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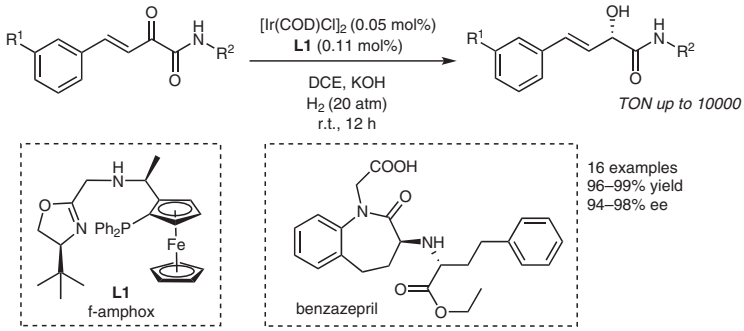
Iridium/f-Amphox-Catalyzed Asymmetric Hydrogenation of Styrylglyoxylamides

Simin Wang[a]
Yuena Yu[a]
Jialin Wen[*a,b]
Xumu Zhang[*a,c]

[a] Department of Chemistry, Southern University of Science and Technology, 1088 Xueyuan Road, Shenzhen, 518055, P. R. of China
wenjl@sustc.edu.cn
zhangxm@sustc.edu.cn
[b] Academy for Interdisciplinary Studies, Southern University of Science and Technology, 1088 Xueyuan Road, Shenzhen, 518055, P. R. of China
[c] Shenzhen Grubbs Institute, Southern University of Science and Technology, 1088 Xueyuan Road, Shenzhen, 518055, P. R. of China



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Abstract We report an iridium-catalyzed asymmetric hydrogenation reaction for the preparation of chiral homophenylalanine derivatives. Catalyzed by an iridium/f-amphox complex, the asymmetric hydrogenation of styrylglyoxylamides was conducted smoothly with turnover numbers of up to 10,000 and up to 98% ee. This method was successfully applied in a synthesis of a fragment of benazepril, a drug used for the treatment of high blood pressure.

Key words homophenylalanines, asymmetric catalysis, iridium catalysis, hydrogenation, benazepril

The last two decades have witnessed the widespread application of inhibitors of angiotensin-converting enzyme (ACE).[1] Most ACE inhibitors with therapeutic significance contain a common unit: L-homophenylalanine. This family of building blocks is found in numerous chiral bioactive molecules (Figure 1),[2] including some successful drugs such as ramipril and benazepril. Many efforts have been made to develop a reliable and economical method for preparing optically pure homophenylalanine and its derivatives.[3] Compared with heterogeneous systems,[4] which have advantages in terms of catalyst cost and robustness, homogeneous catalytic hydrogenation have other advantages, such as a high turnover efficiency and a high enantioselectivity (>95% ee). Although chiral amino acids are readily prepared by using the Wilkinson–Osborn Rh/bisphosphine system, cases with a high turnover number (TON) in excess of 10,000 are rare.[5] To develop an efficient approach to optically pure homophenylalanine derivatives, new synthetic methods are still in demand.

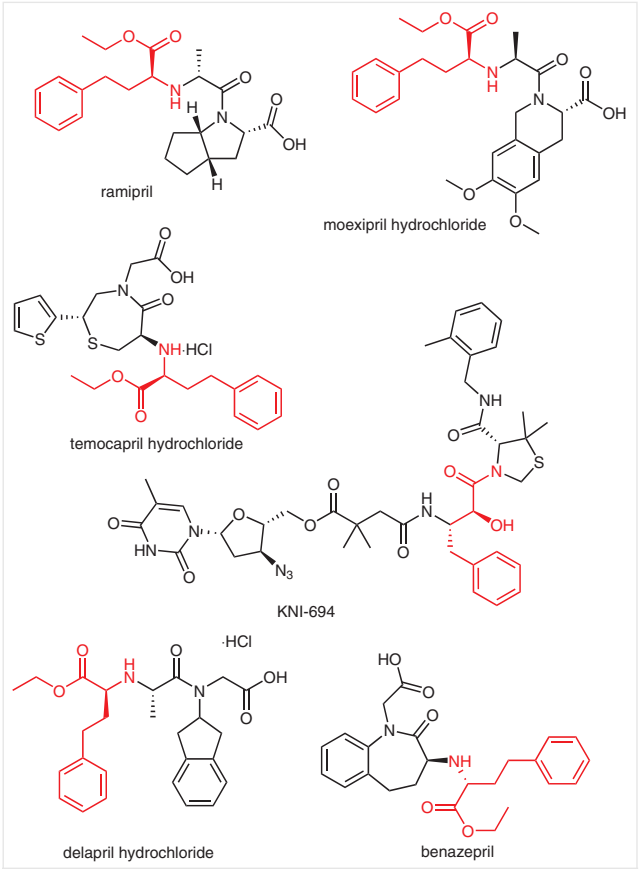
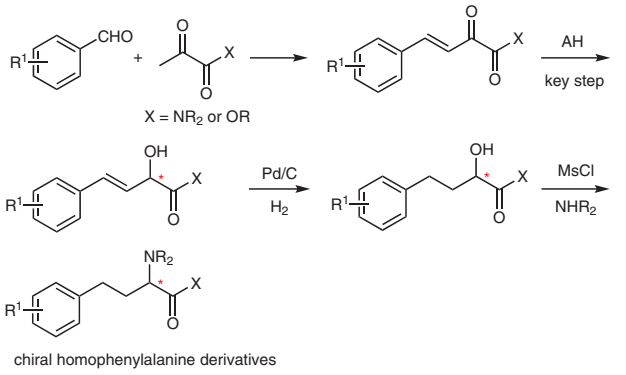


Figure 1 Bioactive molecules containing a homophenylalanine unit

As part of our continuing interest in applying transition-metal-catalyzed asymmetric hydrogenation (AH) in the preparation of chiral molecules, we attempted to design

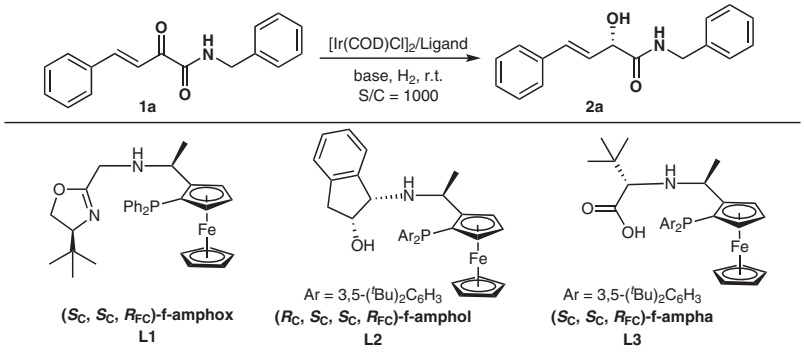


Scheme 1 Synthetic route to chiral homophenylalanine derivatives

a practical synthetic route to chiral homophenylalanine derivatives (Scheme 1). As hydrogenation substrates, styrylglyoxylic acid derivatives can be readily obtained by aldol condensation. The resulting chiral alcohols can be transformed into the desired amino acids in two steps with inversion of the chiral center. The challenges in the hydrogenation step lies in both its chemoselectivity and its enantioselectivity: selective 1,2-reduction of conjugated ketone and differentiation between the vinyl and the carboxy group must be achieved in a single step.

We recently developed a series of ferrocene-based tridentate ligand for Ir-catalyzed AH: f-amphox (**L1**),[6] f-amphol (**L2**),[7] and f-ampha (**L3**).[8] This family of ligands showed excellent reactivities and stereoselectivities in AH of simple and functionalized ketones. In these successful examples of ketone reduction reactions, an NH effect was proposed to be responsible for the high TON with such polarized double bonds as carbonyl.[9] We surmised that the polar C=O bond in a styrylglyoxylamide might be reduced in the presence of an iridium complex, with retention of the C=C bond.

Table 1 Optimization of the Asymmetric Hydrogenation of **1a**[a]

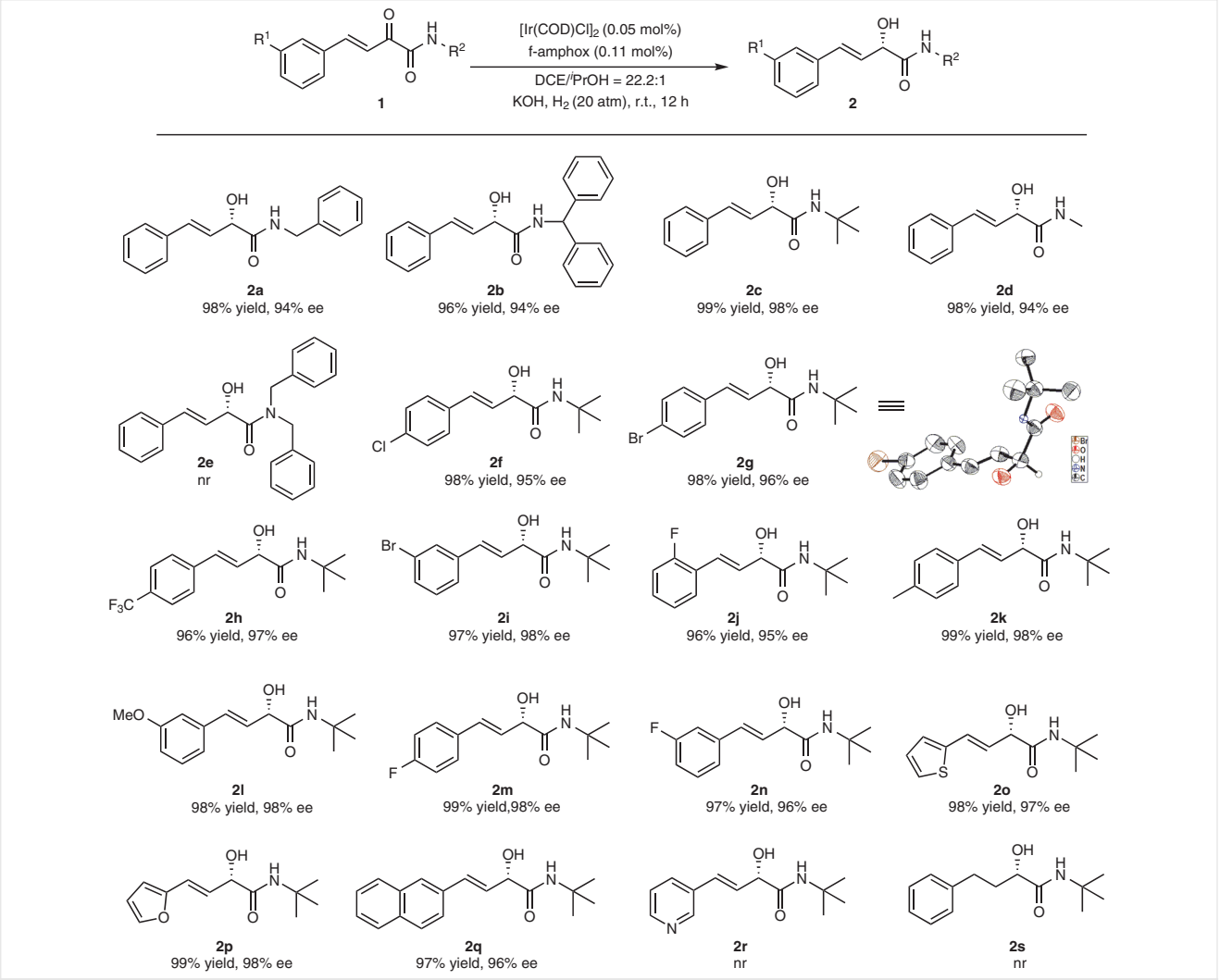


Entry	Ligand	Solvent	Base	Conversion[b] (%)	ee[c] (%)
1	**L1**	*i*-PrOH	*t*-BuOK	99	92
2	**L2**	*i*-PrOH	*t*-BuOK	trace	ND[d]
3	**L3**	*i*-PrOH	*t*-BuOK	trace	ND
4	**L1**	toluene	*t*-BuOK	99	89
5	**L1**	CH_2Cl_2	*t*-BuOK	99	82
6	**L1**	THF	*t*-BuOK	99	85
7	**L1**	F_3CCH_2OH	*t*-BuOK	NR[e]	ND
8	**L1**	EtOH	*t*-BuOK	55	83
9	**L1**	DCE	*t*-BuOK	99	94
10	**L1**	DCE	*t*-BuONa	99	79
11	**L1**	DCE	MeONa	77	92
12	**L1**	DCE	Cs_2CO_3	81	91
13	**L1**	DCE	KOH	99	94
14	**L1**	DCE	MeOK	91	90
15[f]	**L1**	DCE	KOH	99	94

[a] Reaction conditions: **1a** (0.1 mmol), $[Ir(COD)Cl]_2$ (0.05 mol%), ligand (0.11 mol%), solvent (1 mL), H_2 (50 atm), 12 h.
[b] Determined by ^1H NMR analysis.
[c] Determined by HPLC analysis.
[d] ND = not determined.
[e] NR = no reaction.
[f] 20 atm.

We commenced our study by testing the reactivity of these tridentate ligands in Ir-catalyzed AH of *N*-benzyl-2-hydroxy-4-phenylbut-3-enamide (**1a**). The reaction was carried out at room temperature in *i*-PrOH in the presence *t*-BuOK and an iridium catalyst generated in situ by mixing $[Ir(COD)Cl]_2$ with **L1**–**L3** [substrate/catalyst ratio (S/C) = 1000] (Table 1). Although iridium complexes of these three ligands are all excellent catalysts for AH of acetophenone, their performances in this case were totally different. It was interesting to find that f-amphol and f-ampha lacked activity (Table 1, entries 2 and 3), whereas f-amphox showed a high enantioselectivity (92% ee) with full conversion in the AH of the model substrate (entry 1). Careful screening of the solvent revealed that this reaction proceeded smoothly in DCE with a high conversion and high enantioselectivity (entries 4–9). Further evaluation of various bases were carried out in an attempt to improve the enantioinduction with **L1** as the ligand. Whereas sodium and cesium bases produced slightly lower enantioselectivities, potassium bases (*t*-BuOK and KOH) emerged as better choices (entries 10 and 14), providing higher enantioselectivities (94% ee) and conversions (99%). When we reduced the hydrogenation pressure from 50 to 20 atm (entry 15), no significant change occurred in the conversion or the ee.

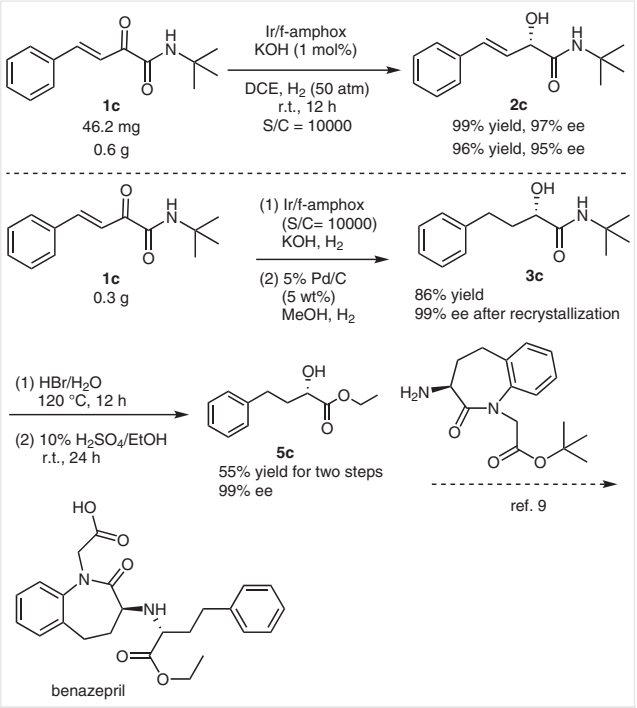
With the optimal reaction conditions (Table 1, entry 15) in hand, we investigated the substrate scope of this asymmetric hydrogenation of styrylglyoxylamides. A wide range of substrates were investigated. In general, the AH reactions proceeded smoothly to afford the desired chiral α-hydroxy β-enamides in excellent yields and high enantiomeric ex-



Scheme 2 Scope study for the asymmetric hydrogenation of α-keto amides **1** with Ir/f-amphox *Reaction conditions*: **1** (0.2 mmol), $[Ir(COD)Cl]_2$ (0.05 mol%), ligand **L1** (0.11 mol%), DCE (2 mL), *i*-PrOH (90 μL), r.t., 12 h. Isolated yields are reported, and the ee values were determined by HPLC analysis. The absolute configuration of **2c** was determined by comparing its optical rotation with that reported in the literature.[10] The structure of **2g** was confirmed by single-crystal X-ray diffraction analysis.[11]

cesses (Scheme 2). Various secondary amides **1a–d** were investigated, and the *tert*-butyl amide **1c** was found to give the corresponding chiral alcohol **2c** with excellent selectivity (99% yield, 98% ee). Tertiary amide **1e**, however, was not hydrogenated under these conditions. Substrates containing *para*-, *ortho*-, or *meta*-substituents with various electronic effects on the benzene ring provided hydrogenated products with satisfactory yields and enantioselectivities. Gratifyingly, substrates containing heterocycles such as thiophene or furan also reacted smoothly (**2o**: 98% yield, 97% ee; **2p**: 99% yield, 98% ee). Regrettably, pyridylvinyl and alkyl substrates did not react smoothly under these conditions (**2r** and **2s**).

To demonstrate a synthetic application of this method, a scaled-up reaction of **1c** was conducted and **2c** was obtained in 96% yield and 95% ee (Scheme 3). In accordance with the high efficiency in the previously reported Ir/f-amphox catalyzed AH of ketones, the turnover number in the case was up to 10,000 with a low loading of base (1 mol% KOH) under 50 atm of H_2 at 25 °C.



Scheme 3 Scaled-up AH of a styrylglyoxylamide and a practical synthetic route to benazepril

Transformations of the chiral alcohol **2c** were performed. A Pd/C-catalyzed reduction of the C=C double bond was conducted with the crude AH reaction mixture to give chiral α-hydroxybutamide **3c** in 86% yield and 99% ee after crystallization. Hydrolysis with aqueous HBr and sequential esterification gave ethyl (2*S*)-2-hydroxy-4-phenylbutanoate (**5c**), with retention of the chirality at the C-2 position. Benazepril can be readily prepared from the α-hydroxy ester **5c** by a known method[12] (Scheme 2).

In summary, we have developed a straightforward method for preparing chiral 2-hydroxy-4-phenylbutanoic acid derivatives by using an AH strategy.[13] Styrylglyoxylamides can be efficiently hydrogenated with high chemoselectivity and high enantioselectivity in the presence of an Ir/f-amphox complex catalyst. We believe that this method will benefit the synthesis community in facilitating the preparation of chiral homophenylalanine derivatives. The presence of the homophenylalanine unit in many drugs, such as benazepril and ramipril, highlights the potential industrial applications of this method.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1609623.

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(11) CCDC 1862847 contains the supplementary crystallographic data for compound **2g**. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/getstructures.

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(13) **Asymmetric Hydrogenation of Styrylglyoxylamides 1a–r; General Procedure**

In an argon-filled glove box, a 10 mL vial was charged with $[Ir(COD)Cl]_2$ (4.0 mg, 5.9×10^{-3} mmol), f-amphox (7.3 mg, 13.1×10^{-3} mmol), and anhyd *i*-PrOH (3 mL). The mixture was stirred for 2 h at 25 °C to give an orange-red solution. The resulting solution (50 μL, $c = 4 \times 10^{-3}$ mmol/mL) and a solution of KOH in *i*-PrOH (40 μL, $c = 0.05$ mmol/mL) were transferred by a syringe into a 5 mL vial charged with the appropriate α-keto β-enamide (0.2 mmol) in DCE (2 mL). The vial was transferred to an autoclave, which was then charged with 20 atm of H_2 and the mixture was stirred at r.t. for 12 h. The hydrogen gas was released slowly in a well-ventilated hood, and the solution was passed through a short column of silica gel to remove the metal complex. The product was analyzed by ^{1}H NMR for conversion, and the ee was determined by HPLC.

(14) **(*S*,3*E*)-*N*-(*tert*-Butyl)-2-hydroxy-4-phenylbut-3-enamide (2c)**

White solid; yield: 46 mg (99%; conversion: 99%; 98% ee); mp 71–74 °C; $[\alpha]_D^{24}$ –7.8 (*c* 0.5, MeOH). HPLC: Chiracel AD-3 column [254 nm, 25 °C, hexane–*i*-PrOH (80:20); flow: 1.0 mL/min]; $t_R^1 = 4.0$ min, $t_R^2 = 4.4$ min. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.29 (m, 2 H), 7.25 (dd, *J* = 9.9, 4.7 Hz, 2 H), 7.21–7.15 (m, 1 H), 6.65 (d, *J* = 15.9 Hz, 1 H), 6.18 (dd, *J* = 15.9, 7.0 Hz, 1 H), 5.97 (s, 1 H), 4.51 (d, *J* = 6.9 Hz, 1 H), 3.52 (s, 1 H), 1.29 (s, 9 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.5, 136.3, 132.6, 128.6, 128.0, 127.4, 126.8, 73.0, 51.4, 28.8. HRMS-ESI: *m/z* $[M + Na]^+$ calcd for $C_{14}H_{19}NNaO_2$: 256.1305; Found: 256.1308.