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Ru-Catalyzed Asymmetric Hydrogenation of Racemic Aldehydes via Dynamic Kinetic Resolution: Efficient Synthesis of Optically Active Primary Alcohols

Jian-Hua Xie, Zhang-Tao Zhou, Wei-Ling Kong, and Qi-Lin Zhou*

State Key Laboratory and Institute of Elemento-organic Chemistry, Nankai University, Tianjin 300071, China

Received November 9, 2006; E-mail: qlzhou@nankai.edu.cn

Catalytic asymmetric hydrogenation is one of the most elegant and reliable methods for the preparation of optically active compounds and has been widely used in industry.[1] Among the numerous chiral catalysts developed in past decades, the Noyori [$RuCl_2$(BINAP)(diamine)] catalyst has proved to be the most efficient, catalyzing the hydrogenation of prochiral ketones with excellent enantioselectivity with an extremely high turn-over number.[2] Using different [$RuCl_2$(diphosphine)(diamine)] catalysts, a variety of chiral secondary alcohols now can be easily synthesized from the hydrogenation of prochiral ketones in high enantiomeric excesses.[3] Although the chiral primary alcohols are exceedingly significant compounds for both academic research and industrial production,[4] few catalytic methods for their synthesis by asymmetric hydrogenation have appeared in the literature.[5]

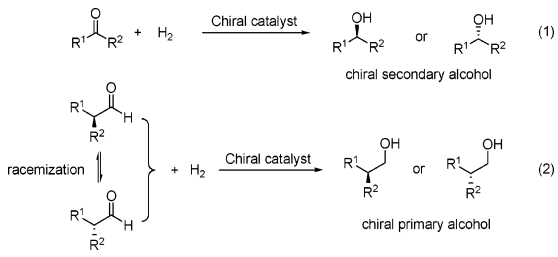
In the catalytic asymmetric hydrogenation of prochiral ketones, at least one new stereogenic center was generated (Scheme 1, eq 1).[6] However, no new stereogenic center was generated in the hydrogenation of α-branched aldehydes, which makes the enantiocontrol of the reaction extremely difficult. Thus, the asymmetric hydrogenation of α-branched aldehydes still remains a challenge to chemists.[7] If a catalyst can selectively hydrogenate one of two enantiomers of the racemic aldehyde and the remaining enantiomer can be rapidly racemized under the same reaction conditions, then ultimately two enantiomers of aldehyde will be fully converted to primary alcohol enantioselectively (Scheme 1, eq 2). This process is termed the asymmetric hydrogenation of racemic aldehydes via dynamic kinetic resolution (DKR).[8]

In studying the synthesis of biologically active compounds such as chiral pesticides and enzyme inhibitors, we became interested in developing methods for the asymmetric synthesis of chiral primary alcohols. The complexes [$RuCl_2$(SDPs)(diamine)] recently developed by us,[3f,9] were found to be competent catalysts for the asymmetric hydrogenation of racemic α-branched aldehydes via DKR, which provided a practical access to chiral primary alcohols in high enantiomeric excess (up to 96% ee) and in high yields (Scheme 2).

Initially, we chose as catalyst [$RuCl_2$((*S*)-Xyl-SDP)((*R*,*R*)-DPEN)] ((*S*,*RR*)-**3a**), which has been demonstrated to be very efficient for asymmetric hydrogenation of ketones[3f,9] and, as the standard substrate, the commercially available α-phenylpropionaldehyde (**1a**). When racemic **1a** was hydrogenated in ^{i}PrOH containing (*S*,*RR*)-**3a** and KO^{t}Bu (*S*/*C* = 1000, [**1a**] = 0.2 M, [KO^{t}Bu] = 0.04 M) under 50 atm of H_2 at room temperature for 8 h, (*S*)-2-phenylpropan-1-ol (**2a**) was obtained in 95% yield with 69% ee (Table 1, entry 1). Systematic investigation of Ru complexes with different combinations of chiral spirobiindane diphosphines and chiral diamines, showed that the complex [$RuCl_2$((*S*)-DMM-SDP)((*R*,*R*)-DACH)] ((*S*,*RR*)-**3j**) was the best choice of catalyst (Table 1, entry 10).

Using catalyst (*S*,*RR*)-**3j**, a range of racemic α-arylaldehydes **1** have been hydrogenated, and the results are summarized in Table 2. It is evident that a bulky alkyl group at the α-position of the aldehydes **1** is crucial for obtaining high enantioselectivity. The highest enantioselectivity (96% ee) was achieved in the hydrogenation of the aldehyde with a *i*-Pr group at the α-position (Table 2, entry 3). The position and electronic property of substituents on the aryl ring of the substrate has very little influence on the enantiomeric excess of products. The catalyst loading can be lowered to 0.02 mol % (*S*/*C* = 5000). Of special note, the hydrogenation

Scheme 1



Scheme 2

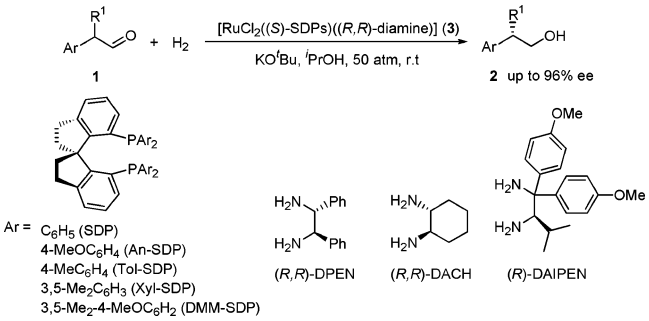
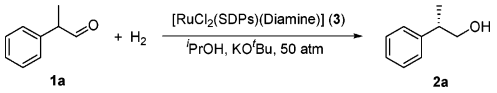


Table 1. Asymmetric Hydrogenation of Racemic **1a** with [$RuCl_2$(SDPs)(diamine)] Catalysts **3**[a]



entry	catalyst	SDPs	diamine	ee (%)[b]
1	(*S*,*RR*)-**3a**	(*S*)-Xyl-SDP	(*R*,*R*)-DPEN	69
2	(*S*,*SS*)-**3b**	(*S*)-Xyl-SDP	(*S*,*S*)-DPEN	12
3	(*S*,*RR*)-**3c**	(*S*)-SDP	(*R*,*R*)-DPEN	45
4	(*S*,*RR*)-**3d**	(*S*)-An-SDP	(*R*,*R*)-DPEN	47
5	(*S*,*RR*)-**3e**	(*S*)-Tol-SDP	(*R*,*R*)-DPEN	43
6	(*S*,*RR*)-**3f**	(*S*)-DMM-SDP	(*R*,*R*)-DPEN	70
7	(*R*,*S*)-**3g**	(*R*)-Xyl-SDP	(*S*)-DAIPEN	6
8	(*S*,*S*)-**3h**	(*S*)-Xyl-SDP	(*S*)-DAIPEN	58
9	(*S*,*RR*)-**3i**	(*S*)-Xyl-SDP	(*R*,*R*)-DACH	77
10	(*S*,*RR*)-**3j**	(*S*)-DMM-SDP	(*R*,*R*)-DACH	78

[a] Reaction conditions: *S*/*C* =1000, [**1a**] = 0.2 mmol/mL, [^{t}BuOK] = 0.04 mmol/mL, ^{i}PrOH, room temperature (25 to 30 °C), 50 atm of H_2, 8 h, 100% conversion. [b] Determined by chiral GC (Supelco β-DEX 225 column). The absolute configuration was *S*.

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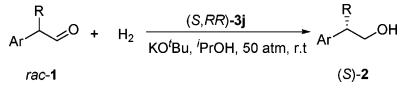
Table 2. Asymmetric Hydrogenation of Racemic α-Arylaldehydes **1** Catalyzed by (*S*,*RR*)-**3j**[a]

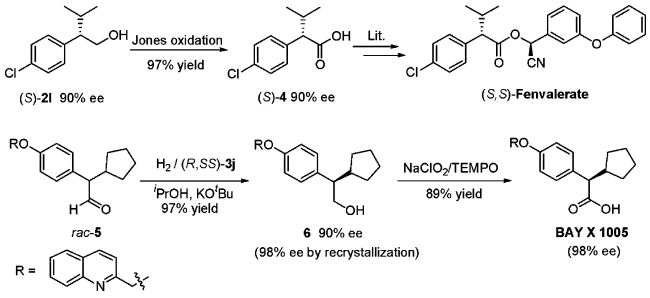


rac-**1** (*S*)-**2**

entry	substrate	R	Ar	ee (%)[b]
1	**1a**	Me	C_6H_5	78
2	**1b**	Et	C_6H_5	86
3	**1c**	*i*-Pr	C_6H_5	96 (91)[c,d]
4	**1d**	*c*-Pent	C_6H_5	92
5	**1e**	*c*-Hex	C_6H_5	92
6	**1f**	*i*-Pr	2-MeC_6H_4	95
7	**1g**	*i*-Pr	2-ClC_6H_4	93
8	**1h**	*i*-Pr	3-MeC_6H_4	89
9	**1i**	*i*-Pr	3-$MeOC_6H_4$	93
10	**1j**	*i*-Pr	4-MeC_6H_4	93
11	**1k**	*i*-Pr	4-$MeOC_6H_4$	94
12	**1l**	*i*-Pr	4-ClC_6H_4	90
13	**1m**	*i*-Pr	2-Naphthyl	89
14	**1n**	*c*-Hex	4-MeC_6H_4	92
15	**1o**	*c*-Hex	4-$MeOC_6H_4$	94

[a] Reaction conditions are same as those in Table 1; 100% conversion. [b] The ee values were determined by chiral GC or HPLC. The absolute configuration was *S*. [c] The data in parentheses was obtained by using 0.02 mol % catalyst, 32 h. [d] An amount of 94% ee was obtained by using the catalyst [$RuCl_2$((*R*)-Xyl-BINAP)((*R*,*R*)-DACH)].

Scheme 3



of aldehyde **1k** afforded the alcohol **2k** in 94% ee (Table 2, entry 11). This product is the key intermediate for the synthesis of natural product (1*S*,4*S*)-*cis*-7-methoxy-calamenene.[10]

The prepared chiral primary alcohols are very useful in the synthesis of chiral pharmaceuticals, pesticides, and natural products. For example, the alcohol **2l** (90% ee) was oxidized by Jones reagent to (*S*)-2-(4-chlorophenyl)-3-methylbutanoic acid ((*S*)-**4**), which is the key chiral intermediate for the preparation of pyrethroid pesticide (*S*,*S*)-fenvalerate, in 97% yield without loss of optical purity (Scheme 3). Quinolylmethoxyphenyl acetic acid derivatives were important leukotriene receptor antagonists and lipoxygenase inhibitors such as BAY × 1005[11] and can be easily synthesized by our method. The hydrogenation of racemic substrate **5** with catalyst (*R*,*SS*)-**3j** produced the chiral primary alcohol **6** in 97% yield with 90% ee (98% ee after recrystallization). Oxidation of the alcohol **6** by $NaClO_2$/TEMPO gave the compound BAY × 1005 in 89% yield with 98% ee (Scheme 3).[12] These examples illustrate the wide applicability of the catalytic asymmetric hydrogenation of aldehydes.

To determine that the asymmetric hydrogenation via DKR is performed by hydrogenation of the carbonyl group, instead of the enol form of aldehydes, a deuteration of **1c** was carried out. The ^{1}H NMR analysis of the hydrogenation product showed that the majority of the deuteration took place at the α-position (58%), with less than 5% deuterium observed at the β-position, thus confirming that the hydrogenation of aldehyde with [$RuCl_2$(SDPs)(diamine)] catalysts occurs on the carbonyl group.[13]

In conclusion, this Ru-catalyzed asymmetric hydrogenation of racemic α-arylaldehydes via dynamic kinetic resolution provided a highly efficient and economical method for the synthesis of chiral primary alcohols. The method shows great potential for wide application in the synthesis of optically active pharmaceuticals and natural products.

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Supporting Information Available: Experimental procedures, the characterizations of substrates and products, and the analysis of ee values of hydrogenation products (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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