknowledgment. We are grateful to the National Natural Science Foundation of China (No.20772036) and the Natural Science Foundation of Guangdong Province (No.8251063101-000002 and No.7005804) for financial support.

Supporting Information Available: Experimental procedures and full characterization data for all new products including optical rotations, IR, ^{1}H NMR and ^{13}C NMR, MS, elemental analysis, and X-ray structure data for compound **2w**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL801768E

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