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Ir-catalyzed asymmetric hydrogenation of simple ketones with chiral ferrocenyl P,N,N-ligands

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ABSTRACT

The Ir-catalyzed asymmetric hydrogenation of simple aromatic ketones with chiral ferrocenyl P,N,N-ligands has been developed. Under the optimized conditions, a wide range of ketones were hydrogenated to afford the corresponding chiral alcohols in good to excellent enantioselectivities (up to 98% ee).

Introduction

Chiral secondary alcohols are important key structural motifs in a number of pharmaceutical products, such as aprepitant, crizotinib, duloxetine and ezetimibe (Fig. 1).[1] Due to their importance, significant effort has been devoted to developing efficient methods to synthesize chiral alcohols in the past decades.

The transition-metal catalyzed asymmetric hydrogenation of ketones is one of the most direct and convenient methods for the synthesis of chiral alcohols due to its high atom economy and activity. Thus, a number of efficient catalysts have been developed for the asymmetric hydrogenation of functionalized ketones with a secondary coordination group to the metal center. However, only a few catalysts have been reported for the asymmetric hydrogenation of simple unfunctionalized non-chelating ketones. A breakthrough was achieved by Noyori and co-workers[2] in the 1990s, who developed the highly effective BINAP-ruthenium-diamine catalyst system for the asymmetric hydrogenation of various simple aromatic ketones. Since this work, a number of chiral diphosphine ligands, such as TolBINAP,[3] XylBINAP,[4] BICP,[5] SDP,[6] TunePhos,[7] P-Phos,[8] and PhanePhos,[9] have been developed and proved to be efficient in the ruthenium catalyzed asymmetric hydrogenation of ketones. Subsequent mechanistic studies showed that this catalyst system has a nonclassical metal-ligand bifunctional mechanism, whereby a Ru-H and NH_2 are simultaneously transferred to the carbonyl *via* a six-membered transition state.[10]

In addition to the Noyori's diphosphine-ruthenium-diamine catalysts (Type A in Fig. 2), a few groups have developed other catalyst systems to expand this important asymmetric reduction. In 2011, Clarke and co-workers[11] developed a different ruthenium catalyst with a tridentate P,N,N-ligand in place of diphosphine and diamine ligands (Type B in Fig. 2). These catalysts showed unusual reactivity and high enantioselectivity in the hydrogenation of low-reactivity bulky ketones. Changing from ruthenium to iridium, Clarke and co-workers[12] demonstrated the hydrogenation of ketones bearing an aryl substituent and a secondary alkyl group with a iridium-P,N,N-ligand catalyst (Type C in Fig. 2), which showed higher reactivity and selectivity than that obtained with a ruthenium catalyst derived from the same ligand.

Recently, Zhou and co-workers developed chiral iridium catalysts containing chiral spiro P,N,N-ligands, SpiroPAP (Fig. 3), which showed excellent enantioselectivities and extremely high TON (as high as 4,550,000) for the hydrogenation of simple ketones.[13] These catalysts are likely to have a metal-ligand bifunctional mechanism, similar to the Noyori's diphosphine-ruthenium-diamine catalysts. Inspired by SpiroPAP-type P,N,N-ligands,[14,15] we have developed a highly efficient iridium catalyzed asymmetric hydrogenation of β-keto esters with a new class of chiral ferrocenyl P,N,N-ligands.[16] More importantly, with these iridium-P,N,N ligand

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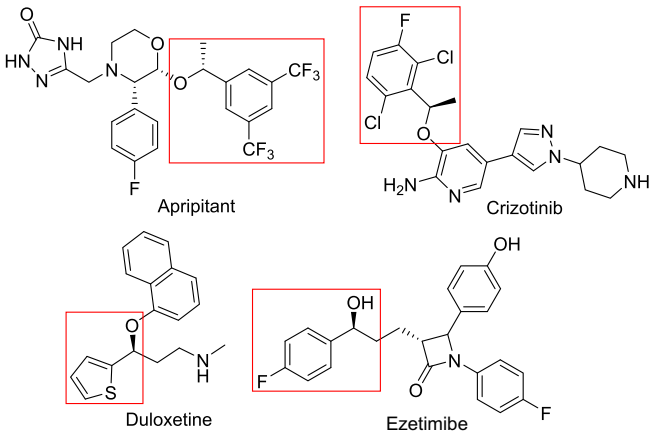


Fig. 1. Representative pharmaceuticals containing chiral alcohols as key motifs.

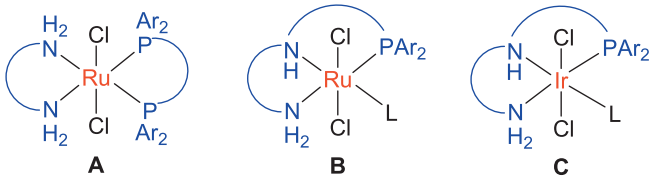


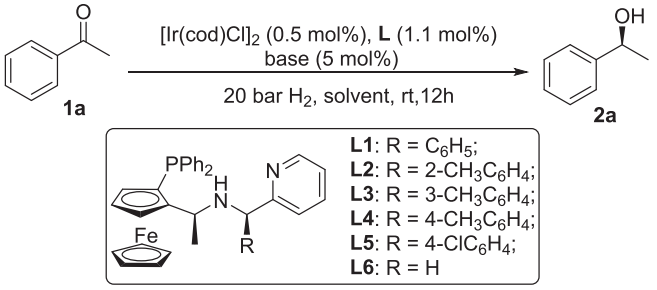
Fig. 2. Catalysts related to Noyori's diphosphine-ruthenium-diamine (A) and Clarke's ruthenium-P,N,N ligand (B) and iridium-P,N,N ligand (C).

catalysts, various α-alkyl-substituted β-aryl-β-ketoesters can be hydrogenated to afford the corresponding β-hydroxyesters with high *anti*-diastereoselectivity and excellent enantioselectivity. Encouraged by these results, we wished to expand the hydrogenation to a wider substrate scope. As a result, herein, we report our studies regarding the iridium catalyzed asymmetric hydrogenation of simple aromatic ketones with chiral ferrocenyl P,N,N-ligands, which provides the corresponding chiral alcohols with excellent enantioselectivity (up to 98% ee) under mild conditions.

Result and discussion

The chiral ferrocenyl P,N,N-ligands **L1**–**L6** were prepared from (S_c,R_p)-PPFNH$_2$ as previously reported.[16] With these ligands in hand, we began our studies by evaluating them for the iridium catalyzed asymmetric hydrogenation of ketones. Acetophenone (**1a**) was selected as the model substrate and the hydrogenation was carried out under 20 bar H_2 in the presence of catalysts generated *in situ* by mixing [Ir(cod)Cl]$_2$ with ligands **L1**–**L6** (S/C = 100) in MeOH. As shown in Table 1, ligands **L1**–**L5** displayed good to excellent enantioselectivities (Entries 1–5) and ligand **L2** bearing a 2-methyl phenyl group at the pyridinylmethyl position afforded the best result with 92% ee (Entry 2). The ligand screening results

Table 1
Asymmetric hydrogenation of acetophenone (**1a**): reaction conditions optimisation.



Entry	Ligand	Base	Solvent	Conv. (%)[a]	ee (%)[b]
1	**L1**	*t*-BuOK	MeOH	100	69
2	**L2**	*t*-BuOK	MeOH	100	92
3	**L3**	*t*-BuOK	MeOH	100	84
4	**L4**	*t*-BuOK	MeOH	100	79
5	**L5**	*t*-BuOK	MeOH	100	61
6	**L6**	*t*-BuOK	MeOH	100	33
7	**L2**	*t*-BuONa	MeOH	100	92
8	**L2**	KOH	MeOH	100	89
9	**L2**	NaOH	MeOH	100	93
10	**L2**	K_2CO_3	MeOH	100	94
11	**L2**	K_2CO_3	EtOH	100	69
12	**L2**	K_2CO_3	*i*-PrOH	100	65
13	**L2**	K_2CO_3	Toluene	NR	_
14	**L2**	K_2CO_3	CH_2Cl_2	NR	_
15[c]	**L2**	K_2CO_3	MeOH	100	91
16[d]	**L2**	K_2CO_3	MeOH	100	85
17[e]	**L2**	K_2CO_3	MeOH	100	65
18[f]	**L2**	K_2CO_3	MeOH	100	65

[a] Conversion determined by ^{1}HNMR analysis of the crude products.
[b] Enantiomeric excess determined by HPLC using a chiral stationary phase.
[c] S/C = 1000.
[d] S/C = 2000
[e] S/C = 5000.
[f] S/C = 10,000.

demonstrated that the substituents on the phenyl ring had a significant effect on the enantioselectivity. Additionally, the substituents at the pyridinylmethyl position are critical for the enantioselectivity. Thus, low enantioselectivity was obtained when ligand **L6** was applied to this transformation (Entry 6), which is accordance with result reported by Zhang and co-workers.[17]

Subsequently, different bases were screened for this transformation catalyzed by Ir-**L2**. All of the examined bases, such as *t*-BuOK, *t*-BuONa, KOH, NaOH and K_2CO_3, showed good results (Entries 7–10), and K_2CO_3 was identified as the best choice with 94% ee (Entry 10). The solvent was investigated next and was found to greatly affected this transformation (Entries 10–14). Alcohols proved to be suitable solvents and MeOH was the best choice in terms of reactivity and enantioselectivity (Entry 10). We also obtained similar results when the catalyst loading was reduced to 0.1 mol% (S/C = 1000, Entry 15). However, only moderate

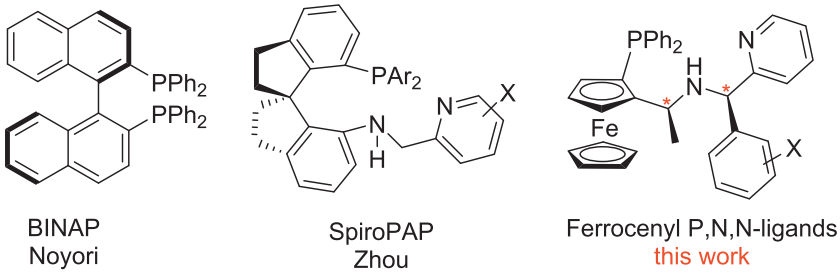


Fig. 3. Examples of efficient chiral ligands for the asymmetric hydrogenation of ketones.