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Iridium-Catalyzed Asymmetric Hydrogenation of Tetrasubstituted α-Fluoro-β-enamino Esters: Efficient Access to Chiral α-Fluoro-β-amino Esters with Two Adjacent Tertiary Stereocenters

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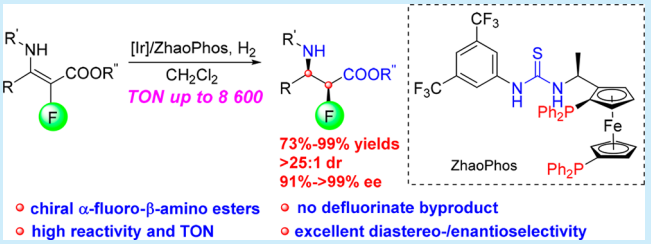
Supporting Information

ABSTRACT: An iridium-catalyzed highly efficient asymmetric hydrogenation of challenging tetrasubstituted α-fluoro-β-enamino esters was successfully developed using bisphosphine−thiourea (ZhaoPhos) as the ligand, which prepared a series of chiral α-fluoro-β-amino esters containing two adjacent tertiary stereocenters with high yields and excellent diastereoselectivities/enantioselectivities (73%−99% yields, >25:1 dr, 91%−>99% ee, and turnover number (TON) values up to 8600), and no defluorinate byproduct was detected.



The organofluorine compounds always exhibit distinctive properties from their parent compounds, because of the unique characters of the F atom, including high electronegativity, small steric size, and C−F bond strength.[1] The chemistry of chiral organofluorine compounds is a fast-developing research area and has attracted great attention, because of their wide range of applications in some important fields, such as agriculturals, pharmaceuticals, and materials.[1d,2,3a,c] For example, fluorination of drug molecules may modify metabolic stability, biological activity, and protein−drug interactions.[1d,3] Fluorinated amino acids and peptides have wide application in bioorganic and medical fields, such as biological tracers, enzyme inhibitors, mechanistic probes.[3b,4,5] Compared with other chiral fluorinated amino acids and derivatives, there are a limited number of synthetic methods for the construction of highly stereoselective chiral α-fluoro-β-amino acids and derivatives.[6−8] Most synthetic methodologies for the construction of chiral α-fluoro-β-amino acids and derivatives have been well-established through asymmetric α-fluorination of carbonyl compounds or nucleophilic addition of fluorinated ketoesters.[8]

Asymmetric reduction of prochiral functionalized enamides is regarded as one of the most powerful and important approaches to chiral amine derivatives, but it is mainly restricted to disubstituted and trisubstituted enamides.[9,10] It is challenging to realize the asymmetric hydrogenation of tetrasubstituted enamides, because of their unfavorable steric hindrance.[11,12] To the best of our knowledge, there is seldom an asymmetric catalytic reduction of tetrasubstituted α-fluoro-β-enamino esters to prepare chiral α-fluoro-β-amino esters.[12] Since our privileged bisphosphine-thiourea (ZhaoPhos) ligand has proven to be highly efficient in Rh-catalyzed asymmetric hydrogenations of prochiral disubstituted and trisubstituted unsaturated functionalized compounds,[13] we were convinced that this challenging asymmetric hydrogenation of tetrasubstituted α-fluoro-β-enamino esters could be achieved through this unique thiourea motif-assisted catalytic system. Indeed, we herein successfully realized a highly efficient Ir/bisphosphine-thiourea (ZhaoPhos)-catalyzed asymmetric hydrogenation of tetrasubstituted α-fluoro-β-enamino esters; various chiral α-fluoro-β-amino esters containing two adjacent tertiary stereocenters were prepared with high yields and excellent diastereoselectivities/enantioselectivities (Scheme 1; 73%−99% yields, >25:1 diastereomeric ratio (dr), and 91%−>99% enantiomeric excess (ee), turnover number (TON) values up to 8600), and no defluorinate byproduct was detected in this catalytic system.

We started our initial research of the asymmetric hydrogenation of tetrasubstituted α-fluoro-β-enamino esters using compound **1a**[12] as a model substrate to investigate metal precursors at room temperature. Trace conversion and messy

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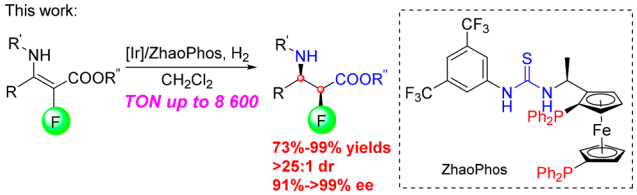
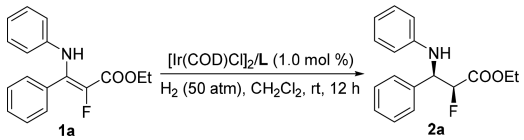
Scheme 1. Ir-Catalyzed Asymmetric Hydrogenation of α-Fluoro-β-enamino Esters



reaction system were observed using $Rh(NBD)_2BF_4$, $Rh(COD)_2BF_4$, and $[Rh(COD)Cl]_2$ as metal precursors (Table 1, entries 1−3). Full conversion, >25:1 dr, and 98% ee were obtained in the presence of $[Ir(COD)Cl]_2$ (Table 1, entry 4). This Ir-catalyzed asymmetric hydrogenation was then performed in different solvents to examine the effect of solvent. High conversions, excellent diastereoselectivities/enantioselectivities can be obtained in 1,2-dichloroethane (DCE) and $CHCl_3$ (97%−99% conversions, >25:1 dr, and 93%−96% ee; Table 1, entries 6 and 9). No desired hydrogenation products were detected when other usual solvents were tested, such as tetrahydrofuran (THF), toluene, 1,4-dioxane, MeOH (Table 1, entries 5, 7, 8, 10). When this asymmetric hydrogenation was conducted under 10 atm H_2, moderate conversion was obtained (77% conversion; Table 1, entry 11). In addition, this hydrogenation can be finished within 12 h (>99% conversion, >25:1 dr, and 98% ee; Table 1, entry 12), and there is no defluorinate byproduct in the reaction system.

Several bisphosphine−(thio)urea ligands were then applied into the iridium-catalyzed asymmetric hydrogenation of tetrasubstituted α-fluoro-β-enamino ester **1a**. As shown in Table 2, high reactivity and excellent diastereoselectivity/enantioselectivity can be obtained in the presence of ZhaoPhos **L1** (>99% conversion, 98% ee, >25:1 dr; Table 2, entry 1). The *N*-methylation of ZhaoPhos **L2** provided poor conversion and moderate enantioselectivity (49% conversion, 76% ee, >25:1 dr; Table 2, entry 2). The ligand **L3** without two trifluoromethyl groups on the phenyl ring displayed very poor reactivity, and <5% conversion was observed (Table 2, entry 3). The ligand **L4** bearing a urea motif and **L5** without a

Table 2. Screening Ligands for Asymmetric Hydrogenation of Ethyl (*E*)-2-Fluoro-3-phenyl-3-(phenylamino)acrylate 1a[a]



entry	ligand	conversion[b] (%)	diastereomeric ratio, dr[b]	enantiomeric excess, ee[c] (%)
1	ZhaoPhos **L1**	>99	>25:1	98
2	**L2**	49	>25:1	76
3	**L3**	<5	NA[d]	NA[d]
4	**L4**	NR[e]	NA[d]	NA[d]
5	**L5**	NR[e]	NA[d]	NA[d]

[a]Reaction conditions: 0.05 mmol **1a** in 1.0 mL CH_2Cl_2, S/C = 100, 50 atm H_2, room temperature, 12 h. [b]Determined by ^1H NMR analysis. [c]Determined by HPLC analysis using a chiral stationary phase. [d]NA = not available. [e]NR = no reaction.

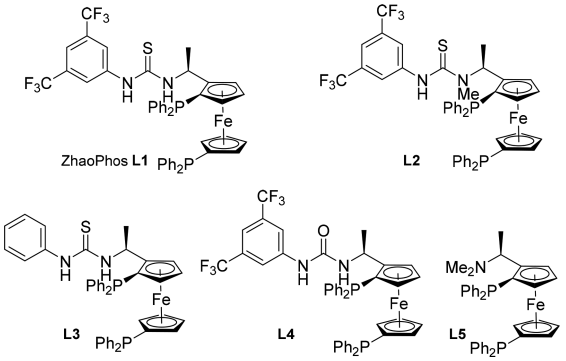
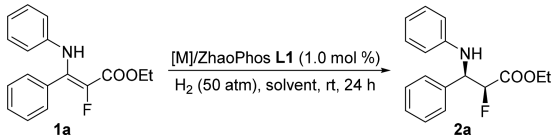


Table 1. Optimization of Reaction Conditions for Asymmetric Hydrogenation of Ethyl (*E*)-2-Fluoro-3-phenyl-3-(phenylamino)acrylate 1a[a]



entry	metal precursor	solvent	conversion[b] (%)	diastereomeric ratio, dr[b]	enaniomeric excess, ee[c] (%)
1	$Rh(NBD)_2BF_4$	CH_2Cl_2	<5	NA[d]	NA[d]
2	$Rh(COD)_2BF_4$	CH_2Cl_2	<5	NA[d]	NA[d]
3	$[Rh(COD)Cl]_2$	CH_2Cl_2	<5	NA[d]	NA[d]
4	$[Ir(COD)Cl]_2$	CH_2Cl_2	>99	>25:1	98
5	$[Ir(COD)Cl]_2$	THF	NR[e]	NA[d]	NA[d]
6	$[Ir(COD)Cl]_2$	DCE	97	>25:1	93
7	$[Ir(COD)Cl]_2$	toluene	NR[e]	NA[d]	NA[d]
8	$[Ir(COD)Cl]_2$	1,4-dioxane	NR[e]	NA[d]	NA[d]
9	$[Ir(COD)Cl]_2$	$CHCl_3$	99	>25:1	96
10	$[Ir(COD)Cl]_2$	MeOH	NR[e]	NA[d]	NA[d]
11[f]	$[Ir(COD)Cl]_2$	CH_2Cl_2	77	>25:1	98
12[g]	$[Ir(COD)Cl]_2$	CH_2Cl_2	>99	>25:1	98

[a]Reaction conditions: 0.05 mmol **1a**, 1.0 mL solvent, 50 atm H_2, room temperature, 24 h. For entries 4−12: the catalyst was precomplexed with 0.05 mmol $[Ir(COD)Cl]_2$ and 0.011 mmol ligand **L1** in 1.0 mL CH_2Cl_2 (50 μL for each reaction vial). [b]Determined by ^1H NMR analysis. [c]Determined by HPLC analysis using a chiral stationary phase. [d]NA = not available. [e]NR = no reaction. [f]10 atm H_2. [g]Reaction time is 12 h.

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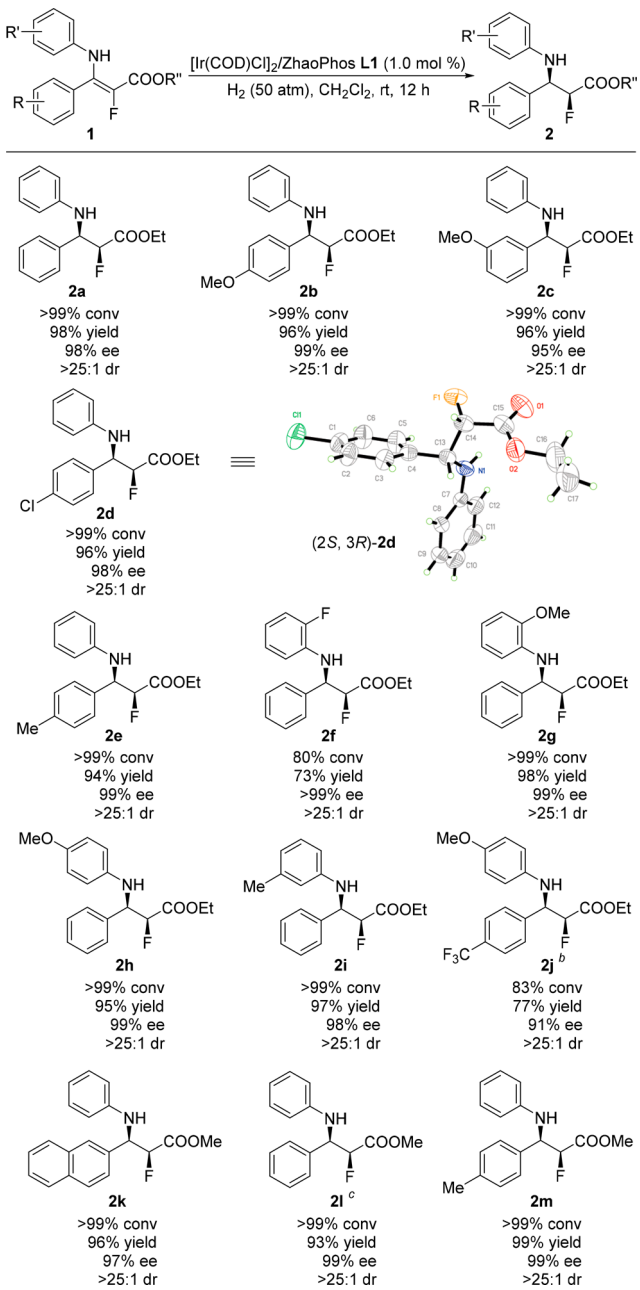
thiourea motif did not promote this asymmetric hydrogenation successfully (Table 2, entries 4 and 5).

With the optimized reaction conditions in hand, we turned our attention to investigating the substrate generality of this Ir/ZhaoPhos-catalyzed asymmetric hydrogenation of tetrasubstituted α-fluoro-β-enamino esters. The results are summarized in Scheme 2. A wide range of tetrasubstituted α-fluoro-β-enamino ethyl esters substrates with different substituents on the phenyl ring were hydrogenated smoothly with excellent results (73%−99% yields, 91%−>99% ee, >25:1 dr). The *N*-phenyl amine-derived α-fluoro-β-enamino ethyl ester substrates (**1a**−**1e**) with an R group that is either an electron-rich or electron-poor group proceeded well with full conversion, excellent enantioselectivities, and high diastereoselectivities (94%−98% yields, 95%−99% ee, >25:1 dr). In addition, the Ir-catalyzed asymmetric hydrogenation of tetrasubstituted α-fluoro-β-enamino ethyl ester substrates with different substituted groups on the phenyl ring of the aniline motif was also performed, the hydrogenation products chiral α-fluoro-β-amino ethyl esters (**2f**−**2j**) were afforded with good to excellent results (80%−>99% conversions, 73%−98% yields, 91%−>99% ee, >25:1 dr). When the ethyl ester group was changed to a methyl ester group, the substrates (**1k**−**1m**) also worked well in this transformation, and excellent results were achieved (>99% conversion, 93%−99% yields, 97%−99% ee, >25:1 dr).

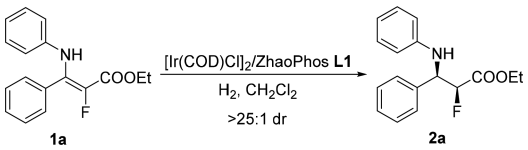
Scheme 2. Substrate Scope Study for Asymmetric Hydrogenation of Tetrasubstituted α-Fluoro-β-enamino Esters[a]



[a]Reaction conditions: 0.05 mmol substrate **1** in 1.0 mL CH_2Cl_2, S/C = 100, 50 atm H_2, room temperature, 12 h. Conversion and dr was determined by ^1H NMR analysis; ee was determined by HPLC analysis using a chiral stationary phase. [b]S/C = 50, reaction time is 36 h. [c]S/C = 50.

To our delight, the Ir-catalyzed asymmetric hydrogenation of model substrate tetrasubstituted α-fluoro-β-enamino ethyl ester **1a** could be performed with very low catalyst loading. When the catalyst loading was gradually decreased from 1.0 mol % (S/C = 100) to 0.2 mol % (S/C = 500) and 0.1 mol % (S/C = 1000), the hydrogenation product **2a** could be still obtained with excellent results (full conversion, >25:1 dr, and 98% ee; Table 3, entries 1−3). This asymmetric hydrogenation also proceeded smoothly with only 0.02 mol % catalyst (S/C = 5000), full conversion, and excellent diastereoselectivity/enantioselectivity was achieved (>99% conversion, >25:1 dr, and 98% ee; Table 3, entry 4). Good conversion and excellent diastereoselectivity/enantioselectivity was obtained even with 0.01 mol % catalyst (S/C = 10000) (86% conversion, TON = 8600, >25:1 dr, and 98% ee; Table 3, entry 5). These results indicate that our Ir/ZhaoPhos **L1** catalytic system possessed high activity in this asymmetric hydrogenation.

Table 3. TON Experiments for the Iridium-Catalyzed Asymmetric Hydrogenation of Ethyl (*E*)-2-Fluoro-3-phenyl-3-(phenylamino)acrylate 1a[a]



entry	S/C	temperature (°C)	H_2 (atm)	time (h)	conversion[b] (%)	ee[c] (%)
1	100	25	50	12	>99	98
2	500	25	70	24	>99	98
3	1000	45	80	48	>99	98
4	5000	45	80	60	>99	98
5	10000	45	80	60	86	98

[a]Unless otherwise noted, all reactions were performed with a $[Ir(COD)Cl]_2$/ZhaoPhos **L1** = 0.5:1.1 in CH_2Cl_2. [b]Determined by ^1H NMR analysis. [c]Determined by HPLC analysis using a chiral stationary phase.

As shown in Scheme 3, it is possible that the equilibration of the enamine **1h** and the imine **1h′** exists in the reaction system, and they may participate in this asymmetric hydrogenation. In order to investigate the reaction mechanism, this asymmetric hydrogenation of the enamine **1h** in the presence of D_2 was conducted under the optimizated reaction conditions. We found that the product was extensively deuterated at both the

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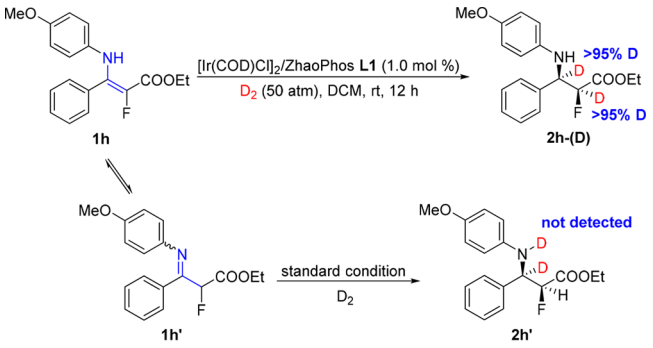
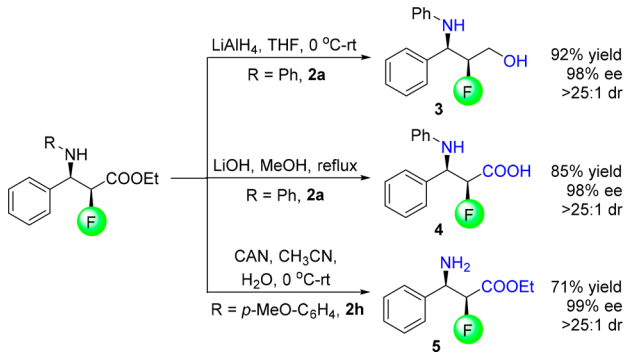
Scheme 3. Deuterium-Labeling Experiment



α- and β-positions. These observations suggest that the enamine **1h** was involved in this asymmetric hydrogenation and the imine **1h′** was much less likely.

The hydrogenation products **2** containing two adjacent tertiary stereogenic centers can be readily converted to other synthetic useful compounds, as exemplified in Scheme 4. The hydrogenation product **2a** was efficiently reduced by lithium aluminum hydride ($LiAlH_4$) to afford chiral β-fluoro-γ-amino alcohol **3** without loss of stereoselectivity (92% yield, >25:1 dr, 98% ee).[14] Hydrolysis of compound **2a** provided chiral α-fluoro-β-amino acid **4** with 85% yield, >25:1 dr, and 98% ee.[15] The chiral unprotected α-fluoro-β-amino ester **5** can be easily obtained from compound **2h** in the presence of ceric ammonium nitrate (CAN) with 71% yield, >25:1 dr, and 99% ee.[16]

Scheme 4. Synthetic Transformations of Hydrogenation Product 2



In summary, we successfully developed Ir/ZhaoPhos-catalyzed asymmetric hydrogenation of challenging tetrasubstituted α-fluoro-β-enamino esters. Various chiral α-fluoro-β-amino esters containing two adjacent tertiary stereocenters were obtained with high yields and excellent diastereoselectivities/enantioselectivities (73%−99% yields, >25:1 dr, 91%−>99% ee). In addition, our catalytic system displayed very high activity in this challenging asymmetric hydrogenation (up to TON = 8600). Moreover, this powerful synthetic utility of hydrogenation products was performed to construct other useful chiral compounds, such as chiral β-fluoro-γ-amino alcohol, α-fluoro-β-amino acid, and unprotected α-fluoro-β-amino ester in high yields and without any loss of stereoselectivity.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02503.

Optimization reaction conditions; procedures; NMR and HPLC spectra (PDF)

Accession Codes

CCDC 1844417 (for product **2d**) and 1844690 (for substrate **1g**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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