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Enantioselective Synthesis of Chiral β-Aryloxy Alcohols by Asymmetric Hydrogenation of α-Aryloxy Aldehydes *via* Dynamic Kinetic Resolution

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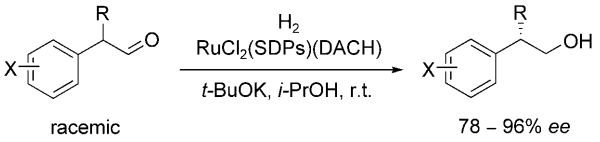
Abstract: A catalytic enantioselective hydrogenation of racemic α-aryloxy aldehydes *via* dynamic kinetic resolution has been developed by using (diamine)(spirodiphosphine)ruthenium(II) chloride [$RuCl_2$(SDPs)(diamine)] catalysts. Employing this new reaction system a variety of optically active β-aryloxy primary alcohols were synthesized in high yields and moderate to good enantioselectivities.

Keywords: aldehydes; β-aryloxy primary alcohols; asymmetric catalysis; dynamic kinetic resolution; ruthenium

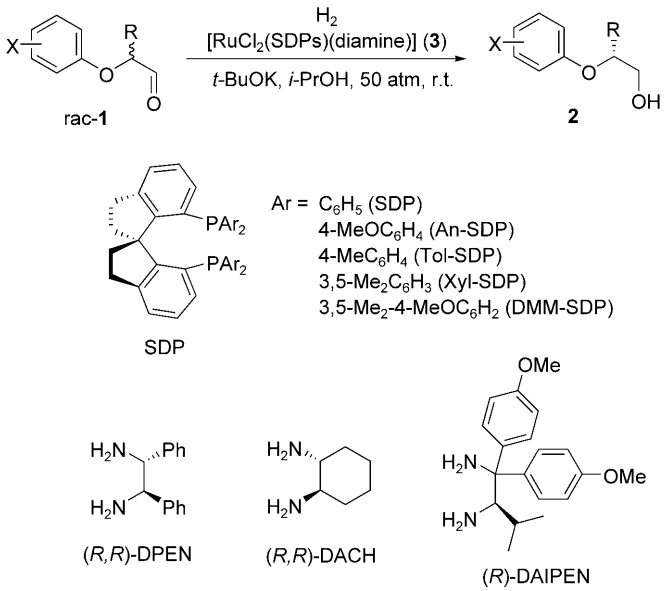
The catalytic asymmetric hydrogenation of prochiral ketones appears to be the most attractive route to produce enantiomerically enriched secondary alcohols.[1] One of the most efficient catalysts for this transformation is the chiral $RuCl_2$(diphosphine)-(diamine) complexes initially reported by Noyori and co-workers.[2] In the presence of base in 2-propanol, a wide range of simple ketones can be hydrogenated by chiral $RuCl_2$(diphosphine)(diamine) catalysts to the corresponding secondary alcohols in high enantiomeric excess at a very low catalyst loading.[3] However, due to the hydrogenation of the carbonyl group in aldehydes the latter cannot provide chiral alcohols, and people rarely consider to use an asymmetric hydrogenation of aldehydes to synthesize optically active compounds containing a primary alcohol function.[4] Recently, we reported the first example of the asymmetric hydrogenation of racemic α-aryl aldehydes *via* dynamic kinetic resolution (DKR) catalyzed by ruthenium complexes of chiral spirodiphosphines (SDPs) (Scheme 1).[5] As a continuing effort in this significant reaction, we herein disclose an enantioselective synthesis of chiral β-aryloxy alcohols by asymmetric hydrogenation of α-aryloxy aldehydes *via* DKR.

The enantiomerically enriched β-aryloxy primary alcohols are a very important class of building blocks for the synthesis of a wide variety of biologically active compounds. For example, enantiomerically pure 2-aryloxy-1-propanols are starting materials for the synthesis of sorbinil homologues,[6] juvenile hormones[7] and glucokinase activating agents.[8] However, the methods for the preparation of optically active β-aryloxy primary alcohols are limited to the ring-opening of chiral epoxides with phenol and its derivatives,[9] the resolution of racemic α-aryloxy alcohols with lipase-catalyzed enantioselective acylation,[10] and the conversions of lactic acid derivates.[11] Encouraged by the high activities and enantioselectivities of the $RuCl_2$(SDPs)(diamine) catalysts in the hydrogenation of α-aryl aldehydes, we investigated the asymmetric hydrogenation of α-aryloxy aldehydes catalyzed by $RuCl_2$(SDPs)(diamine) *via* DKR, targeting on the development of a new strategy for the preparation of enantiomerically enriched β-aryloxy primary alcohols (Scheme 2).

The asymmetric hydrogenation of 3-methyl-2-phenoxybutanal (**1a**) was chosen as a standard reaction to optimize the reaction conditions. The reaction was carried out in *i*-PrOH containing the catalyst {$RuCl_2$[(*S*)-SDP][(*R*,*R*)-DPEN]} [(*S*,*R*,*R*)-**3a**] and *t*-BuOK ([**1a**] = 0.2 mmol mL^{-1}, [*t*-BuOK] =



Scheme 1. Asymmetric hydrogenation of racemic α-aryl aldehydes.



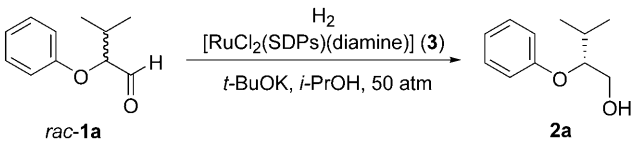
Scheme 2. Asymmetric hydrogenation of racemic α-aryloxy aldehydes *via* DKR.

0.04 mmol mL^{-1}, *S/C* = 1000) under 50 atm of H_2 at room temperature. After reacting for 8 h, the hydrogenation product, 3-methyl-2-phenoxybutanol (**2a**), was isolated in 98% yield with 62% *ee* (Table 1, entry 1). Comparison of spirodiphosphine ligands revealed that the ligand (*S*)-DMM-SDP bearing 4-methoxy-3,5-dimethylphenyls gave the highest enantioselectivity (74% *ee*, entry 5). Different diamines were then examined and the combination of diphosphine (*S*)-DMM-SDP and diamine (*R,R*)-DACH, (*S,R,R*)-**3h** showed to be the best catalyst, affording the hydrogenation product **2a** in 98% yield with 79% *ee* (entry 8). The commercially available Xyl-BINAP was also evaluated and the corresponding catalyst (*R,R,R*)-**4** gave a comparable result with Xyl-SDP catalyst (*S,R,R*)-**3i** (entry 10).

A strong base is essential for the quick racemization of the aldehyde substrate before hydrogenation. Although the base can promote a side reaction of aldehydes, no by-product was observed in the reactions with 0.02 (S/B = 10) and 0.04 mmol mL^{-1} (S/B = 5) of *t*-BuOK. When the concentration of *t*-BuOK was increased to 0.06 mmol mL^{-1} (S/B = 3.3) a trace amount of by-product was detected by TLC, while the yield and *ee* value of hydrogenation product have not been influenced (entry 12).

The substrate scope of the reaction was examined by using catalyst (*S,R,R*)-**3h**. A series of racemic α-aryloxy aldehydes can be hydrogenated to the corresponding primary alcohols in full conversions. As shown in Table 2, the hydrogenation of α-aryloxy aldehydes having a bulky alkyl substituent such as *i*-Pr, *c*-Pent, *c*-Hex and *t*-Bu at the α-position gave higher

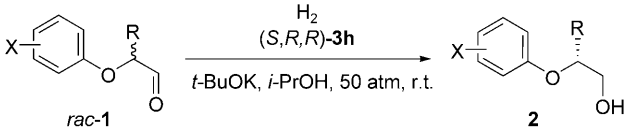
Table 1. Asymmetric hydrogenation of aldehyde **1a**, optimizing the reaction conditions.[a]



Entry	Catalyst	Diphosphine	Diamine	Yield [%][b]	*ee* [%][c]
1	(*S,R,R*)-**3a**	(*S*)-SDP	(*R,R*)-DPEN	98	62
2	(*S,R,R*)-**3b**	(*S*)-Tol-SDP	(*R,R*)-DPEN	96	66
3	(*S,R,R*)-**3c**	(*S*)-An-SDP	(*R,R*)-DPEN	94	70
4	(*S,R,R*)-**3d**	(*S*)-Xyl-SDP	(*R,R*)-DPEN	95	72
5	(*S,R,R*)-**3e**	(*S*)-DMM-SDP	(*R,R*)-DPEN	98	74
6[d]	(*S,S*)-**3f**	(*S*)-DMM-SDP	(*S*)-DAIPEN	54	9
7[e]	(*R,S*)-**3g**	(*R*)-DMM-SDP	(*S*)-DAIPEN	27	0
8	(*S,R,R*)-**3h**	(*S*)-DMM-SDP	(*R,R*)-DACH	98	79
9	(*S,R,R*)-**3i**	(*S*)-Xyl-SDP	(*R,R*)-DACH	93	77
10	(*R,R,R*)-**4**	(*R*)-Xyl-BINAP	(*R,R*)-DACH	95	77
11[f]	(*S,R,R*)-**3h**	(*S*)-DMM-SDP	(*R,R*)-DACH	96	78
12[g]	(*S,R,R*)-**3h**	(*S*)-DMM-SDP	(*R,R*)-DACH	95	77

[a] *Reaction conditions:* S/C = 1000, [**1a**] = 0.2 mmol mL^{-1}, [*t*-BuOK] = 0.04 mmol mL^{-1}, *i*-PrOH, room temperature (20–25 °C), 50 atm of H_2, 8 h, 100% conversion.
[b] Isolated yield from chromatography on silica gel.
[c] Determined by HPLC with a Chiralcel OD-H column.
[d] 56% conversion. The product **2a** has a same optical rotation with the product obtained by catalyst (*S,R,R*)-**3a**.
[e] 32% conversion.
[f] [*t*-BuOK] = 0.02 mmol mL^{-1}.
[g] [*t*-BuOK] = 0.06 mmol mL^{-1}.

Table 2. Asymmetric hydrogenation of racemic α-aryloxy aldehydes **1** catalyzed by (*S,R,R*)-**3h**.[a]



Entry	Substrate	R	X	Yield [%][b]	*ee* [%][c]
1	**1a**	*i*-Pr	H	98	79
2	**1b**	Me	H	94	40 (*R*)
3	**1c**	Et	H	93	53
4	**1d**	Bn	H	95	41
5	**1e**	*c*-Pent	H	96	71
6	**1f**	*c*-Hex	H	97	71
7	**1g**	*t*-Bu	H	94	74
8	**1h**	*i*-Pr	4-Me	95	78
9	**1i**	*i*-Pr	4-MeO	93	81
10	**1j**	*i*-Pr	4-Cl	93	71
12	**1k**	*i*-Pr	4-*t*-Bu	96	78
13	**1l**	*i*-Pr	3-Me	93	76
14	**1m**	*i*-Pr	3-MeO	96	79
15	**1n**	*i*-Pr	3-Br	92	78
16	**1o**	*i*-Pr	2-Me	93	78
17	**1p**	*i*-Pr	2-MeO	98	81
18	**1q**	*i*-Pr	1-Naph	93	74

[a] *Reaction conditions:* S/C = 1000, [substrate] = 0.2 mmol mL^{-1}, [*t*-BuOK] = 0.04 mmol mL^{-1}, *i*-PrOH, room temperature (20–25 °C), 50 atm of H_2, 8 ~ 10 h, 100% conversion.

[b] The yield was obtained by chromatography on silica gel.

[c] The *ee* values were determined by chiral HPLC using chiral OD-H or AD-H column.

enantioselectivities (71–74% *ee*) (Table 2, entries 1 and 5–7). While the substrates with a smaller alkyl group such as Me, Et and benzyl showed lower enantioselectivities (40–53% *ee*) (entries 2–4). This trend is similar to that observed in the asymmetric hydrogenation of α-aryl aldehydes.[5a] The electronic property and the position of the substituent on the aryloxy group of the aldehydes have very little impact on the enantioselectivity of the reaction (71–81% *ee*, entries 8–18).

The asymmetric hydrogenation of racemic α-alkyloxy aldehydes was also evaluated under the same reaction conditions, but low enantioselectivities were obtained. For example, the hydrogenation of racemic 2-(benzyloxy)butanal with catalyst (*S,R,R*)-**3h** furnished the 2-(benzyloxy)butanol in 93% yield with 20% *ee*.

In conclusion, we have developed an efficient enantioselective hydrogenation of racemic α-aryloxy aldehydes *via* dynamic kinetic resolution by using $RuCl_2$(SDPs)(diamine) complexes as catalysts. This reaction provides a new method to the synthesis of optically active β-aryloxy primary alcohols.

Experimental Section

General Procedure for Asymmetric Hydrogenation of Racemic α-Aryloxy Aldehydes

The catalyst (0.002 mmol) was placed in a 30-mL hydrogenation vessel. Anhydrous *i*-PrOH (8.0 mL) was introduced with a syringe and the vessel was purged with hydrogen and pressurized to 40 atm for 5 min. After releasing the pressure, the α-aryloxy aldehyde (2 mmol) and a solution of *t*-BuOK in *i*-PrOH (0.2 mmol mL^{-1}, 2.0 mL, 0.4 mmol) were added. The vessel was purged with hydrogen and pressurized to 50 atm. After stirring at room temperature for 8 h, the reaction was stopped. The solvent was vaporized and the residue was subjected to chromatography on a silica gel column, the pure alcohol was weighed to determine the yield. The enantioselectivity was determined by HPLC using a Chiralpak OD-H column or Chiralpak AD-H column.

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