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Iridium/f-Amphol-catalyzed Efficient Asymmetric Hydrogenation of Benzo-fused Cyclic Ketones

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Abstract. Iridium/f-Amphol-catalyzed asymmetric hydrogenation of various benzo-fused five to seven-membered cyclic ketones was successfully developed, affording a series of chiral benzo-fused cyclic alcohols with excellent results (75%-99% yields, 93%->99% ee, and TON up to 297 000). The enantioenriched products can be employed as key intermediates or motifs for the synthesis of some important biologically active compounds, such as rasagiline mesylate TVP-1012 used for the treatment of Parkinson's disease, the enantiomer of anticonvulsant drug eslicarbazepine acetate (BIA 2-093).

Keywords: Asymmetric hydrogenation, Benzo-fused cyclic ketone, Chiral benzo-fused cyclic alcohol, Enantioselectivity, Phosphorus ligand.

Optically active benzo-fused cyclic alcohols and their derivatives are important core structures in some biologically active compounds,[1] such as rasagiline mesylate TVP-1012 for the treatment of Parkinson's disease,[1b] an anti-HIV agent,[1c] a rigid and potent selective norepinephrine reuptake inhibitor (sNRI) NBI 80532 as antidepressant reagent,[1d] and an anticonvulsant drug eslicarbazepine acetate (BIA 2-093)[1e] (Figure 1).

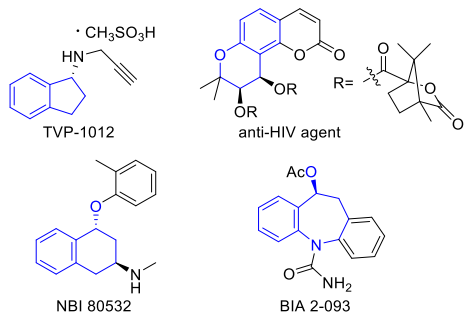
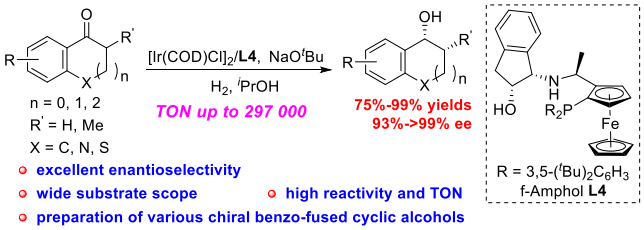


Figure 1. Examples of biologically active compounds containing benzo-fused cyclic alcohols and derivatives.

Asymmetric catalytic reduction of benzo-fused cyclic ketones and derivatives is a straightforward and important synthetic methodology to prepare these chiral benzo-fused cyclic alcohols,[2-6] including asymmetric hydrogenation,[2] asymmetric hydrosilylation,[3] asymmetric hydroboration,[4] asymmetric bioreduction,[5] and asymmetric transfer hydrogenation[6]. Although significant advances have been made in this research area, most of these catalytic systems focused on the reduction of prochiral simple ketones. Additionally, they are generally sensitive to the structure of benzo-fused cyclic ketones, especially for different ring sizes. To date, there are few catalytic systems to engage in systematical research to investigate asymmetric hydrogenation of various benzo-fused cyclic ketones with different ring sizes. In 2004, Noyori and coworkers developed $RuCl_2$(binap)(1,4-diamine) complex-catalyzed efficient asymmetric hydrogenation of 1-tetralone derivatives with excellent results.[2a] In 2014, Rodríguez and coworkers explored chiral bisdihydrobenzooxaphosphole (BIBOP)/ diamineruthenium complexes for the catalytic asymmetric hydrogenation of aryl and heteroaryl six-membered cyclic ketones with good to excellent enantioselectivities.[2j] Therefore, it is necessary to develop a highly efficient catalytic system for the asymmetric hydrogenation of various benzo-fused cyclic ketones with different ring sizes, affording enantioenriched benzo-fused cyclic alcohols. Recently, we developed a series of tridentate ferrocene aminophosphoxazoline (f-amphox) ligands,[7] ferrocene-based amino-phosphine acid (f-Ampha) ligands[8] and ferrorence-based amino-phosphine-alcohol (f-Amphol) ligands[9], which achieved excellent results in iridium-catalyzed asymmetric hydrogenation of prochiral simple ketones and derivatives.[7-9] Based on these results, we herein successfully realized Ir-catalyzed asymmetric hydrogenation of various benzo-fused

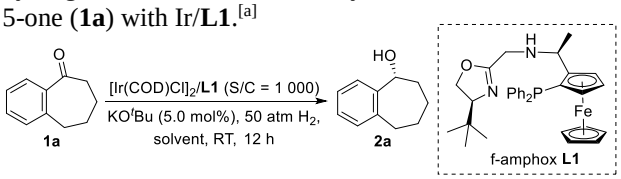
five to seven-membered cyclic ketones, preparing a series of chiral benzo-fused cyclic alcohols with excellent results (Scheme 1, 75%-99% yields and 93%->99% ee, up to 297 000 TON).



Scheme 1. Ir-catalyzed asymmetric hydrogenation of benzo-fused five to seven-membered cyclic ketones.

Our initial study was carried out by investigating solvent effect for this asymmetric hydrogenation using benzo-fused seven-membered cyclic ketone 6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-one **1a** as a model substrate at room temperature with the catalyst generated *in situ* by mixing $[Ir(COD)Cl]_2$ with ligand **L1** (S/C = 1 000) in ^{i}PrOH (Table 1). The reaction proceeded well and gave excellent results in ^{i}PrOH, PhMe, THF (tetrahydrofuran), 1,4-dioxane and hexane (>99% conversions, 91%-92% ee, Table 1, entries 3, 5, 7, 9, 11). 78% conversion and 87% ee were observed in CH_2Cl_2 (Table 1, entry 4). Poor conversions and moderate enantioselectivities were observed in EtOH and $ClCH_2CH_2Cl$ (10%-13% conversions, 60%-73% ee, Table 1, entries 2, 6). Trace conversion or no reaction was observed in MeOH, $CHCl_3$ and CF_3CH_2OH (Table 1, entries 1, 8, 10).

Table 1. Screening solvents for the asymmetric hydrogenation of 6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-one (**1a**) with Ir/**L1**.[a]

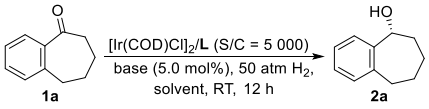


entry	solvent	conv. (%)[b]	ee (%)[c]
1	MeOH	trace	NA
2	EtOH	13	60
3	^{i}PrOH	>99	92
4	CH_2Cl_2	78	87
5	PhMe	>99	92
6	$ClCH_2CH_2Cl$	10	73
7	THF	>99	91
8	$CHCl_3$	NR	NA
9	1,4-dioxane	>99	92
10	CF_3CH_2OH	trace	NA
11	hexane	>99	92

[a] Reaction conditions: 0.2 mmol **1a**, 0.0001 mmol $[Ir(COD)Cl]_2$, 0.00021 mmol ligand **L1**, 1.0 mL solvent, KO^{t}Bu (5.0 mol%). The catalyst was pre-complexed in ^{i}PrOH (0.1 mL for each reaction vial). Configuration of **2a** was determined by comparing the optical rotation data with reported in the literature. [2b] NR = no reaction, NA = not available.
[b] Determined by ^{1}H NMR analysis.
[c] Determined by HPLC analysis.

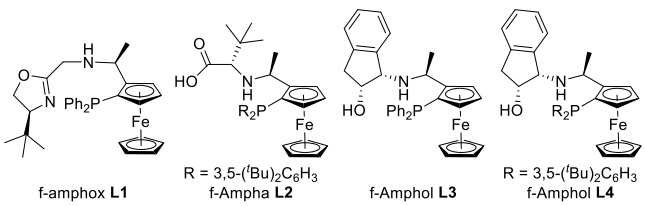
Subsequently, the ratio of substrate/catalyst loading was increased from 1 000 to 5 000 for further screening solvents for the asymmetric hydrogenation of benzo-fused seven-membered cyclic ketone 6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-one **1a** in the presence Ir/f-amphox **L1** catalyst and KO^{t}Bu. The reaction can proceed smoothly with excellent results in ^{i}PrOH, PhMe, THF, hexane and 1,4-dioxane (97%->99% conversions, 91%-93% ee, Table 2, entries 1-5). ^{i}PrOH was the best choice as the reaction solvent (>99% conversion, 93% ee, Table 2, entry 1). This Ir-catalyzed asymmetric hydrogenation was then studied with different ligands (**L1**, **L2** and **L3**) in ^{i}PrOH with KO^{t}Bu as the base. The ligand **L3** gave the best result with >99% conversion and 95% ee (Table 2, entry 7). Different bases were then screened for this Ir/**L3**-catalyzed asymmetric hydrogenation (seeing the Supporting Information), and NaO^{t}Bu was found to be the best base with >99% conversion and 98% ee (Table 2, entry 8). To our delight, the ligand **L4** with 3,5-di-tert-butylphenyl group provided better enantioselectivity (>99% conversion, >99% ee, Table 2, entry 9). The same result was obtained when the amount of NaO^{t}Bu was decreased from 5.0 mol% to 1.0 mol% (Table 2, entry 10).

Table 2. Optimization conditions for Ir-catalyzed asymmetric hydrogenation of 6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-one (**1a**).[a]



entry	ligand	solvent	base	conv. (%)[b]	ee (%)[c]
1	**L1**	^{i}PrOH	KO^{t}Bu	>99	93
2	**L1**	PhMe	KO^{t}Bu	97	91
3	**L1**	THF	KO^{t}Bu	>99	92
4	**L1**	hexane	KO^{t}Bu	>99	92
5	**L1**	1,4-dioxane	KO^{t}Bu	>99	92
6	**L2**	^{i}PrOH	KO^{t}Bu	73	93
7	**L3**	^{i}PrOH	KO^{t}Bu	>99	95
8	**L3**	^{i}PrOH	NaO^{t}Bu	>99	98
9	**L4**	^{i}PrOH	NaO^{t}Bu	>99	>99
10[d]	**L4**	^{i}PrOH	NaO^{t}Bu	>99	>99

[a] Reaction conditions: 1.0 mmol **1a**, 0.0001 mmol $[Ir(COD)Cl]_2$, 0.00021 mmol ligand, 1.0 mL solvent, base (5.0 mol%). The catalyst was pre-complexed in ^{i}PrOH (0.1 mL for each reaction vial).
[b] Determined by ^{1}H NMR analysis.
[c] Determined by HPLC analysis.
[d] NaO^{t}Bu (1.0 mol%).



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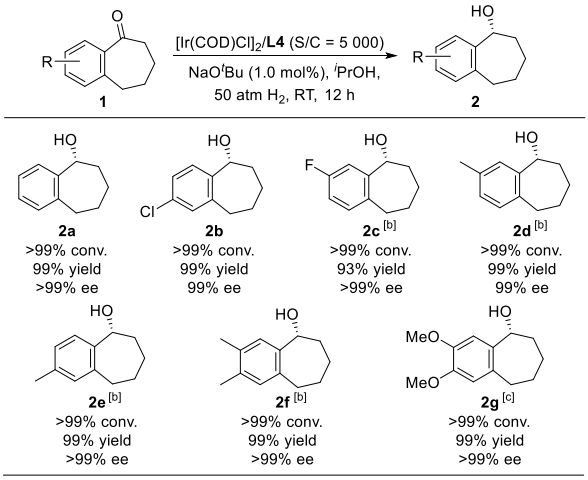
Under the optimal reaction conditions, a series of benzo-fused seven-membered cyclic ketones was hydrogenated to inspect the substrate generality. These results were summarized in Table 3. Various benzo-fused seven-membered cyclic ketones proceeded well to afford the corresponding chiral benzo-fused seven-membered cyclic alcohols (**2a-2g**) with full conversions, high yields and excellent enantioselectivities (>99% conversions, 93%-99% yields and 99%->99% ee). We found that the position and electronic property of the substituents on the phenyl ring have a little influence on this reaction. The electron-donating substituent groups (**1d-1g**) on the phenyl ring displayed relatively lower reactivity, which need a little higher catalyst loading (0.1 mol%-0.4 mol%) to give full conversion.

Table 3. Scope study for Ir/f-Amphol **L4**-catalyzed asymmetric hydrogenation of benzo-fused seven-membered cyclic ketones.[a]



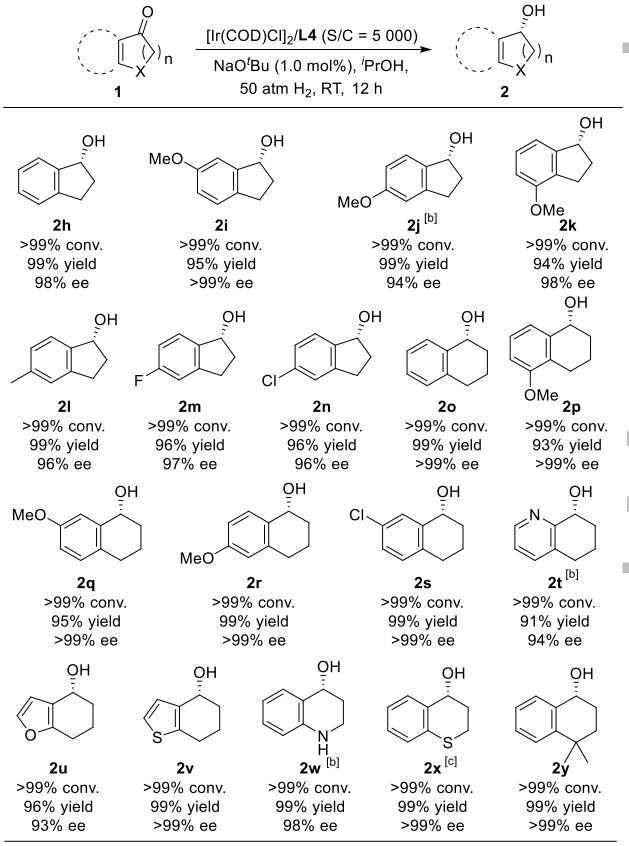
[a] Reaction conditions: 1.0 mmol substrate, 0.0001 mmol $[Ir(COD)Cl]_2$, 0.00021 mmol ligand, NaO^{t}Bu (1.0 mol%), 1.0 mL ^{i}PrOH. The catalyst was pre-complexed in ^{i}PrOH. Conversion was determined by ^{1}H NMR analysis, yield reported is the isolated yield, ee was determined by HPLC analysis.

[b] S/C = 1 000, 0.2 mmol substrate, 0.0001 mmol $[Ir(COD)Cl]_2$, 0.00021 mmol ligand, NaO^{t}Bu (1.0 mol%), 1.0 mL ^{i}PrOH.

[c] S/C = 250, NaO^{t}Bu (5.0 mol%), 0.2 mmol substrate, 0.0004 mmol $[Ir(COD)Cl]_2$, 0.00084 mmol ligand, 1.0 mL ^{i}PrOH.

Encouraged by these excellent results, we turned our attention to investigate the asymmetric hydrogenation of benzo-fused five/six-membered cyclic ketones. As shown in Table 4, various benzo-fused five/six-membered cyclic ketones were hydrogenated smoothly, affording the corresponding chiral alcohols with excellent results (>99% conversions, 91%-99% yields and 93%->99% ee). The ring size of substrates have little effect on the reactivity and enantioselectivity. The benzo-fused five or six-membered cyclic ketones substrates with electron-donating (**1i-1l**, **1p-1r**) or electron-withdrawing (**1m-1n**, **1s**) substituent groups on the phenyl ring performed well in this transformation. The challenging hetero-aromatic substrates **1t**, **1u** and **1v** worked smoothly to prepare hydrogenation products with >99% conversion, 91%-99% yields and 93%->99% ee. Other benzo-fused six-membered cyclic ketones substrates, such as 2,3-dihydroquinolin-4(1*H*)-one **1w**, thiochroman-4-one **1x**, 4,4-dimethyl-3,4-dihydronaphthalen-1(2*H*)-one **1y** were also hydrogenated successfully with >99% conversions, 99% yields and 98%->99% ee. It is worth noting that the hydrogenation product **2h** is the important intermediate for the synthesis of rasagiline mesylate TVP-1012.[1b]

Table 4. Scope study for Ir/f-Amphol **L4**-catalyzed the asymmetric hydrogenation of benzo-fused five/six-membered cyclic ketones.[a]



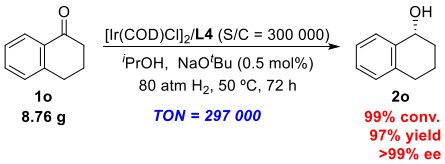
[a] Reaction conditions: 1.0 mmol substrate, 0.0001 mmol $[Ir(COD)Cl]_2$, 0.00021 mmol ligand, 1.0 mL ^{i}PrOH, NaO^{t}Bu (1.0 mol%). The catalyst was pre-complexed in ^{i}PrOH. Conversion was determined by ^{1}H NMR analysis, yield reported is the isolated yield, ee was determined by HPLC analysis.

[b] S/C = 500, NaO^{t}Bu (5 mol%), 0.2 mmol substrate, 0.0002 mmol $[Ir(COD)Cl]_2$, 0.00042 mmol ligand, 1.0 mL ^{i}PrOH.

[c] S/C = 1 000, 0.2 mmol substrate, 0.0001 mmol $[Ir(COD)Cl]_2$, 0.00021 mmol ligand, 1.0 mL ^{i}PrOH.

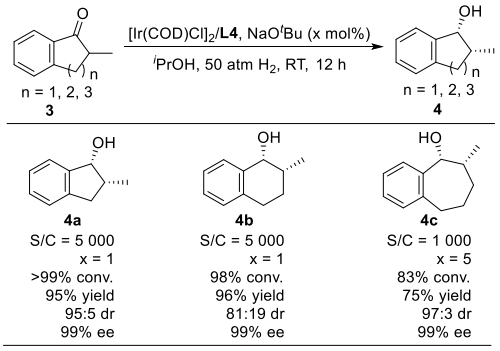
The gram-scale asymmetric hydrogenation of benzo-fused six-membered cyclic ketone 3,4-dihydronaphthalen-1(2*H*)-one **1o** performed smoothly with S/C = 300 000, affording the product (*R*)-1,2,3,4-tetrahydronaphthalen-1-ol **2o** with 99% conversion, 97% yield and >99% ee (up to 297 000

TON, Scheme 2). It displayed that our Ir/f-Amphol **L4** catalytic system owned extremely high activity in this asymmetric hydrogenation.



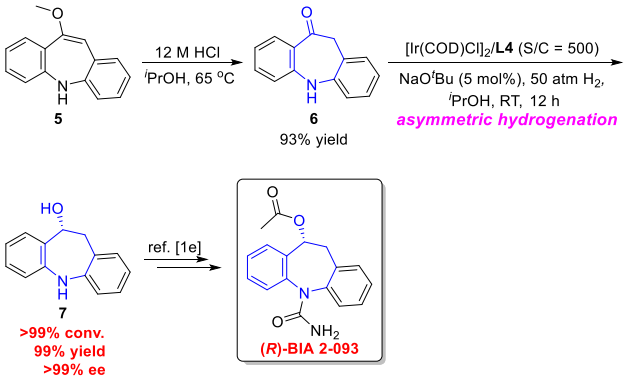
Scheme 2. Gram-scale asymmetric hydrogenation of benzo-fused six-membered cyclic ketone 3,4-dihydronaphthalen-1(2*H*)-one **1o** with high TON.

In addition, racemic α-substituted benzo-fused five to seven-membered cyclic ketones were investigated, which involved dynamic kinetic resolution process.[2a, 2j, 6g, 10] As shown in Scheme 3, racemic α-methyl substituted benzo-fused five/six-membered cyclic ketones (**3a**-**3b**) worked well, providing the hydrogenation products (**4a**-**4b**) with high conversions, excellent enantioselectivities and good to excellent diastereoselectivities (98%->99% conversions, 95%-96% yields, 99% ee, 81:19-95:5 dr). Although racemic α-methyl substituted benzo-fused seven-membered cyclic ketone (**3c**) provided lower conversion, excellent diastereo-/enantioselectivity was obtained (83% conversion, 75% yield, 99% ee, 97:3 dr).



Scheme 3. The asymmetric hydrogenation of racemic α-methyl substituted benzo-fused five to seven-membered cyclic ketones.

This Ir/f-amphol **L4**-catalyzed asymmetric hydrogenation of benzo-fused cyclic ketones can be applied to construct some important intermediates of biologically active compounds. As shown in Scheme 4, the benzo-fused seven-membered cyclic ketone 5,11-dihydro-10H-dibenzo[*b*, *f*]azepin-10-one **6** was easily obtained with 93% yield,[1e] which went through highly efficient asymmetric hydrogenation in the presence of 0.2 mol% (S/C = 500) Ir/f-amphol **L4** catalyst. The chiral alcohol product **7** was obtained with full conversion, 99% yield and >99% ee, which is the key intermediate of the enantiomer of an anticonvulsant drug eslicarbazepine acetate (BIA 2-093).[1e]



Scheme 4. Synthetic application for the preparation of key intermediate of (*R*)-BIA 2-093.

In summary, we successfully developed the Ir/f-amphol **L4**-catalyzed asymmetric hydrogenation of a series of benzo-fused five to seven-membered cyclic ketones to prepare the corresponding chiral alcohols with high yields and excellent enantioselectivities (75%-99% yields and 93%->99% ee, up to 297 000 TON). In addition, our Ir/f-Amphol **L4**-catalyzed asymmetric hydrogenation of benzo-fused cyclic ketones can be applied to provide the key intermediate for the synthesis of the enantiomer of an anticonvulsant drug eslicarbazepine acetate (BIA 2-093) with excellent result (full conversion, 99% yield and >99% ee).

Experimental Section

General procedure for the asymmetric hydrogenation with S/C = 5 000: To a 4.0 mL vial was added the metal precursor $[Ir(COD)Cl]_2$ (1.4 mg, 2.0×10^{-3} mmol), ligand **L4** (3.4 mg, 4.2×10^{-3} mmol) and anhydrous ^{i}PrOH (2.0 mL) in the argon-filled glovebox. The mixture was stirred for 2.0 h at 25 °C giving an orange solution. Then 1.0 mmol of benzo-fused cyclic ketones were added into a 5.0 mL hydrogenation vessel. Dissolve NaO^{t}Bu (1.0 mg, 0.01 mmol) in 1.0 mL anhydrous ^{i}PrOH was added and a solution of Ir/f-amphol **L4** in anhydrous ^{i}PrOH (100 μL) was added *via* an injection port. Then the vessel was placed in an autoclave, closed it and moved it out from glovebox. The autoclave quickly purged with hydrogen gas for three times, then pressurized to 50 atm H_2. The reaction solution was stirred at room temperature (25 °C-30 °C) until for 12 h, then released pressure carefully. The solution of reaction mixture was purified by a flash chromatography on a silica gel with ethyl acetate and the solvent was removed under reduced pressure. The ee value was determined by chiral HPLC analysis of the hydrogenation product chiral benzo-fused cyclic alcohols directly.

Acknowledgements

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