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Ir-catalyzed Asymmetric Hydrogenation of α-Imino Esters with Chiral Ferrocenylphosphine-Phosphoramidite Ligands

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Abstract. An Ir-catalyzed asymmetric hydrogenation of α-imino esters with unsymmetrical hybrid chiral ferrocenylphosphine-phosphoramidite ligands for the synthesis of optically active α-aryl glycines has been described. The result indicated that the presence of the iodo-substitutent at the 3/3'-position of the binaphthyl unit of ligand could significantly improve the catalytic performance. This method features high asymmetric induction and reasonable functional group tolerance, thus providing a concise and efficient approach toward chiral α-aryl glycine derivatives with up to 96% ee.

Keywords: hydrogenation; asymmetric catalysis; iridium; α-iminoester; chiral phosphine-phosphoramidite ligand

Enantiomerically enriched α-amino acids and their derivatives are vitally important intermediates for chemical, pharmaceutical and biological syntheses,[1,2] which play crucial roles in modern protein and peptide research.[3] To satisfy the enormous demand for various optically active amino acid compounds, some highly efficient asymmetric catalytic methods[4-8]have been developed, including the catalytic enantioselective Strecker reaction,[4h,4k-l] Sharpless asymmetric amino-hydroxylation of aryl alkenes,[4j] asymmetric amination of enolate intermediates,[4m] dynamic kinetic resolution,[4n-q] asymmetric reduction of α-dehydroamino acid derivatives or α-imino esters,[5-6] asymmetric biomimetic transamination of α-keto acid derivatives,[7] and others.[8]

Among these methods, the most convenient and straightforward pathway to optically pure α-amino acid derivatives is the catalytic asymmetric hydrogenation of corresponding α-dehydroamino acid derivatives or α-imino esters. In the past decades, asymmetric hydrogenation of α-dehydroamino acid derivatives has been widely investigated,[5] affording broad ranges of α-alkyl amino acids and their derivatives in high optical purity. However, as an important category of α-amino acids, the catalytic asymmetric synthesis of chiral α-aryl glycines via the hydrogenation remains less investigated, although they have been found wide applications in the synthesis of some significant drugs such as antibacterial agents, β-lactam antibiotics, glycopeptides antibiotics and cardiovascular drugs (Figure 1).[9]

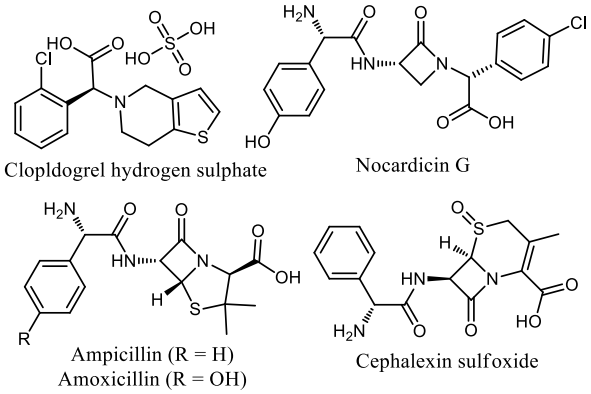
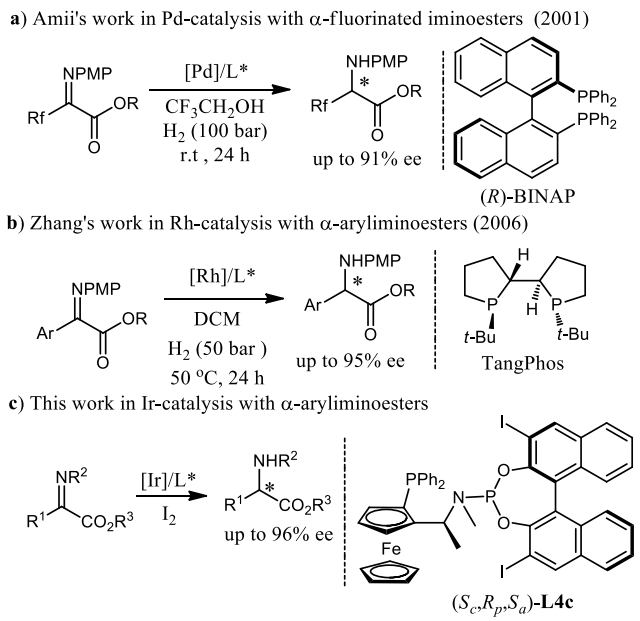


Figure 1. Practical chiral α-aryl glycine derivatives.

Owing to the lack of the β-hydrogen atom, the synthesis of these compounds via asymmetric hydrogenation of the corresponding α-dehydroamino acid derivatives is therefore impossible. An alternative access to α-aryl glycines should be the hydrogenation or transfer hydrogenation of α-imino esters with metal-based catalysts or organocatalysts. In recent years, some progress has been made in the area of organocatalysis.[6a-g] In contrast, the transition metal-catalyzed asymmetric hydrogenation of α-imino esters to prepare such compounds is still far from satisfactory (Scheme 1), presumably due to the presence of the *E*/*Z* isomers and the poor reactivity of α-imino ester substrates.[6j,6m-n] To the best of our knowledge, only two efficient catalytic systems have been developed for the asymmetric hydrogenation of α-imino esters so far. Amii and co-workers[6j] documented the enantioselective hydrogenation of α-fluorinated imino esters in 2001, but only a limited range of substrates were hydrogenated successfully. Notably, in 2006, Zhang et al.[6m] reported a highly asymmetric hydrogenation of α-aryl imino esters via

the Rh-tangphos catalyst, affording α-aryl amino esters with high ees up to 95%. In addition, Kadyrov and Börner et al. have developed a Rh-catalyzed asymmetric reductive amination of α-keto acids with benzylamine, giving chiral α-amino acids with up to 98% ee.[6k] However, only a limited number of substrates were suitable to the reaction. Therefore, the development of an efficient catalytic system that can work well for the hydrogenation of α-imino esters is highly desirable and remains a challenging task.



Scheme 1. Catalytic asymmetric synthesis of chiral aryl glycine derivatives.

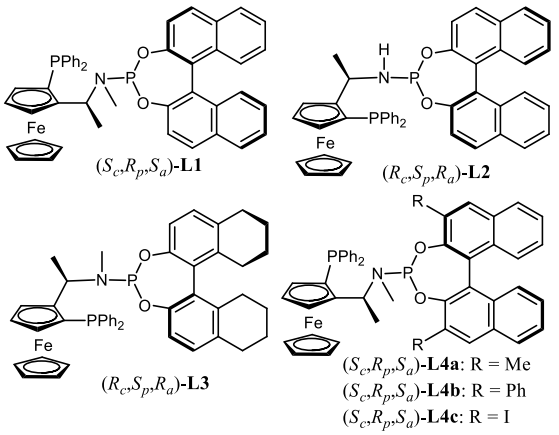
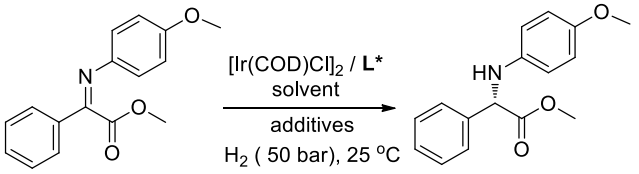


Figure 2. Unsymmetrical hybrid chiral ferrocenylphosphine-phosphoramidite ligands.

Inspired by our recent success in the use of unsymmetrical hybrid chiral phosphine-phosphoramidite ligands for various asymmetric hydrogenations,[10] in particular Ir-catalyzed asymmetric hydrogenation of sterically hindered N-arylimines,[10e] we envisioned that this kind of ligands may also be efficient to the Ir-catalyzed asymmetric hydrogenatrion of α-aryl imino esters. As a result, herein we described the first successful iridium-catalyzed enantioselective hydrogenation of α-imino esters with unsymmetrical hybrid chiral ferrocenylphosphine-phosphoramidite ligands developed within our group (Figure 2).

Table 1. Optimization of reaction conditions for the asymmetric hydrogenation of **1a**.[a]



Entry	L*	Solvent	Additive	Conv (%)[b]	ee (%)[c]
1	**L1**	THF	NIS	>99	63
2	**L2**	THF	NIS	95	57
3	**L3**	THF	NIS	>99	51
4	**L4a**	THF	NIS	>99	74
5	**L4b**	THF	NIS	43	51
6	**L4c**	THF	NIS	>99	83
7	**L4c**	DCM	NIS	>99	69
8	**L4c**	DCE	NIS	93	67
9	**L4c**	Dioxane	NIS	95	83
10	**L4c**	Toluene	NIS	94	77
11	**L4c**	THF	NCS	<10	-
12	**L4c**	THF	NBS	53	67
13	**L4c**	THF	I_2	>99	91
14	**L4c**	THF	none	<10	-
15[d]	**L4c**	THF	I_2	97	91
16[d][e]	**L4c**	THF	I_2	>99	92

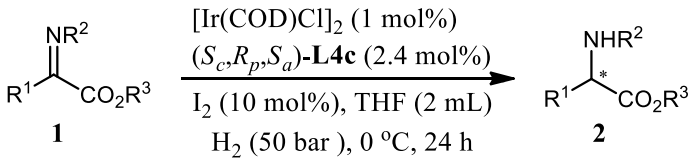
[a] Reaction conditions unless otherwise noted: **1a** (0.4 mmol), $[Ir(COD)Cl]_2$ (2 μmol), **L*** (4.8 μmol), H_2 (50 bar), solvent (2.0 mL), additives (5 mol%), 24 h, 25 ℃.
[b] Determined by GC.
[c] Determined by chiral HPLC.
[d] The reaction was carried out at 0 ℃.
[e] The reaction was performed with **1a** (0.2 mmol) and I_2 (10 mol%).
NIS = *N*-iodosuccinimide, NCS = *N*-chlorosuccinimide, NBS = *N*-bromosuccinimide.

The initial attempt used *N*-*p*-methoxyphenyl (PMP)-protected methyl imino ester **1a** as the model substrate, and the hydrogenation was conducted in THF under 50 bar of H_2 pressure at 25 ℃ with 1 mol% $[Ir(COD)Cl]_2$/**L1** as the catalyst and 5 mol% of NIS as the additive. To our delight, the reaction proceeded smoothly, giving the corresponding hydrogenation product **2a** in full conversion albeit with moderate enantioselectivity (63% ee, Table 1, entry 1). Subsequent ligand screening disclosed that the presence of an *N*-H proton in the ligand structure was not tolerated, leading to the inferior conversion and enantioselectivity (Table 1, entry 2). H_8-binaphthyl derived ligand **L3** was also tested but gave

the moderate enantioselectivity of 51% ee (Table 1, entry 3). To further improve the catalytic performance, the modification of ligand skeleton via the introduction of the substituent into the 3/3'-position of the binaphthyl unit was performed.[10a,11] To our delight, the introduction of the methyl substituent (**L4a**) significantly promoted the enantioselectivity to 74% ee (Table 1, entry 4). However, the presence of the phenyl substituent proved to be detrimental to the hydrogenation, affording 43% conversion and 51% ee (Table 1, entry 5). The best result was achieved with the iodine-modified ligand **L4c**, with which an enantioselectivity of 83% ee was obtained (Table 1, entry 6). With the optimal ligand in hand, the effect of solvent, additive and temperature were then examined (Table 1, entries 7-16). Initially, the influence of the solvent on the conversion and enantioselectivity were examined, and an obvious solvent dependence on the enantioselectivity and reactivity was observed with THF chosen as the best one (Table 1, entries 7-10). Next, the effect of the additive was studied by use of various halogen sources (Table 1, entries 11-14). Halogen-additives were crucial to the hydrogenation as very low conversion was observed in its absence. It was found that the use of iodine additive could significantly increase the enantioselectivity to 91% ee (Table 1, entry 13). Better result obtained with iodine additive are presumably caused by elevating the valence state of the metal center (Ir^{I} to Ir^{III}).[12] Lowering the reaction temperature and increasing the catalyst loading could further improve the catalytic performance, giving the enantioselectivity of up to 92% ee (Table 1, entries15-16). The absolute stereochemistry of the resulting phenylglycine methyl ester was determined to be *S* by the comparison of the optical rotation with the reported value in the literature.[6d,6m]

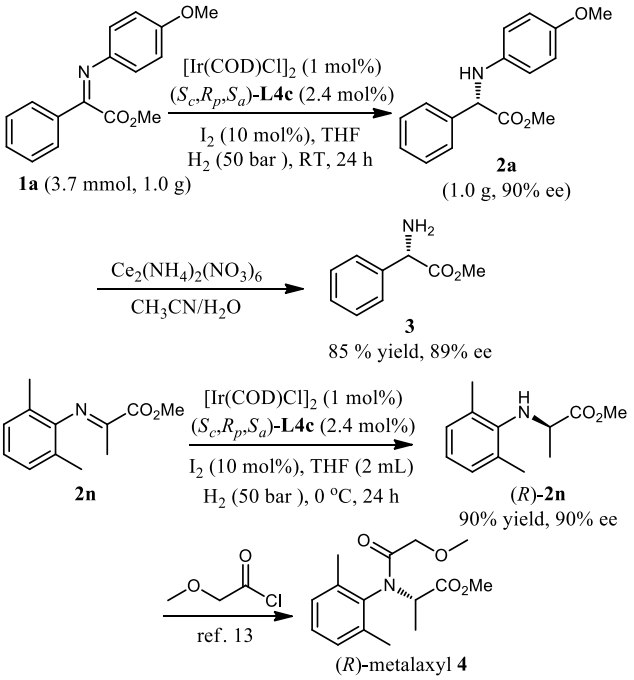
Having established the optimal hydrogenation conditions, we then examined the generality of the Ir/**L4c** catalytic system in the hydrogenation of α-iminoesters. As shown in Table 2, good to excellent yields with ee values ranging from 77% to 96% were obtained for all substrates tested. The position of the substituent on the phenyl ring obviously affected the enantioselectivity but showed less effect in the reactivity (Table 2, entries 2-4). The *ortho*-substituted substrate **1b** led to much lower enantioselectivity in comparison with its *meta*- and *para*-analogues (**1c** and **1d**), presumably due to the steric hindrance of the *ortho*-substituent. The reaction was not sensitive to the electronic character of the *para*-substituent on the phenyl ring. All imino esters**1d-i** bearing the *para*-substituent gave the corresponding hydrogenation products **2d-i** in high yields (92-98%) and with excellent enantioselectivities (92-95% ee), regardless of the electronic property of the substituent (Table 2, entries 4-9). 2-Naphthyl derivative **1j** was suitable to the hydrogenation although the hydrogenation product **2j** was obtained in not so satisfactory enantioselectivity (Table 2, entry 10). A series of different esters **1k** and **1l** were submitted to the hydrogenation, and high yield and excellent enantioselectivity were obtained in both cases (Table 2, entries 11 and 12). *N*-Phenyl iminoester **1m** also proved to be a suitable substrate, affording the corresponding hydrogenation product **2m** in 95% yield and with 90% ee (Table 2, entry 13). Aliphatic substrate was also tolerated with the present catalytic system. For an example, high yield and enantioselectivity were obtained for the hydrogenation of substrate **1n** with a methyl group (Table 2, entry 14).

Table 2. Ir-catalyzed asymmetric hydrogenation of α-iminoesters **1**.[a]



Entry	Substrate	R^1	R^2	R^3	Product	Yield (%)[b]	Ee (%)[c]	Configuration
1	**1a**	C_6H_5	4-$MeOC_6H_4$	Me	**2a**	96	92	(*S*)
2	**1b**	2-$MeOC_6H_4$	4-$MeOC_6H_4$	Me	**2b**	93	77	(+)
3	**1c**	3-$MeOC_6H_4$	4-$MeOC_6H_4$	Me	**2c**	95	87	(+)
4	**1d**	4-$MeOC_6H_4$	4-$MeOC_6H_4$	Me	**2d**	97	95	(+)
5	**1e**	4-$CH_3C_6H_4$	4-$MeOC_6H_4$	Me	**2e**	96	93	(+)
6	**1f**	4-FC_6H_4	4-$MeOC_6H_4$	Me	**2f**	92	93	(+)
7	**1g**	4-ClC_6H_4	4-$MeOC_6H_4$	Me	**2g**	98	93	(+)
8	**1h**	4-BrC_6H_4	4-$MeOC_6H_4$	Me	**2h**	97	93	(+)
9	**1i**	4-$CF_3C_6H_4$	4-$MeOC_6H_4$	Me	**2i**	97	92	(+)
10	**1j**	2-naphthyl	4-$MeOC_6H_4$	Me	**2j**	94	80	(+)
11	**1k**	C_6H_5	4-$MeOC_6H_4$	Et	**2k**	94	93	(+)
12	**1l**	C_6H_5	4-$MeOC_6H_4$	*i*-Pr	**2l**	96	96	(+)
13	**1m**	C_6H_5	C_6H_5	Me	**2m**	95	90	(+)
14	**1n**	Me	2,6-diMeC_6H_3	Me	**2n**	90	90	(*R*)

[a] Reaction conditions: **1** (0.2 mmol), $[Ir(COD)Cl]_2$ (2 μmol), (S_c,R_p,S_a)-**L4c** (4.8 μmol), H_2 (50 bar), THF (2.0 mL), I_2 (10 mol%), 24 h, 0 °C.
[b] Isolated yields.
[c] Determined by chiral HPLC.



Scheme 2. Gram-scale synthesis and synthetic utility.

To demonstrate the practicality of our method to the synthesis of aryl glycine derivatives, the asymmetric hydrogenation of **1a** was carried out on gram scale, and the desired product **2a** was achieved in nearly quantitative yield and with 90% ee. The *N*-protected group of **2a** could be readily removed by use of cerium ammonium nitrate (CAN) to give primary amine **3** in high yield and without significant loss of enantioselectivity.[6m] A practical utility of this method as the key step for the enantioselective synthesis of chiral fungicide (*R*)-metalaxyl is shown in Scheme 2.[13]

In summary, we have realized an efficient Ir-catalyzed asymmetric hydrogenation of α-imino esters by the employment of an unsymmetrical hybrid chiral ferrocenylphosphine-phosphoramidite ligand developed within our group. The optimization of ligand structure disclosed that the introduction of the iodo substituent into the 3/3'-position of the binaphthyl moiety is crucial for this hydrogenation to achieve high enantioselectivity. The hydrogenation displays broad substrate scope, thus providing a facile access to various optically active α-aryl glycine derivatives. The present method represents an efficient complement to the Rh-catalytic asymmetric hydrogenation of α-dehydrogenated amino acid derivatives for the enantioselective synthesis of structurally diverse and biologically important chiral α-amino acids. A further investigation on the catalytic asymmetric hydrogenation with unsymmetrical hybrid phosphine-phosphoramidite ligands is ongoing in our laboratory.

Experimental Section

In a nitrogen-filled glovebox, a mixture of $[Ir(COD)Cl]_2$ (1.3 mg, 2 μmol) and **L4c** (4.4 mg, 4.8 μmol) were dissolved in 1 mL of degassed tetrahydrofuran in a Schlenk tube under N_2. After stirring at room temperature for 1 h, α-iminoester **1** (0.2 mmol) and I_2 (5.1 mg, 20 μmol) in 1 mL of THF was added to the catalyst solution and the resulting mixture was transferred to an autoclave, which was then charged with H_2 (50 bar). The hydrogenation was performed at 0 °C for 24 h. After carefully releasing the hydrogen gas, the solvent was removed under reduced pressure. The crude product was purified through a silica gel plug (eluting with a mixture of hexanes/EtOAc = 10/1) to afford the corresponding glycines **2**. The enantiomeric excess was determined by chiral HPLC.

Acknowledgements

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