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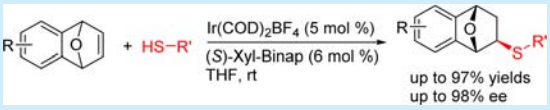
Iridium-Catalyzed Asymmetric Addition of Thiophenols to Oxabenzonorbornadienes

Sifeng Li, Zhiwu Lu, Ling Meng, and Jun Wang*

Department of Chemistry, South University of Science and Technology of China, Shenzhen 518055, China

Supporting Information

ABSTRACT: A highly efficient asymmetric ring addition reaction of oxabenzonorbornadienes with thiophenols using an iridium/(*S*)-xyl-binap catalyst is developed. This catalyst system overcomes catalyst poisoning and background reactions and allows the formation of exclusive thiol addition products in high yields (up to 97% yield) with excellent enantioselectivities (up to 98% ee). Particularly noteworthy is that no competitive ring-opened side products are observed. X-ray crystal structure analysis confirmed the adduct is solely in the *exo*-configuration.



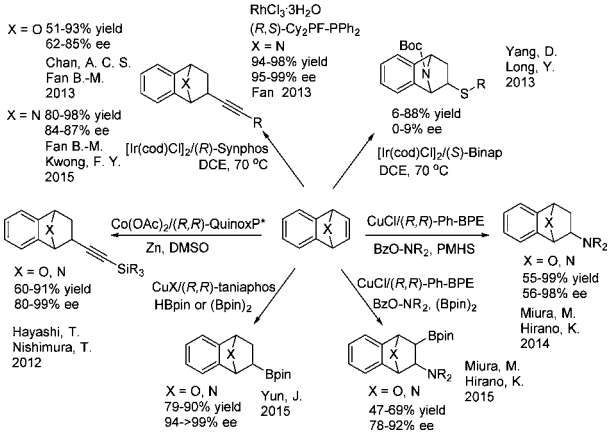
Heterobicyclic alkenes are versatile building blocks for the synthesis of stereochemically defined complex molecules.[1] Considerable progress has been made in transition-metal-catalyzed asymmetric ring opening (ARO) reactions since Lautens's seminal work. With the aid of various chiral transition-metal catalysts, a variety of carbo and heteroatom nucleophiles react with oxa- or aza-benzonorbornadienes successfully, leading to substituted hydroxyl dihydronaphthalenes.[2] In fact, there are two possible reaction pathways between heterobicyclic alkenes and nucleophiles; one affords ring-opening products, while the other gives addition products (Scheme 1). Former investigations revealed that the product

Scheme 1. Two Pathways of Reactions between Oxa- or Aza-Benzonorbornadienes and Nucleophiles

selectivity (the ratio between ring-opening products and addition products) could be switched by the nature of the catalyst.[3] Despite the success of asymmetric ring opening reactions, there were only a few examples with Co, Ir, Rh, or Cu catalysts for the solely asymmetric ring addition reactions of oxa- or aza-benzonorbornadienes with nucleophiles.[4−11]

In 2012, Hayashi and Nishimura reported colbalt-catalyzed asymmetric addition of bulky silylacetylenes to oxa- and azabenzonorbornadienes (Scheme 2).[4] Later, Fan and Kwong employed the $[Ir(cod)Cl]_2$/(*R*)-Synphos catalyst to expand the alkyne scope, which allowed more general arylacetylenes/alkylacetylenes to react with oxa- or azabenzonorbornadienes.[5] Recently, a more efficient $RhCl_3{\cdot}3H_2O$/(*R*,*S*)-$Cy_2PF{-}PPh_2$ catalyst was developed for the hydroalkynylation reaction of azabenzonorbornadienes with high yields (94−98%) and high enantioselectivities (95−99% ee).[6] In 2014, a CuCl/(*R*,*R*)-Ph-BPE-catalyzed enantioselective hydroamination of oxa- and azabenzonorbornadienes with *O*-benzoylhydroxylamines was reported by Miura and Hirano.[7] They also applied this catalyst

Scheme 2. Asymmetric Ring Addition Reactions of Oxa- or Aza-Benzonorbornadienes with Nucleophiles



to aminoboration of oxa- and azabenzonorbornadienes successfully.[8] This transformation adds both amine and boron functional groups across the olefinic moiety in one synthetic operation with perfect *exo* selectivity. In 2015, Yun reported copper(I)/(*R*,*R*)-taniaphos-catalyzed hydroboration of bicyclic alkenes with excellent enantioselectivities.[9] The asymmetric ring opening reaction of oxabenzonorbornadienes with thiophenols was achieved with good yields and high ee by Lautens using halide and protic additives, radical inhibitors, and slow addition of substrate.[10] However, for the ring addition reactions of azabenzonorbornadienes with thiols, only up to 9% ee was observed with the $[Ir(cod)Cl]_2$/(*S*)-Binap catalyst.[11] In fact, the affinity of sulfur for transition metals invariably makes the catalytic reaction complicated, and the high polarizability and redox capability of sulfur always lead to catalyst poisoning and background reactions.[12] Consequently, the reports of transition-metal-catalyzed reactions involving thiols to form C−S bonds are

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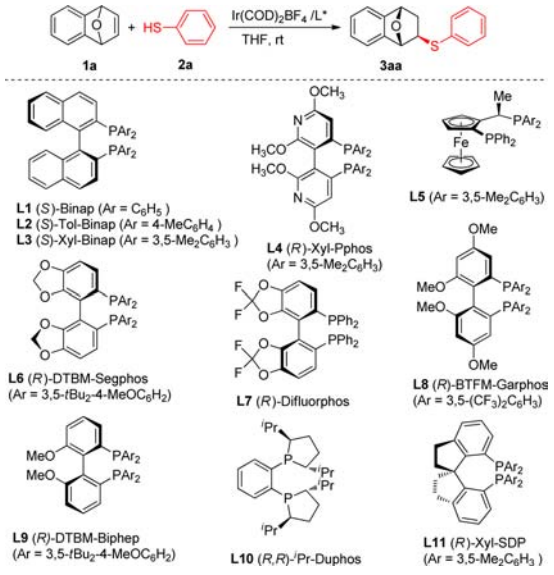
still limited.[13] Notwithstanding, sulfur-containing moieties constitute important scaffolds in many chiral ligands[14] and numerous bioactive compounds in the pharmaceutical industry.[15] Herein, we report an efficient iridium/(*S*)-xyl-binap catalyst which overcomes catalyst poisoning and background reactions and enables the first successful, highly enantioselective ring addition reaction of thiophenols to oxabenzonorbornadienes in good-to-excellent yields and ee.

In continuation of our previous research on the ring opening reaction of oxa- or aza- benzonorbornadienes,[16] we turned our attention to the asymmetric ring addition reaction, which is still underdeveloped. We embarked on this investigation using oxabenzonorbornadiene **1a** and thiophenol **2a** as benchmarked on substrates. Initial screening of iridium precursors revealed that $Ir(COD)_2BF_4$ was superior to other commonly used $[Ir(cod)Cl]_2$, $[Ir(coe)_2Cl]_2$, and $[Ir(cod)_2]$BARF complexes. Further optimizations using $Ir(COD)_2BF_4$ in combination with a series of chiral bisphosphine ligands were carried out (Table 1). Significantly higher ee was observed when a more bulky ligand was employed (Table 1, entries 1−3). Gratifyingly, commercially available (*S*)-Xyl-Binap gave exclusive ring addition product **3aa**

Table 1. Ligand Screening for Ir-Catalyzed Ring Addition Reaction of Oxabenzonorbornadiene 1a with Thiophenol 2a[a]



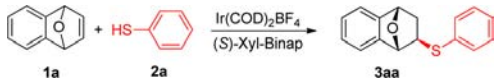
entry	ligand	time (h)	yield (%)[b]	ee (%)[c]
1	(*S*)-Binap **L1**	24	89	5
2	(*S*)-Tol-Binap **L2**	72	78	10
3	(*S*)-Xyl-Binap **L3**	72	71	91
4	(*R*)-Xyl-Pphos **L4**	24	68	17
5[d]	**L5**	72	33	20
6	(*R*)-DTBM-Segphos **L6**	24	91	3
7	(*R*)-Difluorphos **L7**	24	93	1
8	(*R*)-BTFM-Garphos **L8**	24	84	0
9[d]	(*R*)-DTBM-Biphep **L9**	72	79	2
10[d]	(*R,R*)-^{i}Pr-Duphos **L10**	72	53	3
11[d]	(*R*)-Xyl-SDP **L11**	72	44	13

[a]Reaction conditions: $Ir(COD)_2BF_4$ (3.0 mol %) and ligand (3.6 mol %) in THF (2 mL) were stirred at rt for 30 min under an Ar atmosphere. **1a** (0.2 mmol) and **2a** (0.4 mmol) were added, and the reaction mixture was stirred at rt for the indicated period of time. [b]Isolated yields. [c]Determined by HPLC analysis. [d]The reaction was not complete.

in 71% yield and 91% ee in THF at room temperature for 72 h (Table 1, entry 3). Other bulky bisphosphine ligands were tested. However, the best product enantioselectivity was still obtained by employing (*S*)-Xyl-Binap.

The reaction conditions for this $Ir(COD)_2BF_4$-catalyzed asymmetric ring addition reaction were further surveyed (Table 2). The product yield and ee were improved to 96%

Table 2. Optimization of Reaction Conditions[a]



entry	solvent	temp (°C)	time (h)	yield (%)[b]	ee (%)[c]
1[d]	THF	rt	72	71	91
2[e]	THF	rt	48	90	96
3	THF	rt	24	96	97
4	THF	0	72	62	83
5	THF	50	12	90	94
6	DCE	rt	12	96	51
7	DME	rt	12	97	95
8	dioxane	rt	6	91	96
9	toluene	rt	6	95	92
10	DMF	rt	72	41	31
11	CH_3CN	rt	72	22	4

[a]Reaction conditions: $Ir(COD)_2BF_4$ (5.0 mol %) and (*S*)-Xyl-Binap (6 mol %) in THF (2 mL) were stirred at rt for 30 min under an Ar atmosphere. **1a** (0.2 mmol) and **2a** (0.4 mmol) were added, and the reaction mixture was stirred at rt for the indicated period of time. [b]Isolated yields. [c]Determined by HPLC analysis. [d]3 mol % $Ir(COD)_2BF_4$ and 3.6 mol % (*S*)-Xyl-Binap were used. [e]4 mol % $Ir(COD)_2BF_4$ and 4.8 mol % (*S*)-Xyl-Binap were used instead.

and 97%, respectively, when the catalyst loading was increased from 3 mol % to 5 mol % (Table 2, entries 1−3). Lowering the reaction temperature to 0 °C resulted in decreased yield and enantioselectivity (entry 4). A higher reaction temperature accelerated the reaction, but a slightly decreased yield and ee were observed (entry 5). Solvents such as DME, dioxane, and toluene all gave good yields and high ee as compared to THF (Table 2, entries 6−9), yet DMF and CH_3CN made the reaction more prone to background reaction (entries 10−11).

To investigate the substrate scope, a series of substituted thiols **2a−2q** were examined (Table 3). Both the reactivity and enantioselectivity were influenced by the steric and electronic properties of the nucleophile. Sterically hindered 2-chlorothiophenol **2e** and 2,4-dimethylthiophenol **2n** gave slightly lower yields and ee when compared to 3- and/or 4-substituted thiophenols (entries 5 and 14). 2-Thionaphthol also reacted with **1a** smoothly and afforded the desired product in 92% yield with 98% ee (entries 16). It is worth showing the chemoselectivity of 4-mercaptophenol (entry 10). Substrate **2j** with a naked hydroxyl group was an applicable substrate; only the thiol part reacted with alkene to provide 82% yield and 88% ee (entry 10). However, the standard conditions were not quite suitable for aliphatic thiols; benzyl thiol only gave the addition products in 56% yield with 14% ee (entry 17). The *exo*-configuration of the exclusive addition product was further confirmed by X-ray crystal structure analysis (**3af**, Figure 1).[17]

We next probed the substrate scope of oxabenzonorbornadienes **1b−g** with various substituents (Scheme 3). No significant electronic effects were observed as the desired adducts were obtained with good yields (81−92%) and consistently

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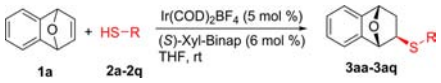
Table 3. Ir-Catalyzed Asymmetric Ring Addition Reaction of Oxabenzonorbornadiene 1a with Various Thiophenols[a]



entry	aryl thiophenols		time (h)	yield (%)[b]	ee (%)[c]
1	C_6H_5	**2a**	24	96	97
2	4-FC_6H_4	**2b**	24	91	97
3	4-ClC_6H_4	**2c**	24	92	97
4	3-ClC_6H_4	**2d**	48	88	97
5	2-ClC_6H_4	**2e**	60	64	48
6	4-BrC_6H_4	**2f**	24	92	98
7	3-BrC_6H_4	**2g**	48	86	96
8[d]	4-$CF_3C_6H_4$	**2h**	24	89	91
9	4-$OMeC_6H_4$	**2i**	24	88	93
10[e]	4-OHC_6H_4	**2j**	60	82	88
11	4-MeC_6H_4	**2k**	24	97	96
12	3-MeC_6H_4	**2l**	48	90	98
13	3,5-$Me_2C_6H_3$	**2m**	48	93	97
14	2,4-$Me_2C_6H_3$	**2n**	48	85	75
15	4-$^iPrC_6H_4$	**2o**	24	91	96
16	2-Napth	**2p**	48	92	98
17[d]	Bn	**2q**	72	56	14

[a]Reaction conditions: $Ir(COD)_2BF_4$ (5.0 mol %) and (*S*)-Xyl-Binap (6 mol %) in THF (2 mL) was stirred at rt for 30 min under an Ar atmosphere. **1a** (0.2 mmol) and **2a**–**2q** (0.4 mmol) were added, and the reaction mixture was stirred at rt for the indicated period of time. [b]Isolated yields. [c]Determined by HPLC analysis. [d]The reaction was performed at 90 °C. [e]The reaction was performed at 50 °C.

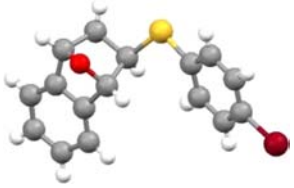
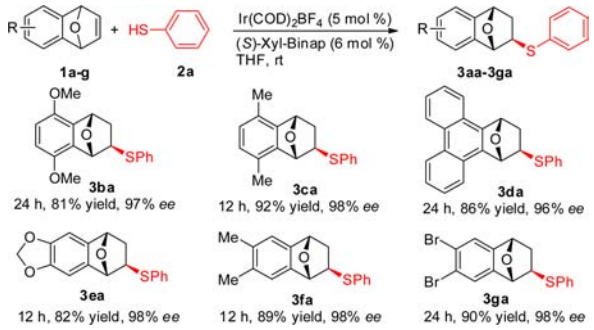


Figure 1. ORTEP drawing of **3af**.

Scheme 3. Ir-Catalyzed Asymmetric Ring Addition Reaction of Substituted Oxabenzonorbornadienes with Thiophenol 2a[a]



[a]Reaction conditions: $Ir(COD)_2BF_4$ (5.0 mol %) and (*S*)-Xyl-Binap (6 mol %) in THF (2 mL) were stirred at rt for 30 min under an Ar atmosphere. **1a**–**g** (0.2 mmol) and **2a** (0.4 mmol) were added, and the reaction mixture was stirred at rt for 24 h. Isolated yields were shown; ee were determined by HPLC analysis.

excellent enantioselectivities (96–98% ees). Particularly noteworthy is that the steric hindrance caused by the substituents at the oxabenzonorbornadienes **1b** and **1c** did not have a deleterious effect on either yields or ee of the products (**3ba**, **3ca**). Substrate **1d** with an extended aromatic structure also resulted in a good yield with high ee (**3da**). The bromo group remained intact under these reaction conditions (**3ga**), which allows further functionalization using traditional cross-coupling methods.

The accelerating effect of the catalyst is shown in Figure 2. Temperature is critical to the reactivity and enantioselectivity in this addition. When the reaction was carried out at 70 °C, the addition product **3aa** was formed in 98% yield in 5 h in the absence of any catalyst (▽). Suppression of the background reaction could be achieved by controlling the reaction temperature at rt, for the reaction is sluggish at room temperature (◆). The combination of $Ir(COD)_2BF_4$ and (*S*)-Xyl-Binap is very efficient which make the reaction markedly faster than that carried out in the absence of ligand (▲ vs ○). Radical inhibitor BHT neither obviously improves nor hinders the reaction with the Ir/(*S*)-xyl-binap catalyst.

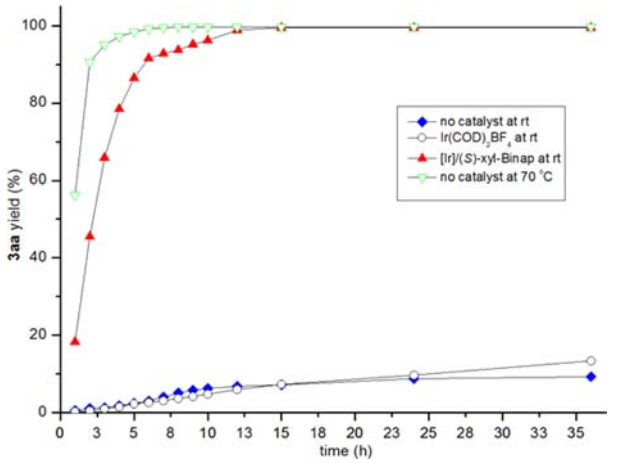
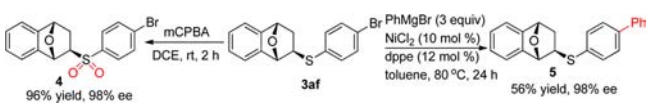


Figure 2. Effect of catalyst and temperature. All reactions were carried out in 2 mL of THF in the presence of oxabenzonorbornadiene **1a** (0.2 mmol), thiophenol **2a** (0.4 mmol), $Ir(COD)_2BF_4$ (5.0 mol %), and (*S*)-Xyl-Binap (6 mol %) if used.

To evaluate the efficacy of this ring addition reaction in gram scale, the reaction was investigated with 0.58 g (4 mmol) of oxabenzonorbornadienes **1a** with the same catalyst loading (5 mol % Ir). The product **3af** was isolated in excellent yield (1.24 g, 93%) in 24 h without compromising the enantioselectivity (98% ee). In addition, sulfide product **3af** can be easily functionalized to other important chemical entities (Scheme 4). For example,

Scheme 4. Functionalization of Sulfide Product 3af



sulfur was oxidized to sulfone **4** with excess *m*-chloroperbenzoic acid without loss of enantiomeric purity. The Br group of sulfide product **3af** was reacted with a Grignard reagent to assemble an elaborated carbon skeleton.

In conclusion, we have successfully developed an efficient iridium/(*S*)-xyl-binap catalyst in asymmetric ring addition reaction of oxabenzonorbornadienes with thiophenols. This protocol overcomes catalyst poisoning and background reactions and gave *exo*-ring addition product exclusively in good yields (up

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to 97% yield) with high level of enantioselectivities (up to 98% ee). Further investigations are underway to explore the nucleophile scope of this addition reaction.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02592.

Experimental procedures and characterization/HPLC data of products (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: wang.j@sustc.edu.cn.

Notes

The authors declare no competing financial interest.

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(17) CCDC 1491950 [for **3af**] contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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