# Ir-Catalyzed Asymmetric Hydrogenation of α-Alkylidene β-Lactams and Cyclobutanones

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**ABSTRACT** Chiral β-lactams and cyclobutanones are present in numerous natural and pharmaceutical products. The stereoselective construction of chiral four-membered cyclic compounds is an ongoing challenge for the chemical community. Herein, we report a highly stereocontrolled construction of four-membered ring (mini-sized) β-lactams and cyclobutanones via an Ir/**In-BiphPHOX**-catalyzed asymmetric hydrogenation, providing the corresponding optically active four-membered ring carbonyl products bearing an α-chiral carbon center with excellent yields (up to 99%) and enantioselectivities (up to 98%) under mild reaction conditions (1.0 - 2.5 bar $H_2$ for 1.0 - 10 h). The reaction presents wide substrate scope. Diverse transformations of the catalyzed products were also conducted to show the potential utility of this protocol.

**KEYWORDS** β-lactam, cyclobutanone, iridium, phosphine-oxazoline ligand, asymmetric hydrogenation.

## Introduction

The preparation of chiral cyclic compounds is of great importance in organic synthesis. Four-membered ring compounds, such as β-lactams and cyclobutanones, are the core scaffolds in biologically active natural products and pharmaceuticals, as well as important intermediates in organic synthesis (Figure 1).[1,2] The asymmetric synthesis of these two types of four-membered ring compounds has remained a long-standing topic of interest.[2,3] Compared to other large-sized and medium-sized cyclic compounds, the construction of small, chiral four-membered cyclic compounds has not been widely reported.[2] Therefore, the development of a universal and facile method for the preparation of chiral four-membered ring appears to be more challenging but desirable.

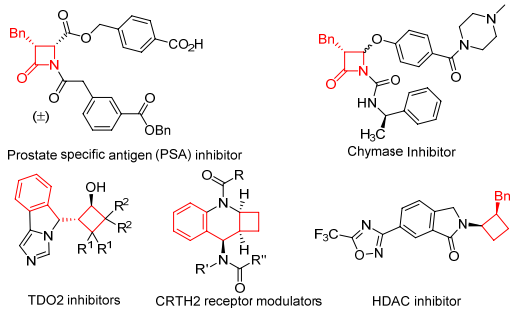
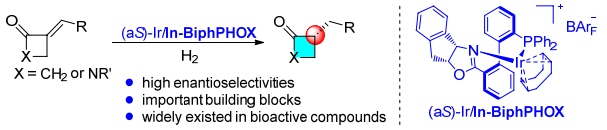



**Figure 1** Representative bioactive molecules bearing four-membered rings

Asymmetric hydrogenation has gained increasing prominence in both academic and industrial research over the past several decades due to its excellent atom economy, high levels of enantioselectivities and simplicity in operation for the construction of enantioenriched compounds.[4] All these features contribute to the method's attractiveness for the preparation of chiral four-membered rings. Unfortunately, a direct preparation of chiral four-membered rings via metal-catalyzed asymmetric hydrogenation is not yet to be described. The huge challenges originate from the control of stereochemistry due to the difficulty of being able to distinguish between the *Re* and *Si* faces when a small-sized substrate interacts with the catalyst pocket. Thus, compared to medium- or large-sized cyclic compounds, a more elegant catalyst is needed in terms of the interaction between the four-membered cyclic substrate and the catalyst.[4b,4d,4e] Since the pioneering work of the Pfaltz group,[5] Ir-catalyzed asymmetric hydrogenation has attracted much attention due to its unique efficiency for the asymmetric hydrogenation of unfunctionalized olefins and olefins bearing weakly coordinating groups.[4e,6,7] However, there is still scope to explore new complexes for the efficient asymmetric hydrogenation of four-membered cyclic substrates. Previously, our group has developed an unique class of *tropos* phosphine-oxazoline biphenyl ligands (**BiphPHOX**) which showed excellent performance in several kinds of metal-catalyzed asymmetric catalysis,[8] including Ir-catalyzed asymmetric hydrogenation.[8b-h] Bearing this in mind, we herein describe an Ir/BiphPHOX-catalyzed asymmetric hydrogenation of α-alkylidene β-lactams and cyclobutanones for the direct preparation of β-lactams and cyclobutanones bearing an α-substituted stereocenter.[9] Our *tropos* phosphine-oxazoline biphenyl ligand is essential for the preparation of the desired products with high enantioselectivities (Scheme 1).

**Scheme 1** Ir/BiphPHOX-catalyzed Asymmetric hydrogenation for synthesis of chiral four-membered rings




## Results and Discussion

Our study began with the asymmetric hydrogenation of β-lactam **1a** as a model substrate (Table 1). Firstly, different ligands were screened using *o*-xylene as the solvent (entries 1-7). Our *tropos* phosphine-oxazoline biphenyl ligand (**BiphPHOX**) bearing an indane-fused chiral oxazoline group gave the desired product with the highest ee compared to ligands bearing an *i*Pr or *t*Bu group on the oxazoline ring (entry 3 vs 1 and 2). A bulky $Ar_2P$ group on the **BiphPHOX** ligand was also evaluated but led to a reduction in enantioselectivity (entries 4 and 5). Other classic types of phosphine-oxazoline ligands with different skeletons

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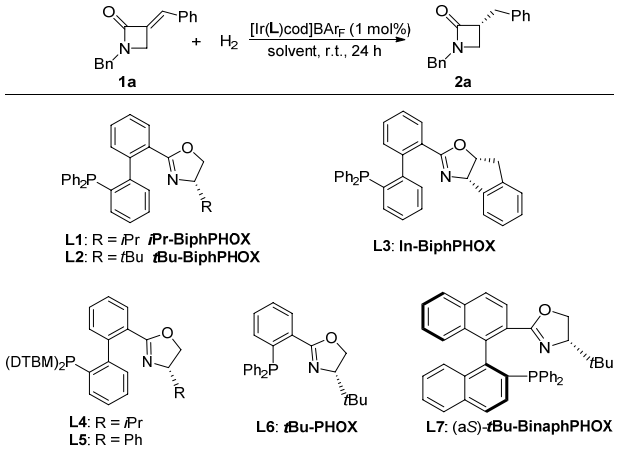
were also tested (entries 6 and 7). The **PHOX** ligand showed poor yield and enantioselectivity. The results of the reaction using an axially-fixed chiral ligand, **BinaphPHOX**,[10] showed that the presence of a binaphthyl backbone could decrease the enantioselectivity compared to chiral ligands bearing a biphenyl backbone (entry 7 vs 2). Next, the screening of different solvents showed that *o*-xylene was the best solvent for this asymmetric hydrogenation (entry 3 vs 8-10). The influence of hydrogen pressure and reaction time were also investigated. To our delight, the enantioselectivity could be improved by reducing the hydrogen pressure (entries 11 and 12), and the reaction can go to completion even within 1 h under 2.5 bar $H_2$ pressure (entry 13). We chose 2.5 bar of $H_2$ as the optimal pressure, in consideration of both conversion and enantiomeric excess (*ee*). (entry 13).

**Table 1** Screening of Reaction Conditions[a]

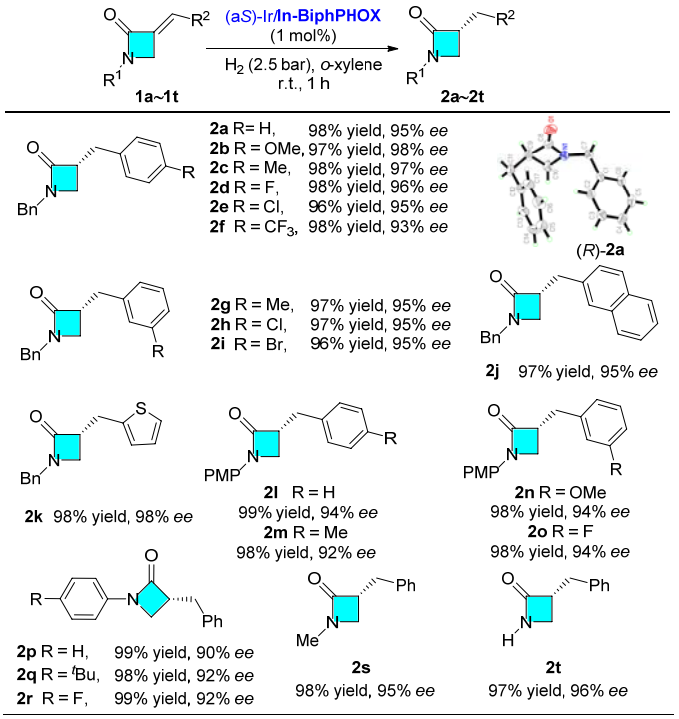



| Entry | Solvent | Ligand[b] | Conv. [%][c] | *ee* [%][d] |
|---|---|---|---|---|
| 1 | *o*-xylene | **L1** | >99 | 88 |
| 2 | *o*-xylene | **L2** | >99 | 87 |
| 3 | *o*-xylene | **L3** | >99 | 92 |
| 4 | *o*-xylene | **L4** | >99 | 42 |
| 5 | *o*-xylene | **L5** | 13 | 27 |
| 6 | *o*-xylene | **L6** | 36 | -6 |
| 7 | *o*-xylene | **L7** | >99 | 74 |
| 8 | $CH_2Cl_2$ | **L3** | >99 | 87 |
| 9 | $ClCH_2CH_2Cl$ | **L3** | >99 | 85 |
| 10 | toluene | **L3** | >99 | 91 |
| 11[e] | *o*-xylene | **L3** | >99 | 95 |
| 12[f] | *o*-xylene | **L3** | 68 | 96 |
| 13[g] | *o*-xylene | **L3** | >99 | 95 |

[a] Reaction conditions: 0.24 mmol scale, ratio of substrate/catalyst (S/C) = 100, 2 mL of solvent, 60 bar of $H_2$. [b] When **L1**~**L5** were used, the axial chirality of catalysts was (a*S*). [c] Determined by $^1$H NMR spectroscopy. [d] Enantioselectivity was determined by HPLC using a chiral column. [e] 2.5 bar of $H_2$. [f] 1 bar of $H_2$. [g] 2.5 bar of $H_2$, 1 h.

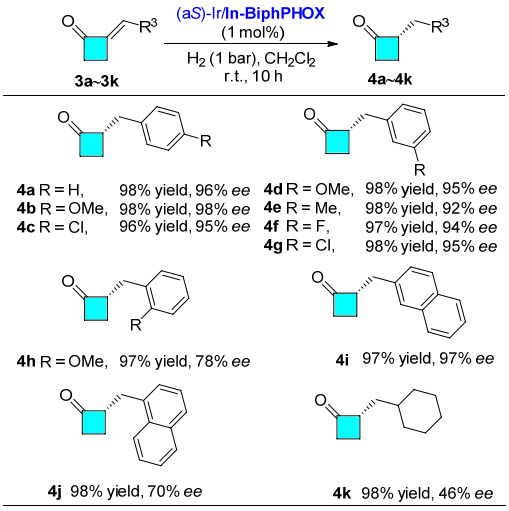
With the optimized conditions in hand, the α-alkylidene β-lactam scope was examined, as shown in Scheme 2. The results showed that α-alkylidene β-lactams bearing either electron-rich or electron-deficient aryl groups as $R^2$ gave the corresponding products in excellent yields and with good to excellent enantioselectivities (**2a**-**2i**). The best *ee* was observed with substrate **1b** bearing an electron-donating MeO group at the *para* position, while the *ee* was slightly lower for a substrate bearing an electron-withdrawing group on the benzene ring (**2f**). Furthermore, substrates possessing fused-ring aryl and heteroaryl $R^2$ groups also gave their corresponding products with excellent yields and enantioselectivities (**2j** and **2k**). The effect of *N*-substitution on this asymmetric hydrogenation was also investigated (**2l**-**2s**). Generally, the hydrogenation products for *N*-aryl substrates were obtained with slightly lower *ee*s compared to that of *N*-Bn substrates. An *N*-methyl substrate was also hydrogenated under the standard catalytic conditions, giving the desired product **2s** efficiently, with a similar *ee* to that of other substrates. A substrate without protecting group **1t** could also be hydrogenated with full conversion and 96% ee. The absolute configurations of **2a** was determined to be (*R*) by X-ray crystallographic analysis.[11]

**Scheme 2** Asymmetric hydrogenation of α-alkylidene β-lactams



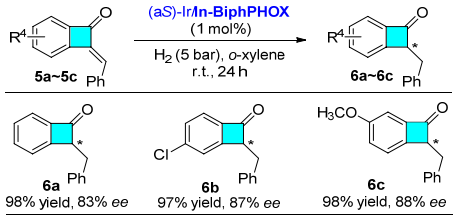

Next, α-alkylidene cyclobutanones were also subjected to our asymmetric hydrogenation conditions. In this case, the optimized conditions used dichloromethane as solvent and the reaction was carried out under 1 bar of hydrogen pressure (Scheme 3). The results show that substrates possessing either electron-donating or electron-withdrawing substituents on the benzene ring gave their corresponding products with excellent yields and enantioselectivities (**4a**-**4g**). The hydrogenation of substrate bearing a *para*-MeO group gave the desired product with the highest *ee* (**4b**, 98%). Substitution at the *ortho* position of the benzene ring had an obvious influence on the enantioselectivity (**4h**). Additionally, excellent enantioselectivity was also observed when the benzene ring was changed to a β-naphthylene ring (**4i**). However, a substrate bearing an α-naphthylene ring gave its reduced product **4j** with moderate *ee*, most likely due to steric effects similar to those observed for the hydrogenation of **3h**. Substrate **3k** bearing a cyclohexyl R group gave its corresponding product **4k** in excellent yield but with low *ee*.

**Scheme 3** Asymmetric hydrogenation of α-alkylidene cyclobutanones

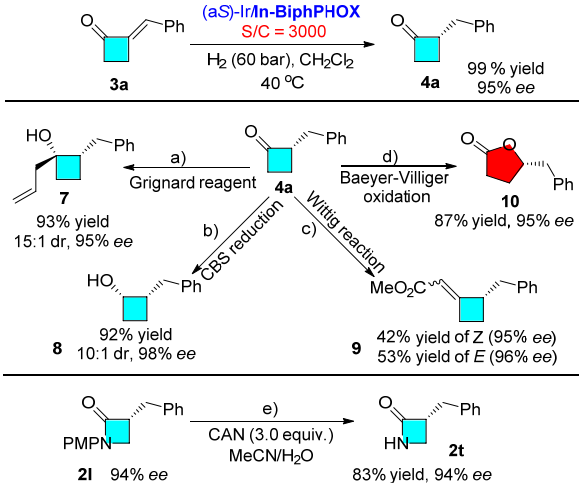



Three α-alkylidene benzo-fused cyclobutanones were also tested as substrates (Scheme 4). Under the newly optimized conditions, chiral α-substituted benzo-fused cyclobutanones could be prepared in excellent yields and with good *ee*s.

**Scheme 4** Asymmetric hydrogenation of α-alkylidene benzo-fused cyclobutanones




**Scheme 5** High S/C reaction and transformations of hydrogenated products




The asymmetric hydrogenation of **3a** could be carried out with a 3000 S/C, and afforded **4a** in 99% yield and 95% *ee* (Scheme 5). Synthetic transformations of **4a** were then performed. The addition of allylmagnesium chloride to the carbonyl group resulted in the generation of **7** in excellent yield and 15:1 dr (Scheme 5, a). Compound **8** can be prepared in high yield and with good diastereoselectivity via the CBS reduction of the carbonyl group of **4a** (Scheme 5, b). A Wittig reaction successfully introduced a C=C double bond at the carbonyl position with no loss in *ee* (Scheme 5, c). The Baeyer-Villiger oxidation of **4a** gave a chiral γ-lactone in 87% yield with no reduction in *ee* (Scheme 5, d). Finally, the protecting group PMP could be removed using CAN, giving compound **2t** in good yield and with the same *ee* as compound **2l** (Scheme 5, e).

## Conclusions

In summary, we have developed a highly efficient asymmetric hydrogenation of α-alkylidene β-lactams and cyclobutanones using the Ir complex of our axially-unfixed biphenyl phosphine-oxazoline ligand as a catalyst. A relatively wide substrate scope of these two classes of substrates are compatible with our reaction conditions. Chiral α-substituted β-lactams, cyclobutanones and benzo-fused cyclobutanones could be prepared with excellent enantioselectivities (up to 98% *ee*) using our catalyst systems. Several transformations of these hydrogenation products were also conducted showing the potential utility of this protocol.

## Experimental

The catalyst (4.0 mg, 0.0024 mmol, 0.01 equiv.) and substrate **1a** (0.24 mmol, 1.0 equiv.) were placed in a 5-mL tube equipped with a magnetic stirrer bar. This tube was then placed into a nitrogen-filled autoclave. Solvent (2.0 mL) was added to the mixture under nitrogen atmosphere. The autoclave was then closed, purged three times with hydrogen (less than the pressure needed), and finally pressurized to 2.5 bar. The reaction mixture was stirred at r.t. for 1.0 h, and the hydrogen gas was slowly released. The conversion of the product was determined by $^1$H NMR spectroscopic analysis of the crude reaction mixture and the product was isolated by chromatography. The ee was determined by chiral HPLC. (*R*)-1,3-Dibenzylazetidin-2-one (**2a**). White solid, m.p. = 30.2 – 31.4 °C. 98% yield. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.17 (m, 8H), 7.04 – 6.97 (m, 2H), 4.44 (d, *J* = 15.2 Hz, 1H), 4.19 (d, *J* = 15.2 Hz, 1H), 3.53 – 3.48 (m, 1H), 3.19 – 3.16 (m, 1H), 3.10 (dd, *J* = 14.4, 4.8 Hz, 1H), 2.98 – 2.93 (m, 1H), 2.89 (dd, *J* = 5.6, 2.4 Hz, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 169.7, 138.0, 135.4, 129.0, 128.7, 128.6, 128.0, 127.5, 126.6, 50.7, 45.8, 44.0, 34.2. HRMS (ESI) calcd for $C_{17}H_{18}NO$ $(M+H)^+$: 252.1388; found: 252.1381. HPLC [DAICEL CHIRALPAK AD-H, hexane/*i*PrOH = 95/5, 210 nm, 1.0 mL/min, 25 °C. $t_{R1}$ = 18.7 min (major), $t_{R2}$ = 17.4 min (minor)]; ee = 95%. $[\alpha]^{25}_D$ = –54.65 (c = 0.63, $CHCl_3$).

## Supporting Information

The supporting information for this article is available on the WWW under https://doi.org/10.1002/cjoc.2018xxxxx.

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[11] CCDC [1559211] for (*R*)-**2a,** CCDC [1559212] for (*R*)-**2r,** which contain the supplementary crystallographic data for this paper. Data are provided free of charge by The Cambridge Crystallographic Data Centre.

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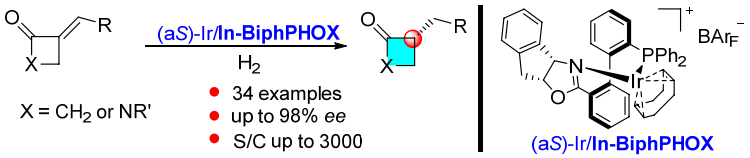


Jingzhao Xia, Yu Nie, Guoqiang Yang, Yangang Liu, Ilya D. Gridnev, Wanbin Zhang*

An asymmetric hydrogenation of α-alkylidene β-lactams and cyclobutanones was developed using the Ir complex of an axially-unfixed biphenyl phosphine-oxazoline ligand as a catalyst. The desired optically active four-membered ring carbonyl compounds were obtained with excellent enantioselectivities.