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Asymmetric ring-opening of oxabenzonorbornadiene with amines promoted by a chiral iridium-monophosphine catalyst†

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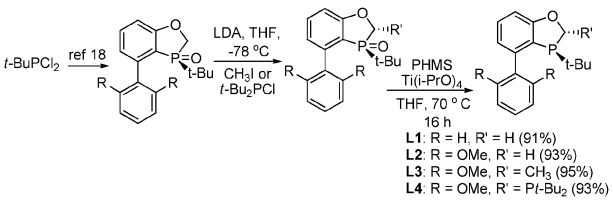
A new iridium-monophosphine catalyst is found to be efficient for asymmetric ring-opening of benzonorbornadiene with amines, providing a series of chiral substituted dihydronaphthalenes in high yields (up to 98%) and excellent enantioselectivities (>99%).

Syntheses of chiral substituted dihydronaphthalene have gained great interest, because it is an important core structure found in many bioactive compounds.[1] Among the chemical synthesis methods of these useful bioactive compounds, the transition metal-catalyzed asymmetric ring-opening (ARO) of oxabicyclic alkenes is the most attractive synthetic strategy. Since initial studies in this field reported by Caple[2] and Lautens,[3] significant progress has been achieved in rhodium-catalyzed asymmetric ring-opening of oxabenzonorbornadiene using a wide range of nucleophiles such as thiols,[4] phenols,[5] organoboronic acids,[6] dialkylzincs,[7] carboxylates,[8] sulfur nucleophiles,[9] amines[10] and alcohols.[11] Besides, other metals including copper,[12] palladium,[7,13] iron,[14] nickel[15] and iridium[16,17] catalyzing asymmetric ring-opening reactions of oxabicyclic alkenes were also reported.

The asymmetric ring-opening of oxabicyclic alkenes with amines is useful for the construction of chiral amino alcohols which can be employed to synthesize bioactive compounds.[10c] In 2009, Yang reported the first iridium-catalyzed asymmetric ring-opening of oxabenzonorbornadiene with amines.[17] However, only moderate to good ees were achieved. Recently we have developed a series of chiral monophosphorus ligands for asymmetric Suzuki–Miyaura coupling reactions[18] and addition of arylboronic acids to aryl aldehydes.[19] We envisioned that the high tunability of these monophosphorus ligands may be able to promote the iridium-catalyzed asymmetric ring-opening of oxabenzonorbornadiene with amines. We report herein the asymmetric ring-opening of oxabenzonorbornadiene with amines catalyzed by iridium-monophosphorus ligand **L1** (Scheme 1).



Scheme 1 Ligand synthesis.

With the phosphorus ligands **L1**–**L4** in hand, we firstly screened the effects of ligands (Table 1). Initial screening of the reaction conditions demonstrated that the additives and ligands had a significant role to play in both reactivity and selectivity (entries 1–9). Using 2.0 mol% $[Ir(coe)_2Cl]_2$ and 4.8 mol% **L1** as the catalyst no ring-opening product was obtained in the absence of an additive or by addition of NaCl (entries 1 and 2), whereas the desired product was achieved in low yield (91%) but a good ee (88% ee) in the presence of 0.2 eq. NaBr (entry 3). Excellent yield and ee (>99% ee) were observed by the use of NaI (entry 4). The fact that NaI gave excellent results may be due to its binding ability to iridium and relative *trans*-effect as well as its size being at the opposite extreme within the group.[20] The enantioselectivities were decreased by the introduction of bulky group at the position of R or R′ (entries 5–7). For example, only 89% ee was obtained with ligand **L2** (entry 5) and sharply reduced ees were observed with the use of ligands **L3** and **L4** with a bulky group at the R′ position (entries 6 and 7). Additives also affected the performance of the catalyst sharply. Only 81% ee and 58% ee were observed for the additives Bu_4NI or KI respectively (entries 8 and 9). The iridium precursors also significantly affected the enantioselectivities of the products. Only moderate enantioselectivities were observed with the iridium precursors $[Ir(cod)Cl]_2$ or $Ir(cod)BF_6$ (entries 10–12). This could be largely

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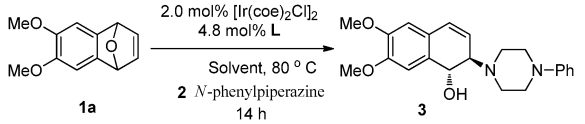
Table 1 Optimization of iridium-catalyzed ring-opening reaction of **1a** with **2**



1a 3

Entry[a]	Solvent	Additive	L*	Yield[b] (%)	ee[c] (%)
1	THF	No	**L1**	<5	ND
2	THF	NaCl	**L1**	<5	ND
3	THF	NaBr	**L1**	35	88
4	THF	NaI	**L1**	91	>99
5	THF	NaI	**L2**	95	89
6	THF	NaI	**L3**	95	13
7	THF	NaI	**L4**	93	−61
8	THF	Bu_4NI	**L1**	93	81
9	THF	KI	**L1**	95	58
10[d]	THF	NaI	**L1**	91	79
11[e]	THF	NaI	**L1**	93	78
12[f]	THF	NaI	**L1**	93	69
13	DME	NaI	**L1**	96	93
14	Toluene	NaI	**L1**	88	80
15[g]	THF	NaI	**L1**	51	>99

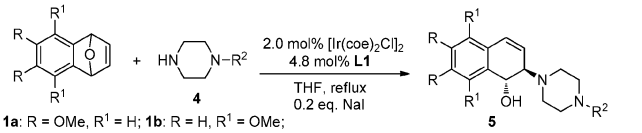
[a] The reactions were carried out at 80 °C in THF (2.0 mL) for 14 h with **1a** (0.35 mmol), **2** (0.105 mmol), and NaI (0.07 mmol) in the presence of $[Ir(coe)_2Cl]_2$ and (2.0 mol%) and ligand (4.8 mol%) under nitrogen. The absolute configurations were assigned on the basis of the absolute configuration of **5ae**[21] (Table 2, entry 5) through a similar stereochemical model. [b] Yield of isolated product. [c] The ee value was determined by HPLC analysis on a chiral phase (Chiralcel Lux Amylose-2 column). [d] $[Ir(cod)Cl]_2$ as the Ir precursor. [e] The ratio of $[Ir(cod)Cl]_2$/**L1** was 1 : 4. [f] $Ir(cod)BF_6$ as the Ir precursor. [g] Performed at RT.

attributed to the slow complex formation between iridium precursors and ligands. A slightly lower enantioselectivity was observed in the solvent DME (entry 13). Only 80% ee was obtained in the solvent toluene (entry 14). The reaction temperature affected the reactivity but not the selectivity (entry 15).

Under the optimized reaction conditions, the Ir–**L1** catalyst proved to be efficient for the synthesis of substituted dihydronaphthalenes in high yields with excellent enantioselectivities (Table 2). For example, various *N*-phenylpiperazines with either electron-donating or electron-withdrawing substituents at the phenyl position afforded excellent yields and enantioselectivities (entries 1–7). *N*-Boc piperazine and *N*-Bn piperazine were also applied to provide high yields and ees with 1,4-dihydro-6,7-dimethoxy-1,4-epoxynaphthalene (**1a**) as the substrate (entries 8 and 9). Other substituted oxabenzonorbornadiene substrates were also applied (entries 10–17). Electron-donating or electron-withdrawing substrate such as **1b** or **1c** could also be employed to provide excellent yields and ees with *N*-phenylpiperazine (entries 10 and 11). High yields and good ees were also obtained with smaller steric substrates such as **1d** and **1e** with various substituted *N*-phenylpiperazines (entries 12–17).

After the success of asymmetric ring-opening reaction of oxabenzonorbornadiene with piperazines, the reaction of other amines was also investigated (Table 3). As can be seen in Table 3, various amines including primary or secondary aromatic amines (entries 1 and 2) and aliphatic amines (entries 4 and 5) can be used in the reaction to get the desired ring-opening products in high yields and enantioselectivities. Disappointingly, no desired products were observed when 2-chloro-*N*-methylaniline and pyrrole were employed in the reaction

Table 2 Substrates scope of iridium-catalyzed ring-opening reaction of oxabenzonorbornadiene with piperazines

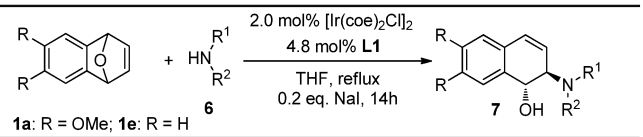


1a: R = OMe, R^1 = H; **1b**: R = H, R^1 = OMe;
1c: R = Br, R^1 = H; **1d**: R = F, R^1 = H;
1e: R = H, R^1 = H;

Entry[a]	1	R^1	Time	Yield[b] (%)	ee[c] (%)
1	**1a**	2-$OMeC_6H_4$	14	93(**5aa**)	>99
2	**1a**	2-FC_6H_4	14	93(**5ab**)	>99
3	**1a**	3-ClC_6H_4	14	95(**5ac**)	95
4	**1a**	4-$CH_3C_6H_4$	14	97(**5ad**)	>99
5	**1a**	4-$CF_3C_6H_4$	14	82(**5ae**)	>99
6	**1a**	2,4-Di-$CH_3C_6H_3$	14	93(**5af**)	89
7	**1a**	3,4-Di-ClC_6H_3	14	92(**5ag**)	>99
8	**1a**	3-Cl-Bn	14	95(**5ah**)	>99
9	**1a**	Boc	12	90(**5ai**)	98
10	**1b**	C_6H_5	14	93(**5ba**)	93
11	**1c**	C_6H_5	12	95(**5ca**)	88
12	**1d**	C_6H_5	12	97(**5da**)	86
13	**1d**	2-FC_6H_4	12	96(**5db**)	86
14	**1d**	4-$OCH_3C_6H_4$	12	98(**5dc**)	88
15	**1e**	C_6H_5	12	93(**5ea**)	83
16	**1e**	2-$OMeC_6H_4$	10	95(**5eb**)	85
17	**1e**	4-$CF_3C_6H_4$	12	87(**5ec**)	86

[a] The reactions were carried out at 80 °C in THF (2.0 mL) for 14 h with **1** (0.35 mmol), **4** (0.105 mmol), and NaI (0.07 mmol) in the presence of $[Ir(coe)_2Cl]_2$ and (2.0 mol%) and ligand (4.8 mol%) under nitrogen. The absolute configurations were assigned on the basis of the absolute configuration of **5ae**[21] through a similar stereochemical model. [b] Yield of isolated product. [c] The ee value was determined using HPLC analysis on a chiral phase (Chiralcel OD-H, AD-H or Lux Amylose-2 column).

Table 3 Substrate scope of iridium-catalyzed ring-opening reaction of oxabenzonorbornadiene with amines

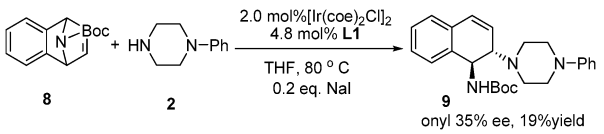


1a: R = OMe; **1e**: R = H

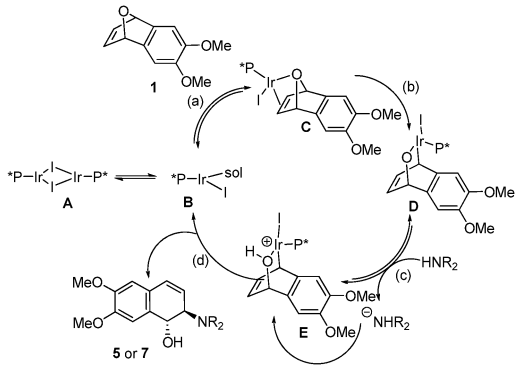
Entry[a]	1	NHR^1R^2	Yield[b] (%)	ee[c] (%)
1	**1a**	Aniline	81(**7aa**)	93
2	**1a**	*N*-Methylaniline	65(**7ab**)	93
3	**1a**	2-Chloro-*N*-methylaniline	<5	ND
4	**1a**	*N*-Methyl-1-phenylmethanamine	95(**7ac**)	89
5	**1a**	1,2,3,4-Tetrahydroisoquinoline	93(**7ad**)	89
6	**1a**	1*H*-Pyrrole	<5	ND
7	**1c**	*N*-Methylaniline	95(**7ca**)	70
8	**1c**	4-Chloro-*N*-methylaniline	91(**7cb**)	77
9	**1c**	*N*,4-Dimethylaniline	93(**7cc**)	87
10	**1c**	*N*-Ethylaniline	91(**7cd**)	80

[a] The reactions were carried out at 80 °C in THF (2.0 mL) for 14 h with **1** (0.35 mmol), **6** (0.105 mmol), and NaI (0.07 mmol) in the presence of $[Ir(coe)_2Cl]_2$ and (2.0 mol%) and ligand (4.8 mol%) under nitrogen. The absolute configurations were assigned on the basis of the absolute configuration of **5ae**[21] (Table 2, entry 5) through a similar stereochemical model. [b] Isolated product. [c] Determined using HPLC (Chiralcel OD-H or AD-H).

(entries 3 and 6). The negative results may be attributed to the hindered *ortho*-substituted group and weak nucleophilic of pyrrole. In the case of the less sterically hindered substrate **1c**, high yield but decreased enantioselectivities were achieved (entries 7–10).



Scheme 2 Iridium-catalyzed asymmetric ring-opening of *N*-phenylpiperazine to aza-benzonorbornadiene.



Scheme 3 The proposed mechanism of the Ir-**L1** catalyzed ring-opening of oxabenzonorbornadiene with amines.

Encouraged by the good results of the iridium-catalyzed ring-opening reaction of oxabenzonorbornadiene, the ring-opening reaction of aza-benzonorbornadiene **8** with *N*-phenylpiperazine was also tested under the above optimized reaction conditions. Unfortunately, only low yield and enantioselectivity were obtained (Scheme 2). Further studies are in progress in our group.

A proposed mechanism for this Ir(I)-catalyzed transformation is illustrated in Scheme 3. When $[Ir(coe)_2Cl]_2$ was used as the iridium source, the dimeric complex was dissociated to form the corresponding monomer by solvent. And then the possible catalytic asymmetric ring-opening cycle with amines may go through four main steps:[10a,b,17a,b] (a) the monomer iridium catalyst complexed with oxabenzonorbornadiene; (b) oxidative insertion to produce the iridium alkoxide; (c) protonation of the iridium alkoxide; (d) nucleophilic attack and regeneration of the monomer iridium(I) species **B**. This stereochemical model is in accordance with the absolute configuration observed in the ring-opening product **5ae**.[21]

In summary, we have disclosed an efficient method for Ir–**L1** catalyzed ring-opening of oxabenzonorbornadiene with amines, leading to the formation of a series of substituted dihydronaphthalenes in high yields and excellent enantioselectivities. The new monophosphorus ligand **L1** with a big steric chiral phosphine center is the key to the success of this asymmetric transformation.

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