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Kinetic Resolution of Racemic Secondary Alcohols Catalyzed by Chiral Diaminodiphosphine–Ir(I) Complexes

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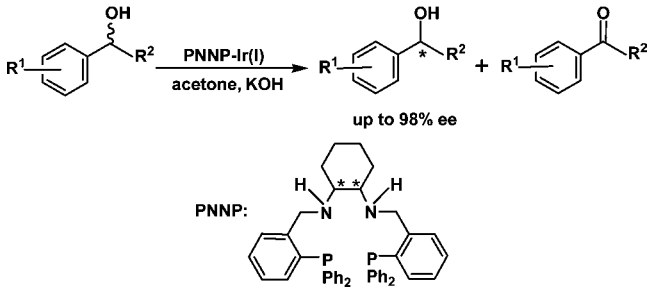
ABSTRACT



Chiral diaminodiphosphine–Ir(I) complexes were found to efficiently catalyze enantioselective oxidation of racemic secondary alcohols in acetone. In the presence of base, oxidative kinetic resolution of the alcohols proceeded smoothly with excellent enantioselectivity (up to 98% ee) under mild conditions.

Optically active alcohols are extremely useful starting materials and intermediates in synthetic organic chemistry and the pharmaceutical industry. For the past 10 years, highly efficient asymmetric hydrogenation, involving asymmetric transfer hydrogenation of prochiral ketones catalyzed by metal complexes to attain chiral alcohols, has made great progress.[1] Besides that, oxidative kinetic resolution of racemic alcohols is also another feasible approach giving optically active alcohols.[2] Recently, several effective non-enzymatic catalysts for the oxidative kinetic resolution of racemic alcohols have been reported.[3] Sigman's group and Stoltz's group intensively studied aerobic oxidative kinetic resolution of secondary alcohols catalyzed by (−)-sparteine/Pd(II) to conveniently access enantiomerically enriched secondary alcohols, respectively.[3a,b] Nishibayashi and co-workers employed [$RuCl_2(PPh_3)$(ferrocenyloxazolinylphosphine)] to catalyze the oxidative kinetic resolution of racemic 1-indanol, obtaining an optically active 1-indanol in good yield (turnover frequency exceeds 80 000 h^{-1}) with high

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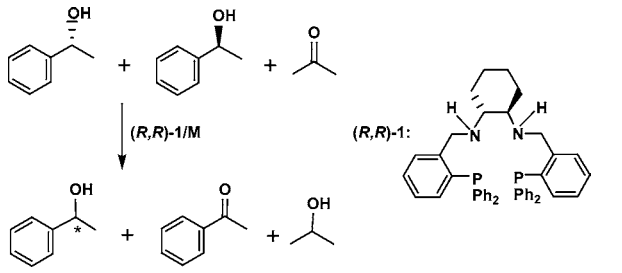
enantioselectivity (up to 94% ee).[3c] Recently, Sun et al. reported chiral Mn(salen)-complex catalyzed kinetic resolution of secondary alcohols with excellent enantioselectivity (up to 98% ee) in water.[3d]

In the past several years, we successfully prepared a class of chiral diaminodiphosphine (PNNP) ligands possessing the dual property of two "soft" phosphorus atoms and two "hard" nitrogen donor atoms, which display rich coordination chemistry and easily modify the steric and electronic properties of the resulting metal complexes.[4] On the basis of these ligands, the chiral PNNP−Ru(II), −Rh(I), and −Ir(I) complexes were prepared and used as catalysts in the asymmetric transfer hydrogenation of aromatic ketones.[5] These metal complexes have proved to be excellent catalyst precursors for the enantioselective reduction of a series of aromatic ketones, leading to corresponding chiral alcohols with up to 99% ee and the molar ratio of ketone to catalyst up to 10 000:1.[5d] Recently, other groups employed ruthenium complexes with these chiral PNNP ligands to catalyze asymmetric epoxidation and asymmetric cyclopropanation of olefins.[6,7] Encouraged by these findings, we extended our study to develop the enantioselective oxidation of racemic secondary alcohols catalyzed by chiral PNNP metal complexes.

In our continuing study, we have successfully found chiral PNNP/Ir(I) complex as a versatile catalyst for the enantioselective redox reaction of ketones and alcohols. The combinations of chiral PNNP ligand with various Rh(I), Ru(II), or Ir(I) complexes have been tested as catalyst precursors for the kinetic resolution of racemic 1-phenylethanol and the results are summarized in Table 1. The enantioselective oxidation of 1-phenylethanol was carried out in anhydrous acetone, using chiral PNNP metal complexes prepared in situ as catalysts.[8] In the presence of KOH, the chiral PNNP/Ir(I) catalyst systems proved to be efficient in catalytic oxidative kinetic resolution of racemic 1-phenylethanol. Especially, the catalyst system generated from $[IrCl(COD)]_2$ and (*R*,*R*)-**1** exhibited high catalytic activity and enantioselectivity (63% conversion, 98% ee; Table 1, run 1). The role of base is presumed to form metal hydride complex, which is a key

Table 1. Kinetic Resolution of Racemic 1-Phenylethanol Catalyzed by Chiral PNNP and Various Metal Complex Systems[a]



run	M	sub:[M]:L*:KOH	conv[b] (%)	ee[b] (%)	conf[c]
1	$[IrCl(COD)]_2$	200:1:1:2	63	98	*R*
2	$[IrHCl_2(COD)]_2$	200:1:1:2	68	79	*R*
3[d]	$Ru(DMSO)_4Cl_2$	200:1:1:6	44	24	*S*
4[d]	$RuCl_2(PPh_3)_3$	200:1:1:6	3		
5[d]	$[RhCl(COD)]_2$	200:1:1:6	4		

[a] Reaction conditions: racemic 1-phenylethanol (1 mmol); L* = (*R*,*R*)-**1**; solvent: anhydrous acetone (10 mL); time: 8 h; temperature: 25 °C. [b] Determined by GC using a chiral column (Chiraldex G-TA column). [c] Determined by comparison of the retention times of enantiomers on the GC traces with literature values. [d] Temperature: 50 °C.

species to promote the reaction. No reaction occurred if the base was absent. However, excess base caused serious side reactions including the aldol reaction of acetone, which would hamper the catalytic cycle.[3j] The oxidation with Ru(II), Rh(I)-based catalyst systems proceeded more slowly. Even in the presence of a large excess of KOH (6 equiv to the catalyst), the oxidation of 1-phenylethanol catalyzed by the $Ru(DMSO)_4Cl_2$/(*R*,*R*)-**1** catalyst system at 50 °C for 8 h only gave 44% conversion and 24% ee (Table 1, run 3). It is noteworthy that the opposite configuration of the chiral alcohol was produced by changing Ir to Ru. Under the same reaction conditions, $RuCl_2(PPh_3)_3$ and $[RhCl(COD)]_2$ were almost inert to the enantioselective oxidation of 1-phenylethanol.

Table 1 indicated the chiral PNNP/Ir(I) catalyst systems were the most effective for the oxidative kinetic resolution of racemic 1-phenylethanol under mild conditions. This preliminary result prompted us to investigate oxidative kinetic resolution of other racemic alcohols in more detail. In our earlier studies, we observed that the preformed chiral PNNP−Ir(I) complexes were excellent catalyst precursors for asymmetric transfer hydrogenation of aromatic ketones.[9] In this work, we examined the chiral PNNP−Ir(I) complex catalyst for enantioselective oxidation of a variety of secondary alcohols; typical results are shown in Table 2. It could be seen that for the oxidative kinetic resolution of racemic 1-phenylethanol (**2a**), the preformed chiral PNNP−Ir(I) complexes exhibited better reactivity and excellent enantioselectivity (69% yield, 98% ee; Table 2, run 1). The kinetic resolution of 1-phenyl-1-propanol (**2b**), 1-phenyl-1-butanol

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(8) A typical experimental procedure of oxidative kinetic resolution of 1-phenylethanol is as follows. To a mixture of (*R*,*R*)-**1** (0.005 mmol) and $[Ir(COD)Cl]_2$ (0.0025 mmol) was added anhydrous acetone (10 mL) under nitrogen. After the solution was stirred for 1 h at 25 °C, a solution of KOH in ^{i}PrOH and then racemic 1-phenylethanol (1 mmol) were slowly added. The solution was stirred at the desired temperature for the required reaction time. The chemical yield and ee of products were determined by chiral GC ananlysis on a Chiraldex G-TA column.

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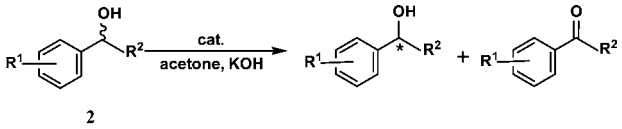
Table 2. Kinetic Resolution of Racemic Secondary Alcohols Catalyzed by Preformed Chiral PNNP−Ir(I) Complexes[a]



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a: R^1 = H, R^2 = CH_3; b: R^1 = H, R^2 = C_2H_5; c: R^1 = H, R^2 = $(CH_2)_2CH_3$; d: R^1 = H, R^2 = $(CH_2)_3CH_3$; e: R^1 = H, R^2 = $CH(CH_3)_2$; f: R^1 = CH_3, R^2 = CH_3; g: R^1 = Cl, R^2 = CH_3

run	alcohol	catalyst	time (h)	conv[b] (%)	ee[b] (%)	*s*
1	**2a**	[IrCl-(*R*,*R*)-**1**]	3	69	98	10
2	**2b**	[IrCl-(*S*,*S*)-**1**]	8	59	98	23
3	**2c**	[IrCl-(*S*,*S*)-**1**]	8	56	98	34
4[c]	**2d**	[IrCl-(*S*,*S*)-**1**]	20	63	97	14
5[d]	**2e**	[IrCl-(*S*,*S*)-**1**]	24	14	13	10
6[e]	*o*-**2f**	[IrCl-(*S*,*S*)-**1**]	20	8	4	3
7	*m*-**2f**	[IrCl-(*S*,*S*)-**1**]	3	62	97	15
8	*m*-**2g**	[IrCl-(*R*,*R*)-**1**]	2	61	88	10
9	*p*-**2g**	[IrCl-(*R*,*R*)-**1**]	5	75	97	7

[a] Reaction conditions: racemic secondary alcohol (1 mmol); catalyst (0.005 mmol); solvent: anhydrous acetone (10 mL); sub:cat.:KOH = 200:1:2; temperature: 25 °C. [b] Determined by GC using a chiral column (Chiraldex G-TA column). [c] Sub:cat.:KOH = 200:1:6. [d] Sub:cat.:KOH = 200:1:10. [e] Sub:cat.:KOH = 200:1:20.

(**2c**), and 1-phenyl-1-pentanol (**2d**) also proceeded smoothly with 97−98% ee (Table 2, runs 2−4). However, when the alkyl substituent group of the substrate was changed to bulkier isopropyl, the reaction proceeded slowly with low enantioselectivity (14% yield, 13% ee; Table 2, run 5). The decrease of reactivity and enantioselectivity may be caused by space handicap. The steric repulsion between alcohol and catalyst might prevent the formation of a favorable transition state, which gives high enantioselectivity.[3c] Next, enantioselective oxidation of phenylethanol derivatives was also investigated. Introduction of an electron-donating methyl to the ortho position of the aromatic ring would sharply decrease the reactivity and enantioselectivity of the reaction. Even with an extreme excess of KOH (20 equiv to the catalyst), the oxidation of racemic 1-(2-methylphenyl)ethanol (*o*-**2f**) for 20 h hardly occurred (8% yield, 4% ee; Table 2, run 6). On the other hand, the oxidative kinetic resolution of racemic 1-(3-methylphenyl)ethanol (*m*-**2f**) was carried out easily with 97% ee (Table 2, run 7). Introduction of an electron-withdrawing group such as an chloro substituent to the meta-position of the aromatic ring would decrease the enantioselectivity (61% yield, 88% ee; Table 2, run 8), while the enantioselective oxidation of racemic 1-(4-chlorophenyl)-ethanol (*p*-**2**g) exhibited a high chiral efficiency, with up to 75% yield and 97% ee (Table 2, run 9).

In summary, this work presents the first successful use of chiral PNNP−Ir(I) complex catalyst for the oxidative kinetic resolution of racemic secondary alcohols with up to 98% ee. The kinetic resolution reactions are carried out under mild conditions, and the workup procedure is simple. This result provides a useful index for designing efficient catalyst systems in achieving optically active alcohols.

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Supporting Information Available: Typical procedures for oxidative kinetic resolution of racemic secondary alcohols and GC analytical data for chiral aromatic alcohols. This material is available free of charge via the Internet at http://pubs.acs.org.

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