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Iridium/Copper-Cocatalyzed Asymmetric Ring Opening Reaction of Azabenzonorbornadienes with Amines

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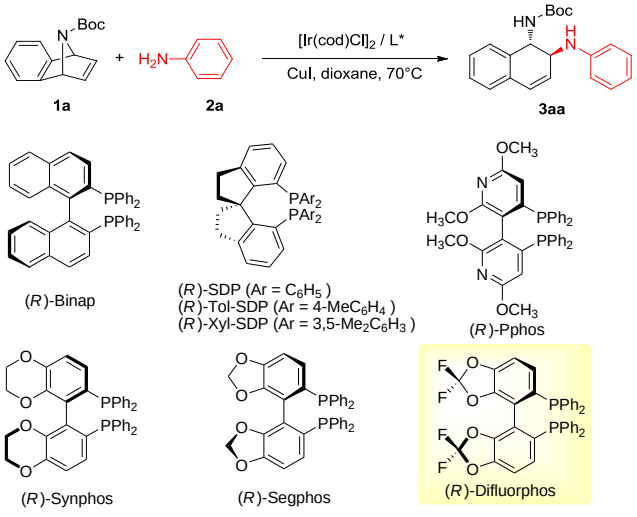
An Iridium/copper associated with (*R*)-Difluorphos catalyst for asymmetric ring opening reaction of azabenzonorbornadienes with amines was developed, which afforded chiral *trans*-vicinal diamines in 80-97% yields with 93-95% enantioselectivities.

Chiral vicinal diamines are versatile building blocks in organic synthesis and important structural motifs in natural products and biologically active compounds[1], and their derivatives have been wildly employed as chiral auxiliaries and ligands in asymmetric catalysis[2]. Conventional synthetic method for chiral vicinal diamines is from 2-amino alcohols[3] or α-amino acids[4], new method for the preparation of functionalized chiral diamines is still demanding. Asymmetric ring opening reactions of azabenzonorbornadienes with amines offer potentially useful synthetic routes to chiral vicinal diamines. After Lautens and co-workers' pioneer work in the Rh-catalyzed asymmetric ring opening reactions of azabenzonorbornadienes with amines[5], Yang and co-workers developed the Ir-catalyzed asymmetric ring opening reactions of azabenzonorbornadiene with amines.[6] Moderate to good yields and *ee*s were achieved in their Ir/Binap-catalyst system with primary and secondary amine nucleophiles. Recently, Luo and Tang applied their chiral monophosphine ligand in Ir-catalyzed asymmetric ring opening of *N*-phenylpiperazine to azabenzonorbornadiene, but the result was not as good as the reaction with oxabenzonorbornadiene for azabenzonorbornadienes were found to be less reactive than the corresponding oxabenzonorbornadienes.[7] Thus, the continuous development of new and efficient catalyst systems for ARO reaction of azabenzonorbornadienes with amine nucleophiles is still desirable and interesting. Based on our previous finding on Pd/Cu-cocatalyzed ARO reaction of azabenzonorbornadienes with terminal alkynes[8] and Ir-catalyzed ARO reaction of oxabenzonorbornadienes with amines[9], herein, we report Ir/Cu cocatalyzed asymmetric ring opening reaction of azabenzonorbornadienes with amine nucleophiles, where 80-97% yields were generally observed with 93-95% enantioselectivities.

We embarked this investigation using azabenzonorbornadiene **1a** and aniline **2a** as benchmark substrates with $[Ir(cod)Cl]_2$ catalyst and Lewis acid CuI as co-catalyst (Table 1). Gratifyingly, commercially available ligand (*R*)-Binap gave *trans*-1,2-diamines **3aa** in 90% yield with 72% *ee* in dioxane at 70 °C for 12 h (Table 1, entry 1). Encouraged by this good result, a range of chiral diphosphine ligands were investigated.[10] Almost same *ee*s (86-88%) were obtained when using (*R*)-SDP, (*R*)-Tol-SDP, or (*R*)-Xyl-SDP as ligand, while (*R*)-Xyl-SDP could give a better yield (96%) (Table 1, entries 2-4). (*R*)-Pphos, (*R*)-Synphos and (*R*)-Segphos are also effective ligands in this reaction, but only afford moderate *ee*s (Table 1, entries 5-7). Under this reaction condition, the best product enantioselectivity (90%) was obtained by employing (*R*)-Difluorphos as the ligand (Table 1, entry 8). Thus, we chose (*R*)-Difluorphos as the ligand of choice for further optimization.

Table 1. Ligand screening for Ir-catalyzed ARO reaction of azabenzonorbornadiene **1a** with aniline **2a**.[a]



Entry	Ligand	Time	Yield	ee

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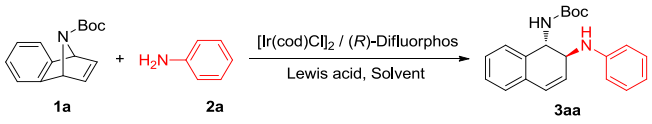
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

		(h) [b]	(%) [c]	(%) [d]
1	(*R*)-Binap	12	90	72
2	(*R*)-SDP	16	91	88
3	(*R*)-Tol-SDP	12	92	86
4	(*R*)-Xyl-SDP	16	96	87
5	(*R*)-Pphos	20	96	75
6	(*R*)-Synphos	24	89	78
7	(*R*)-Segphos	20	92	86
8	(*R*)-Difluorphos	10	94	90

[a] Reaction conditions: $[Ir(cod)Cl]_2$ (5 mol % Ir), CuI (20 mol %), and ligand (6 mol %) in dioxane (2 mL) was stirred at room temperature for 30 min under Ar atm. **1a** (0.2 mmol) and **2a** (0.6 mmol) were added, and the reaction mixture was stirred at 60 °C for indicated period of time. [b] Based on the full conversion of the substrate. [c] Yield of isolated product. [d] Determined by HPLC analysis.

The addition of Lewis acid is crucial for higher yield and enantioselectivity. When the reaction was carried out in the absence of CuI, only 51% yield and 86% ee were obtained (Table 2, entry 1). Many Lewis acids, such as ZnI_2, CuOTf and CuBr were efficient additive in this reaction, giving higher yields and better *ees*. Among them, CuBr, which was used as an effective catalyst in the asymmetric ring opening of oxabicyclic alkenes,[11] gave the best result (98% yield and 94% ee, Table 2, entry 8). The reaction conditions for this $[Ir(cod)Cl]_2$/CuBr co-catalyzed asymmetric ring opening reaction were further surveyed. Solvents such as THF, toluene, DME, and MTBE all resulted in good yields with high *ees* (Table 2, entries 9, 11-13). The highest *ee* of **3aa** (95%) along with a good yield (97%) was afforded in toluene (entry 13). The effects of the temperature were investigated. Decreasing the reaction temperature to 50 °C, decreased the yield of **3aa** to 88% without affecting the *ee*, but 48 h was required for full conversion (Table 2, entry 14). Increasing the reaction temperature to 90 °C resulted in a similar yield but a lower enantioselectivity (Table 2, entry 15). Without using CuBr, the reaction yield and enantioselectivity decreased dramatically (Table 2, entry 16).

Table 2. Optimization of reaction conditions for Ir-catalyzed ARO reaction of azabenzonorbornadiene **1a** with aniline **2a**.[a]



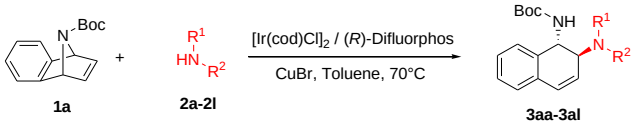
1a 2a 3aa

Entry	Temp (°C)	Lewis acid	solvent	Time (h) [b]	Yield (%) [c]	Ee (%) [d]
1	70	-	Dioxane	24	51	86
2	70	CuI	Dioxane	10	94	90
3	70	ZnI_2	Dioxane	10	98	90
4	70	CuOTf	Dioxane	10	93	92
5	70	$Cu(OTf)_2$	Dioxane	16	48	89
6	70	$Zn(OTf)_2$	Dioxane	16	58	89
7	70	CuCl	Dioxane	16	64	90
8	70	CuBr	Dioxane	10	98	94
9	70	CuBr	THF	16	84	86
10	70	CuBr	DCE	48	18	90
11	70	CuBr	DME	10	98	94
12	70	CuBr	MTBE	10	98	94
13	70	CuBr	Toluene	10	97	95
14	50	CuBr	Toluene	48	88	95
15	90	CuBr	Toluene	4	98	92
16	70	-	Toluene	10	87	79

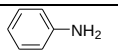
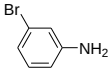
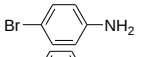
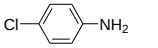
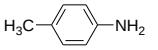
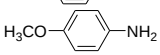
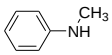
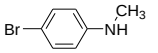
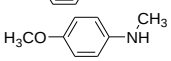
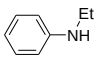
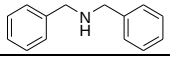
[a] Reaction conditions: $[Ir(cod)Cl]_2$ (5 mol % Ir), Lewis acid (20 mol %), and (*R*)-Difluorphos (6 mol %) in solvent (2 mL) was stirred at room temperature for 30 min under Ar atm. **1a** (0.2 mmol) and **2a** (0.6 mmol) were added, and the reaction mixture was stirred at indicated temperature for indicated period of time. [b] Based on the full conversion of the substrate. [c] Yield of isolated product. [d] Determined by HPLC analysis. THF = tetrahydrofuran, DCE = dichloroethane, DME = dimethoxyethane, MTBE = methyl *tert*-butyl ether.

The substrate scope of amines were summarized in Table 3. No significant electronic effect on primary aniline nucleophile as the corresponding ring-opening products **3aa**-**3af** could be obtained in high yields (95-97%) with good enantioselectivities (91-95%). The sterically hindered 1-naphthylamine **2g** resulted in a lower yield (80%) with good *ee* (93%). Secondly aniline nucleophile, *N*-methylanilines and *N*-ethylaniline reacted with **1a** smoothly, afforded the desired product in good yields with high *ees* (Table 2, entries 8-11). It was observed that dibenzylamine **2l** was also suitable substrate in this catalyst system (Table 3, entry 12).

Table 3. Ir-catalyzed ARO reaction of azabenzonorbornadiene **1a** with various aromatic amines **2a-2l**.[a]



1a 2a-2l 3aa-3al

Entry	Amines	2	Time (h) [b]	Yield (%) [c]	Ee (%) [d]
1		**2a**	10	97	95
2		**2b**	16	95	91
3		**2c**	6	96	95
4		**2d**	6	96	94
5		**2e**	8	97	93
6		**2f**	8	97	94
7		**2g**	16	80	93
8		**2h**	10	94	95
9		**2i**	40	83	94
10		**2j**	10	96	95
11		**2k**	10	96	94
12		**2l**	30	90	93

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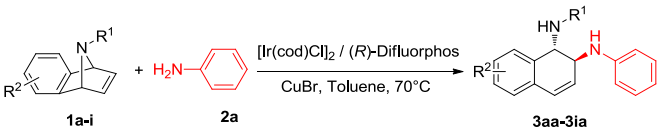
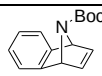
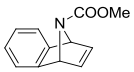
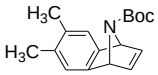
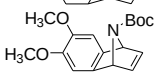
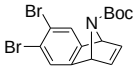
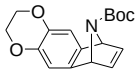
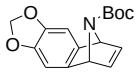
[a] Reaction conditions: $[Ir(cod)Cl]_2$ (5 mol % Ir), CuBr (20 mol %), and (*R*)-Difluorphos (6 mol %) in solvent (2 mL) was stirred at room temperature for 30 min under Ar atm. **1a** (0.2 mmol) and **2a-l** (0.6 mmol) were added, and the reaction mixture was stirred at indicated temperature for indicated period of time. [b] Based on the full conversion of the substrate. [c] Yield of isolated product. [d] Determined by HPLC analysis. ND = not determined.

The nature of the substituent group on the nitrogen in the azabenzonorbornadiene plays a significant role in the yields and enantioselectivities of the products. When electron-withdrawing group Ts, Ns or -COOMe was used to instead of Boc group, the yield of the products decreased though the *ee* value still very high (Table 4, entries 1-4). To further extend the substrate scope of this transformation, substituted azabenzonorbornadienes **1e-1i** with various substituents were examined. All the ring openings products were obtained in 93-95% yield with 93-94% *ee* (Table 4, entries 5-9). The bromide remained intact under the present reaction conditions (**3ga**), that allows further potential functionalization.

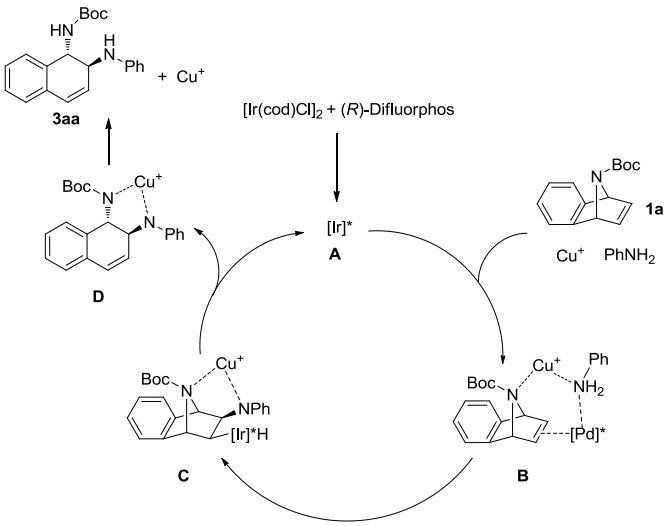
Table 4. Ir-catalyzed ARO reaction of various azabenzonorbornadiene **1a-1i** with aniline **2a**.[a]



Entry	Azabenzonor -bornadiene	1	Time (h) [b]	Yield (%) [c]	Ee (%) [d]
1		**1a**	10	97	95
2		**1b**	48	90	88
3		**1c**	48	86	84
4		**1d**	24	88	84
5		**1e**	24	93	93
6		**1f**	24	94	93
7		**1g**	24	93	94
8		**1h**	5	95	94
9		**1i**	4	95	94

[a] Reaction conditions: $[Ir(cod)Cl]_2$ (5 mol % Ir), CuBr (20 mol %), and (*R*)-Difluorphos (6 mol %) in solvent (2 mL) was stirred at room temperature for 30 min under Ar atm. **1a** (0.2 mmol) and **2a** (0.6 mmol) were added, and the reaction mixture was stirred at indicated temperature for indicated period of time. [b] Based on the full conversion of the substrate. [c] Yield of isolated product. [d] Determined by HPLC analysis.

On the basis of literature[12] and our own observations, the proposed mechanism for this asymmetric ring opening reaction is shown in Scheme 1. The catalytic cycle is initiated by the coordination of $[Ir(cod)Cl]_2$ with (*R*)-Difluorphos to generate the chiral iridium complex **A**, the following coordination with **1a**, cuprous ion, and aniline to afford the intermediate **B**. Subsequently, the intramolecular addition reaction generates intermediate **C**, which then undergoes β-elimination to give the ring-opened species **D**. Finally, the product **3aa** was formed by cation exchange.



Scheme 1. Proposed mechanism for asymmetric ring opening reaction of azabenzonorbornadiene with aniline.

Conclusions

In conclusion, we have successfully developed an asymmetric ring opening reaction of azabenzonorbornadienes with a number of primary and secondary aromatic amine nucleophiles in the presence of Ir/Cu associated with (*R*)-Difluorphos catalyst. It provides an efficient and practical access to *trans*-vicinal diamine derivatives in good yields (80-97%) with high enantioselectivities (93-95%). Further investigations are underway to clarify the mechanism of this transformation and to explore the scope of the cocatalyst system in asymmetric ring opening (ARO) reactions.

Acknowledgements

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