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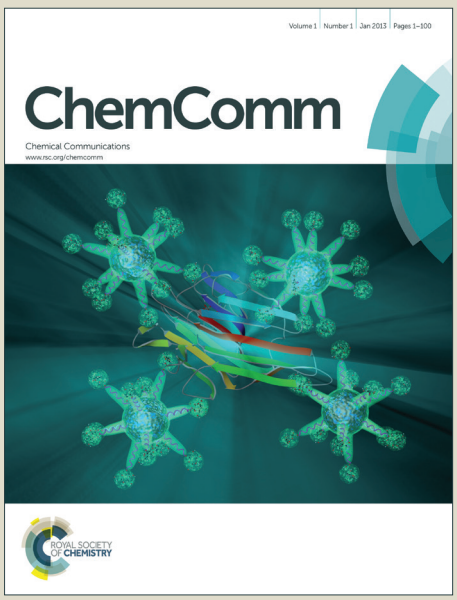

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Efficient Asymmetric Transfer Hydrogenation of Ketones in Ethanol with Chiral Iridium Complexes of SpiroPAP Ligands as Catalysts

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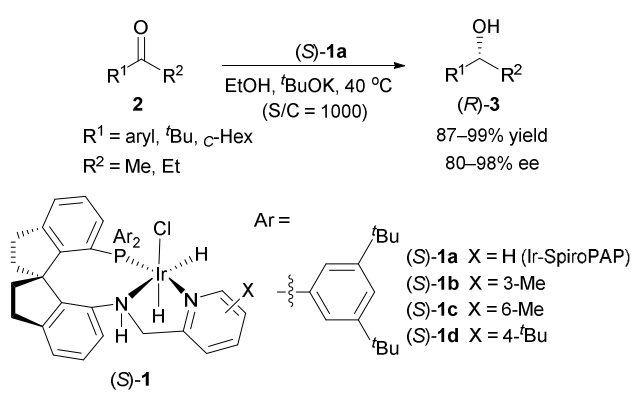
A highly efficient iridium catalyzed asymmetric transfer hydrogenation of simple ketones with ethanol as a hydrogen donor has been developed. By using chiral spiro iridium catalyst (*S*)-1a a series of alkyl aryl ketones were hydrogenated to chiral alcohols with up to 98% ee.

Optically pure alcohols are important chiral building blocks for the preparation of fine chemicals, pharmaceuticals, agrochemicals, bioactive natural products, as well as functional materials. Catalytic asymmetric transfer hydrogenation of ketones is currently recognized as one of the most powerful and valuable synthetic methods for obtaining optically active chiral alcohols because of its operational simplicity, easily availability of hydrogen sources, lower cost and safety.[1] By using 2-propanol or formate salts as hydrogen donor and chiral transition-metal catalysts, a wide range of aromatic ketones have been successfully reduced to chiral secondary alcohols in high enantioselectivity.[2] Recently, as a renewable resource, feedstock for the chemical industry, as well as environmental and human-friendly solvent, ethanol is also found to be efficient hydrogen donor for transfer hydrogenation of ketones.[3] However, the catalytic asymmetric transfer hydrogenation of ketones with ethanol as hydrogen donor is still a challenge. Grützmacher et al reported that the chiral rhodium complexes of bis(olefin)amine ligands can catalyze the transfer hydrogenation of acetophenone with ethanol as hydrogen donor, however with only moderate enantioselectivities (60% ee).[4] The chiral ruthenium catalysts with hydroxyl-amide ligands reported by Lundberg and Adolfsson showed as high as 97% ee for the reduction of alkyl aryl ketones in the mixed solvents of ethanol and THF.[5]

We recently developed a new type of chiral spiro iridium catalysts containing a tridentate spiro pyridine aminophosphine ligand (SpiroPAP) [6] and found they are extremely efficient for the hydrogenation of simple ketones,[7] α,β-unsaturated ketones,[8] ketoesters,[9] and esters[10] in ethanol to chiral alcohols with excellent activity and enantioselectivity. To address more "green", sustainable, safe, as well as highly efficient methods for preparing chiral alcohols, we were therefore interested to the investigation of the asymmetric transfer hydrogenation of simple ketones with chiral spiro iridium catalysts Ir-(*S*)-SpiroPAP ((*S*)-**1**) using ethanol as hydrogen donor and solvent. The results showed that the catalysts (*S*)-**1** were also highly efficient for the asymmetric transfer hydrogenation of simple ketones in ethanol, providing chiral alcohols with up to 98% ee (Scheme 1).

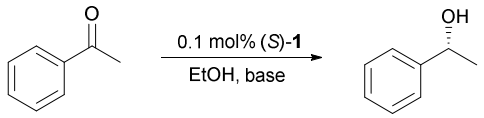


Scheme 1. Asymmetric Transfer Hydrogenation of Ketones Catalyzed by (*S*)-**1**

The asymmetric transfer hydrogenation of acetophenone (**2a**) was initially performed in ethanol at room temperature (25 °C) with 0.1 mol% of catalyst (*S*)-**1a**. After reaction for 15 h the acetophenone was converted in 93% and the hydrogenation product (*R*)-**3a** was obtained with 98% ee (Table 1, entry 1). The reaction became faster as the reaction temperature increased. When the transfer hydrogenation was performed at 40 °C, the conversion of **2a** increased to 99% within 10 h and the enantioselectivity of reaction remained (entry 2). Further increasing reaction temperature to 60 and 75 °C continuously speeded the reaction, however slightly lowered the enantioselectivity of reaction (entries 3 and 4). Using ^{i}PrOH

instead of EtOH as hydrogen donors and solvent led to a moderate enantioselectivity (84% ee, entry 5). In addition to KO^{t}Bu, other bases such as NaO^{t}Bu, KOH, and K_2CO_3 can also be used in the transfer hydrogenation of **2a**, providing (*R*)-**3a** with the same enantioselectivity (entries 6–8). Although the use of HCO_2Na as a base afforded the highest enantioselectivity (99% ee), the conversion of the reaction became very low (18%, 18 h, entry 9). Decreasing the concentration of base from 0.04 mmol/mL to 0.02 mmol/mL resulted in a lower conversion (83%, entry 10). In contrast, lowering the concentration of substrate **2a** led to a faster reaction (entry 12). The catalysts (*S*)-**1** with different substituents on the pyridine ring were also compared in the asymmetric transfer hydrogenation of **2a**. The catalysts (*S*)-**1b** with a 3-Me and (*S*)-**1c** with a 6-Me on the pyridine ring, respectively, afforded slightly lower enantioselectivity (entries 14 and 15). The catalyst (*S*)-**1d** with a 4-*tert*-butyl group on the pyridine ring gave a comparable results to the catalyst (*S*)-**1a** which has no substituent on the pyridine ring (entries 2 and 16). When the loading of the catalyst **1a** was reduced to be 0.05 mol% (S/C = 2000), the reaction still conducted very well and afforded (*R*)-**3a** in 97% conversion with 98% ee (entry 17). In addition, when the transfer hydrogenation of **2a** with catalyst (*S*)-**1a** was performed on a gram scale (*ca*, 12.0 g, 0.1 mol), a comparable reactivity (99% conversion, 96% isolated yield) and enantioselectivity (98% ee) were also obtained within 16 h under similar reaction conditions (entry 18). These results indicated that the iridium complex of the tridentate SpiroPAP ligand are highly efficient chiral catalysts for the asymmetric transfer hydrogenation of ketones with ethanol as a hydrogen donor.

Table 1 Optimization of reaction conditions for asymmetric transfer hydrogenation of **2a**.[a]



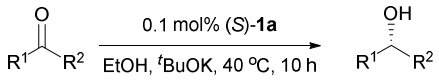
2a (*R*)-**3a**

Entry	(*S*)-**1**	Base	Temp (°C)	Time (h)	Conv. (%)[b]	Ee (%)[c]
1	(*S*)-**1a**	^{t}BuOK	25	15	93	98
2	(*S*)-**1a**	^{t}BuOK	40	10	99	98
3	(*S*)-**1a**	^{t}BuOK	60	8	99	96
4	(*S*)-**1a**	^{t}BuOK	75	5	100	95
5[d]	(*S*)-**1a**	^{t}BuOK	40	10	98	84
6	(*S*)-**1a**	^{t}BuONa	40	10	99	98
7	(*S*)-**1a**	KOH	40	12	97	98
8	(*S*)-**1a**	K_2CO_3	40	12	97	98
9	(*S*)-**1a**	HCO_2Na	40	20	18	99
10[e]	(*S*)-**1a**	^{t}BuOK	40	15	83	98
11[f]	(*S*)-**1a**	^{t}BuOK	40	10	99	98
12[g]	(*S*)-**1a**	^{t}BuOK	40	7	99	98
13[h]	(*S*)-**1a**	^{t}BuOK	40	12	99	98
14	(*S*)-**1b**	^{t}BuOK	40	7	99	96
15	(*S*)-**1c**	^{t}BuOK	40	12	99	93
16	(*S*)-**1d**	^{t}BuOK	40	10	99	98
17[i]	(*S*)-**1a**	^{t}BuOK	40	15	97	98
18[j]	(*S*)-**1a**	^{t}BuOK	40	16	99 (96)	98

[a] Reaction conditions: 2.0 mmol scale, [**2a**] = 0.4 mmol/mL, 0.1 mol% of catalyst, [base] = 0.04 mmol/mL, EtOH (5.0 mL). [b] Determined by 1H NMR. [c] Determined by GC or HPLC by using chiral column, and the configuration was determined as (*R*). [d] Using ^{i}PrOH instead of EtOH. [e] [^{t}BuOK] = 0.02 mmol/mL. [f] [^{t}BuOK] = 0.06 mmol/mL. [g] [**2a**] = 0.2 mmol/mL. [h] [**2a**] = 0.6 mmol/mL. [i] 0.05 mol% catalyst (S/C = 2000). [j] 12.0 g (0.1 mol), 0.05 mol% catalyst. The data in parenthese is isolate yield.

Under the optimal reaction conditions, a variety of alkyl aryl ketones were tested to examine the substrate scope of (*S*)-**1a**-catalyzed asymmetric transfer hydrogenation with ethanol as a hydrogen donor. All the tested substrates gave high yields (93–99%) and excellent enantioselectivities (90–98% ee) (Table 2). The substituents on the phenyl ring of substrates have very little effect on the yield and enantioselectivity of reaction. The transfer hydrogenation of heteroaryl-containing ketones such 3-pyridinyl methyl ketone (**2q**) also gave good yield and enantioselectivity (entry 17). However, (*S*)-**1a** was less efficient for the transfer hydrogenation of dialkyl ketones such as cyclohexyl methyl ketone (**2r**) and *tert*-butyl methyl ketones (**2s**), providing the corresponding chiral aliphatic alcohols with moderate enantioselectivities (entries 18 and 19).

Table 2 Asymmetric transfer hydrogenation of **2** with (*S*)-**1a**.[a]



2 (*R*)-**3**

Entry	R^1	R^2	(*R*)-**3**	Yield (%)[b]	Ee (%)[c]
1	C_6H_5	Me	(*R*)-**3a**	99	98
2	C_6H_5	Et	(*R*)-**3b**	95	97
3	4-ClC_6H_4	Me	(*R*)-**3c**	95	96
4	4-BrC_6H_{44}	Me	(*R*)-**3d**	95	91
5	4-MeC_6H	Me	(*R*)-**3e**	98	90
6	4-$MeOC_6H_4$	Me	(*R*)-**3f**	93	95
7	3-ClC_6H_4	Me	(*R*)-**3g**	93	96
8	3-BrC_6H_4	Me	(*R*)-**3h**	96	93
9	3-MeC_6H_4	Me	(*R*)-**3i**	98	96
10	3-$MeOC_6H_4$	Me	(*R*)-**3j**	95	97
11	2-ClC_6H_4	Me	(*R*)-**3k**	99	98
12	2-BrC_6H_4	Me	(*R*)-**3l**	94	96
13	2-MeC_6H_4	Me	(*R*)-**3m**	96	98
14	2-$MeOC_6H_4$	Me	(*R*)-**3n**	99	96
15	3,5-$(CF_3)_2C_6H_3$	Me	(*R*)-**3o**	98	93
16	2-naphthyl	Me	(*R*)-**3p**	99	95
17[d]	3-pyridinyl	Me	(*R*)-**3q**	87	93
18	*c*-Hex	Me	(*R*)-**3r**	97	83
19	^{t}Bu	Me	(*R*)-**3s**	90	80

[a] Reaction conditions were the same as those listed in Table 1, entry 2. [b] Isolated yield. [c] Determined by GC or HPLC by using chiral column, and the configuration was determined as (*R*). [d] K_2CO_3 as a base.

To understand this iridium-catalyzed asymmetric transfer hydrogenation of ketone with ethanol as a hydrogen donor, we studied the transfer hydrogenation of **2a** in situ by using a ReactIR spectrometer. As the reaction progresses, the peak at 1680 cm^{-1} (**2a**) disappeared within 1.5 h, and a new peak at 1743 cm^{-1} (ethyl acetate) appeared and increased quickly in the beginning and kept nearly unchanged after 1.5 h (Figure 1, *a* and *b*). This result indicated that the ethanol was converted to ethyl acetate[11] and provided hydride, which reduced ketone **2a** to alcohol (*R*)-**3a**. The detection of the reaction by using GC also showed the same phenomenon (Figure 1, *c*). The conversion of **2a** reached to 97% within 1.5 h. Extending reaction time to 3 h slowly increased the conversion of **2a** to 99%. The ee value of the product (*R*)-**3a** was 98.6 % in the beginning and slowly decreased to 98% ee when the conversion reached 99%. The reason for slow decrease of ee value of product in the reaction was ascribed to the slow decomposition of the catalyst.

In conclusion, we developed a highly efficient asymmetric transfer hydrogenation of ketones with ethanol as a hydrogen donor. With chiral spiro iridium catalyst (*S*)-**1a** a variety of alkyl aryl ketones were hydrogenated to chiral alcohols in high yields and excellent enantioselectivities. This reaction provided a practical and "greener" method for the synthesis of optically active alcohols.

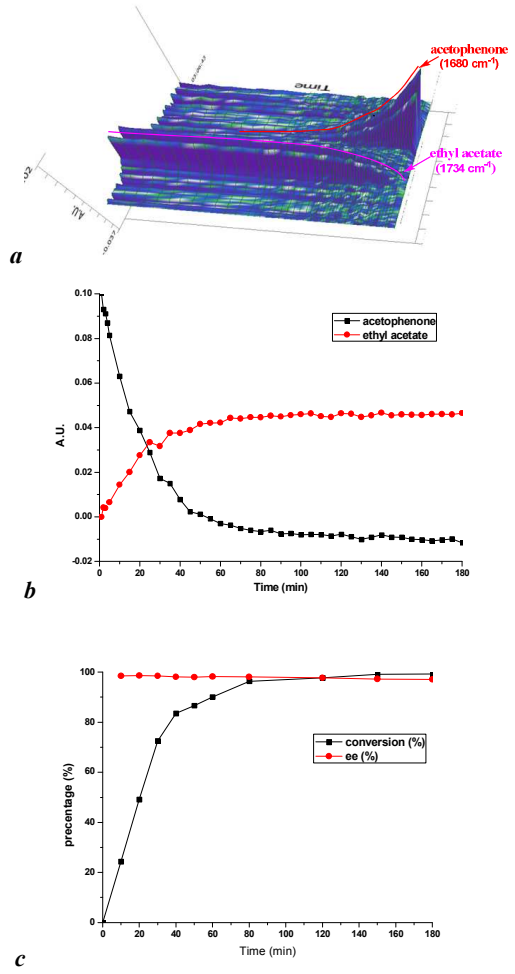


Figure 1. The plots of asymmetric transfer hydrogenation of **2a** (***a*** and ***b***, monitored by ReactIR spectrometer; ***c***, monitored by GC)

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Electronic Supplementary Information (ESI) available: Detailed experimental procedures, and the analysis data of new compounds. See DOI: 10.1039/c000000x/

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