Organic LETTERS

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pubs.acs.org/OrgLett

Sterically Hindered Chiral Ferrocenyl P,N,N-Ligands for Highly Diastereo-/Enantioselective Ir-Catalyzed Hydrogenation of α-Alkyl-β-ketoesters via Dynamic Kinetic Resolution

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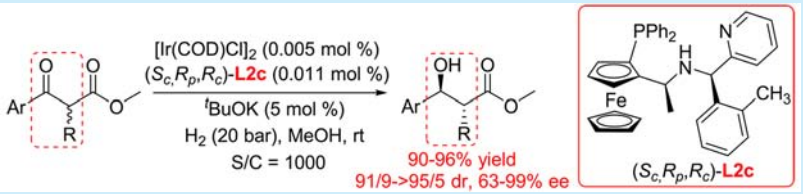
Supporting Information

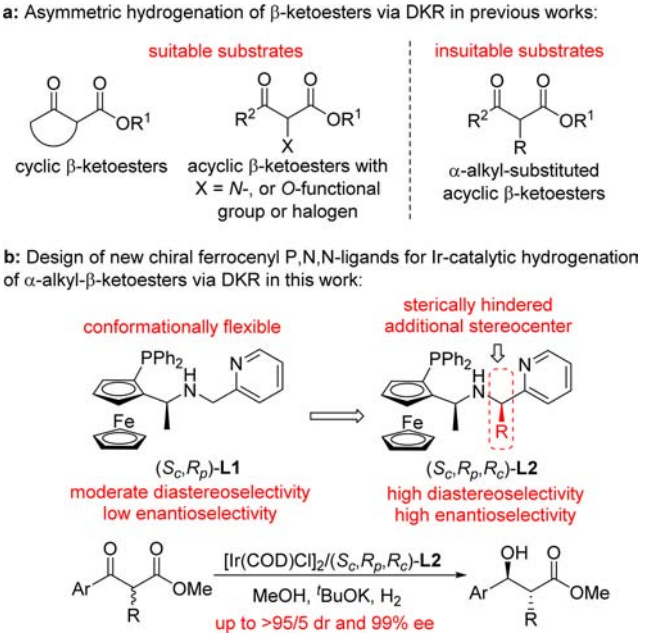


ABSTRACT: A new class of sterically hindered chiral ferrocenyl P,N,N-ligands have been prepared through a two-step transformation from (S_c,R_p)-PPFNH$_2$, in which a new (R)-stereogenic center at the pyridinylmethyl position was generated in high diastereoselectivity. With these newly developed P,N,N-ligands, Ir-catalyzed asymmetric hydrogenation of various α-alkyl-substituted β-aryl-β-ketoesters via dynamic kinetic resolution has been realized in high diastereo- and enantioselectivities for the first time, which led to a variety of optically active *anti*-β-hydroxyesters in up to 99% ee. The study indicated that the additional stereocenter at the pyridinylmethyl position of these ligands is crucial to realize this hydrogenation.

The conversion of racemic compounds into enantiomerically enriched products via the dynamic kinetic resolution (DKR) represents one of the most powerful approaches to asymmetric synthesis.[1] The first demonstration of dynamic kinetic resolution in a metal-catalyzed asymmetric hydrogenation of α-substituted β-ketoesters was reported by Noyori et al. in 1989 with a chiral Ru-BINAP complex,[2] which gave high *syn*-diastereoselectivities and enantioselectivities for cyclic β-ketoesters or certain acyclic substrates bearing an amide or carbamate group at the α-position. However, for acyclic substrates with an alkyl group at the α-position, less satisfactory resolution was observed in most cases. Following this pioneering work, there have been many reports on the dynamic kinetic resolution of labile ketones via asymmetric hydrogenation.[3] However, the scope of β-ketoester substrates is generally limited to aliphatic cyclic β-ketoesters[4] or α-heteroatom-substituted acyclic β-ketoesters (Scheme 1a).[5] To the best of our knowledge, the catalytic asymmetric hydrogenation of α-alkyl-substituted acyclic β-aryl-β-ketoesters via DKR remains unexplored, although the resulting chiral β-hydroxyesters are useful building blocks to access many natural products and pharmaceuticals.[6] Herein we wish to report a highly diastereo- and enantioselective Ir-catalyzed hydrogenation of α-alkyl-substituted β-aryl-β-ketoesters via DKR by the use of a new class of sterically hindered chiral ferrocenyl P,N,N-ligands, which led to a variety of optically active *anti*-β-hydroxyesters.

The development of chiral ligands has played a significant role in the transition-metal catalyzed asymmetric synthesis.[7] Although significant progress has been made in the past decades, the design of new chiral ligands for those challenging catalytic

Scheme 1. Catalytic Asymmetric Hydrogenation of β-Ketoesters via DKR

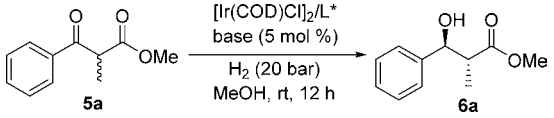


Received: September 20, 2016
Published: October 21, 2016

DOI: 10.1021/acs.orglett.6b02828
Org. Lett. 2016, 18, 5592−5595

process is still an important and desirable goal. Recently, Xie and Zhou et al. have disclosed that the iridium-catalyst decorated with SpiroPAP, a spiro-chiral tridentate P,N,N-ligand, was extremely efficient for the hydrogenation of various ketones.[8] Inspired by SpiroPAP-type P,N,N-ligands[8,9] and our recent success in the development of chiral P,N,N-ligands for asymmetric catalysis,[10] we anticipated that the ferrocene-based P,N,N-framework should provide an ideal ligand platform for the Ir-catalyzed asymmetric hydrogenation of α-alkyl-substituted β-aryl-β-ketoesters via DKR due to the inherent planar chirality of 1,2-disubstituted ferrocene backbone as well as its ready availability and modularity.[11] Unfortunately, however, initial screening with the parent ligand **L1** gave disappointing enantioselectivity (Table 1, entry 1), as also observed in the Ir-

Table 1. Optimization of the Reaction Conditions[a]



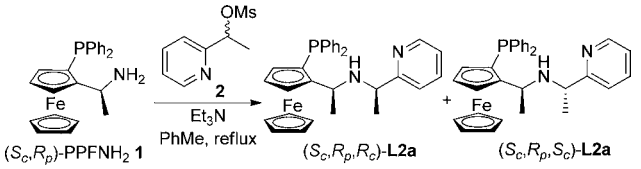
entry	L*	base	conv (%)[b]	dr[c]	ee (%)[d]
1	(S_c,R_p)-**L1**	^{t}BuOK	100	90/10	35
2	(S_c,R_p,R_c)-**L2a**	^{t}BuOK	100	94/6	82
3	(S_c,R_p,S_c)-**L2a**	^{t}BuOK	100	91/9	9
4	(S_c,R_p,R_c)-**L2b**	^{t}BuOK	100	>95/5	96
5	(S_c,R_p,R_c)-**L2b**	KOH	100	>95/5	95
6	(S_c,R_p,R_c)-**L2b**	K_2CO_3	100	>95/5	95
7[e]	(S_c,R_p,R_c)-**L2b**	^{t}BuOK	100	85/15	67
8[f]	(S_c,R_p,R_c)-**L2b**	^{t}BuOK	62	68/32	35
9[g]	(S_c,R_p,R_c)-**L2b**	^{t}BuOK	43	60/40	16
10[h]	(S_c,R_p,R_c)-**L2b**	^{t}BuOK			
11[i]	(S_c,R_p,R_c)-**L2b**	^{t}BuOK	100	>95/5	92
12[i]	(S_c,R_p,R_c)-**L2c**	^{t}BuOK	100	>95/5	97
13[i]	(S_c,R_p,R_c)-**L2d**	^{t}BuOK	100	>95/5	94
14[i]	(S_c,R_p,R_c)-**L2e**	^{t}BuOK	100	>95/5	95
15[i]	(S_c,R_p,R_c)-**L2f**	^{t}BuOK	100	>95/5	79

[a]Reaction conditions: **5a** (1.0 mmol), $[Ir(COD)Cl]_2$ (5.0×10^{-3} mmol), **L*** (1.1×10^{-2} mmol), base (0.05 mmol), solvent (3 mL), H_2 (20 bar), rt, 12 h, unless otherwise noted. [b]The conversion was determined by ^{1}H NMR. [c]The ratio of dr was determined by ^{1}H NMR. [d]The ee values were determined by HPLC analysis on a chiral phase. [e]EtOH was used as the solvent, and the corresponding ethyl ester was obtained. [f]Using toluene as the solvent. [g]Using THF as the solvent. [h]Using CH_2Cl_2 as the solvent. [i]S/C = 1000 with $[Ir(COD)Cl]_2$ (5.0×10^{-4} mmol) and **L*** (1.1×10^{-3} mmol).

catalyzed asymmetric hydrogenation of simple ketones.[12] The reason for this poor result should be that the ligand **L1** is comformationally flexible due to the presence of a methylene group, which cannot transfer the backbone chirality efficiently to the pyridinyl group and therefore makes the stereogenic centers in the ligand far from the substrate. We envisioned that the introduction of an additional group into the pyridinylmethyl position of **L1** should overcome this drawback since a new stereogenic center will be generated that is closer to the pyridine-N-donor atom and also significantly increases the structural rigidity of ligand (Scheme 1b). As a result, herein we reported the diastereoselective synthesis of new sterically hindered chiral ferrocenyl P,N,N-ligands, (S_c,R_p,R_c)-**L2**, which showed high diastereo- and enantioselectivities in the Ir-catalyzed asymmetric hydrogenation of α-alkyl-substituted β-aryl-β-ketoesters via the dynamic kinetic resolution.

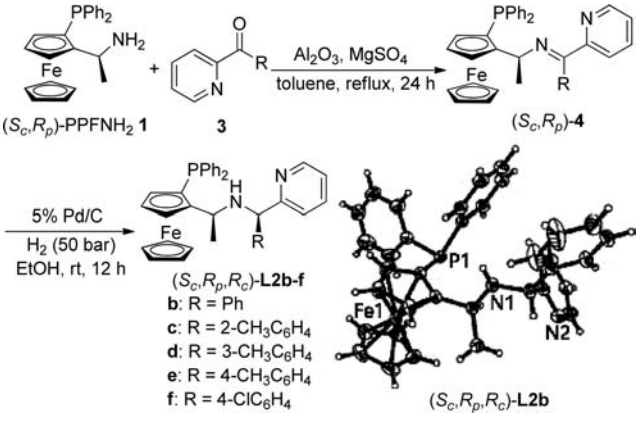
At the outset of this study, we attempted to introduce a methyl group into the pyridinylmethyl position to investigate the influence of the newly generated stereocenter on the enantioselectivity. A substitution reaction between (*S*)-1-[(*R*)-2-(diphenylphosphino)ferrocenyl]ethylamine [(S_c,R_p)-$PPFNH_2$ **1**] with 1-(2-pyridinyl)ethylmethanesulfonate **2** was then performed, which led to a mixture of two diastereomers of the target **L2a** that could be separated by a careful column chromatography (Scheme 2). The evaluation of two diastereomers, (S_c,R_p,R_c)-**L2a** and (S_c,R_p,S_c)-**L2a**, in the Ir-catalyzed hydrogenation of methyl 2-methyl-3-oxo-3-phenylpropanoate **5a** was then carried out. The hydrogenation was performed under a H_2 pressure of 20 bar in MeOH at room temperature for 12 h in the presence of 5 mol % of ^{t}BuOK. As expected, the results in Table 1 indicated the significant influence of the newly formed chiral center at the pyridinylmethyl position on the reaction performance. With (S_c,R_p,R_c)-**L2a**, the enantioselectivity was dramatically promoted to 82% ee (entry 2), much higher than that with the parent ligand (S_c,R_p)-**L1**. In contrast, a decrease in the enantioselectivity was observed by use of (S_c,R_p,S_c)-**L2a** (entry 3). These results indicated that S_c-central chirality at the ferrocenylmethyl position, R_p-planar chirality, and R_c-central chirality at the pyridinylmethyl position are matched absolute configurations.

Scheme 2. Synthesis of Two Diastereoisomers of L2a



The optimization of ligand structure by introducing the different substituent into the pyridinylmethyl position to further improve the hydrogenation performance is therefore anticipated. One major challenge in this study is how to diastereoselectively synthesize (S_c,R_p,R_c)-diastereomer of **L2** in a more convenient manner. After many attempts, we fortunately disclosed that the Schiff base-imines **4**, readily obtained by the condensation of (S_c,R_p)-$PPFNH_2$ **1** with various 2-acylpyridines **3**, could be hydrogenated by 5% Pd/C to give (S_c,R_p,R_c)-**L2** in high yields and with nearly complete diastereoselectivity (Scheme 3). With

Scheme 3. Diastereoselective Synthesis of Chiral Ferrocenyl P,N,N-Ligands (S_c,R_p,R_c)-L2b–f and X-ray Crystal Structure of (S_c,R_p,R_c)-L2b



DOI: 10.1021/acs.orglett.6b02828
Org. Lett. 2016, 18, 5592–5595

this process, a variety of (S_c,R_p,R_c)-**L2** decorated with different substituents on the pyridinylmethyl position were prepared, and the (S_c,R_p,R_c)-absolute configuration of these ligands was unambiguously confirmed by X-ray analysis of **L2b** (Scheme 3).[13] We first examined (S_c,R_p,R_c)-**L2b** bearing a phenyl group on the pyridinylmethyl position on the model reaction, which gave *anti*-β-hydroxyesters in full conversions and with excellent enantioselectivity (96% ee) and perfect diastereoselectivity (>95/5 dr) (entry 4). Further optimization of hydrogenation conditions by screening the different solvents and bases did not improve the hydrogenation outcome (entries 5−10). Lowering the catalyst loading to 0.1 mol % (S/C = 1000) showed only little changes in the reactivity and selectivity (entry 11). Comparison of various ferrocenyl P,N,N-ligands indicated that the introduction of a methyl group into the phenyl ring on pyridinylmethyl position increased the enantioselectivity regardless of the substitution pattern (entries 12−14), with (S_c,R_p,R_c)-**L2c** bearing 2-methyl group to give the best enantioselectivity of 97% ee (entry 12). However, 4-chlorophenyl group on the pyridinylmethyl position led to the obvious decrease in the enantioselectivity (entry 15).

Under the optimal hydrogenation conditions, various α-alkyl-substituted β-aryl-β-ketoesters were hydrogenated over Ir/(S_c,R_p,R_c)-**L2c** at a catalytst loading of 0.1 mol % (S/C = 1000), and the results are summarized in Figure 1. The results indicated that the electronic properties and substitution pattern of the substituent on the phenyl ring of β-aryl-β-ketoesters had little effect on the diastereo- and enantioselectivity, affording the corresponding *anti*-β-hydroxyesters in high yields (90−96%) and with excellent diastereo- and enantioselectivity (91−99% ee). 2-Naphthyl substrate **5i** also served well, giving the hydrogenation product **6i** in 91% yield and with >95/5 dr and 96% ee for *anti*-diastereomer. However, 2-thienyl substrate **5j** resulted in some decrease in the diastereoselectivity. The substrates with different α-alkyl substituents also proceeded smoothly in this hydrogenation. Thus, both ethyl-substituted substrate **5k** and cyclic substrate **5l** gave high diastereo- and enantioselectivities. However, benzyl-substituted substrate **5m** gave only moderate enantioselectivity. For nonaromatic substrate **5n**, less satisfactory resolution was achieved. The absolute configuration of the hydrogenation products was unambiguously determined by X-ray structure analysis of **6f**, which is assigned as having (2*R*,3*S*)-configuration.[13]

To demonstrate the utility of this reaction, further transformation of hydrogenation product **6a** was performed as shown in Scheme 4. For example, the ester group of the hydrogenation product could be easily reduced, therefore converting β-hydroxyester **6a** to chiral 1,3-diol **7** in high yield and without an obvious erosion in the enantioselectivity. Furthermore, β-hydroxyesters were readily transformed into β-lactones, versatile intermediates in organic synthesis.[14]

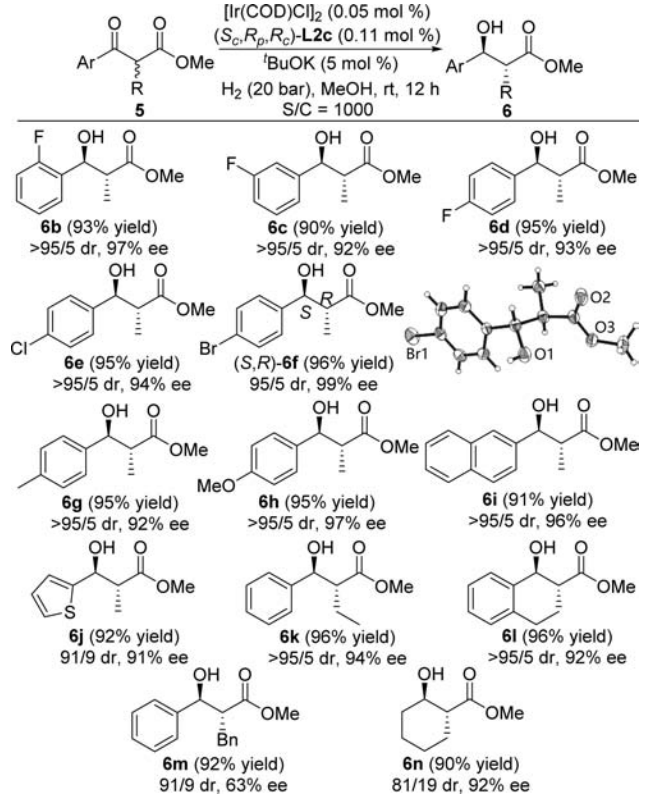
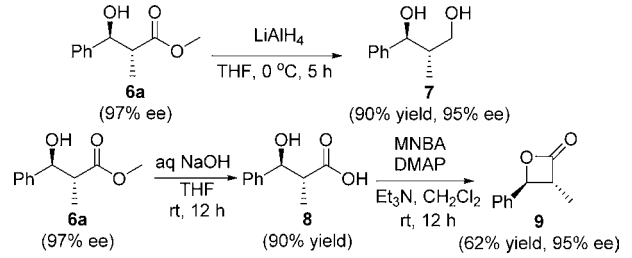


Figure 1. Substrate scope with respect to α-alkyl-substituted β-aryl-β-ketoesters. General conditions: **5** (1.0 mmol), $[Ir(COD)Cl]_2$ (5.0×10^{-4} mmol), (S_c,R_p,R_c)-**L2c** (1.1×10^{-3} mmol), ^{t}BuOK (0.05 mmol), MeOH (3 mL), H_2 (20 bar), rt, 12 h. Yields of isolated product are given, and the ee values were determined by HPLC or GC analysis on a chiral phase.

Scheme 4. Representative Product Transformations



In conclusion, we have developed a new class of chiral ferrocenyl P,N,N-ligands, which were synthesized from (S_c,R_p)-$PPFNH_2$ and 2-acylpyridines through a two-step transformation in highly diastereoselective form. These ligands have been successfully employed in the Ir-catalyzed asymmetric hydrogenation of α-alkyl-substituted β-aryl-β-ketoesters via the dynamic kinetic resolution, thereby affording the corresponding β-hydroxyesters in high *anti*-diastereoselectivity and excellent enantioselectivity (up to 99% ee). This represents the first successful example in the catalytic asymmetric hydrogenation of α-alkyl-substituted β-aryl-β-ketoesters via the dynamic kinetic resolution. The present study indicated that the presence of an additional chiral center at the pyridinylmethyl position of these P,N,N-ligands is crucial to achieve the satisfactory performance in the hydrogenation. Further application of these ferrocenyl P,N,N-ligands in asymmetric catalysis is still in progress.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02828.

Experimental procedures and characterization data for all new compounds (PDF)

X-ray crystallographic data for (S_c,R_p,R_c)-**L2b** (CIF)

X-ray crystallographic data for (*R*,*S*)-**6f** (CIF)

DOI: 10.1021/acs.orglett.6b02828
Org. Lett. 2016, 18, 5592−5595

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

Supports for this research from the National Natural Science Foundation of China (21572226, 21403022) are gratefully acknowledged.

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DOI: 10.1021/acs.orglett.6b02828
Org. Lett. 2016, 18, 5592−5595