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Synthesis of optically active benzyl-α-*d* alcohols by asymmetric hydrogenation of benzaldehyde-α-*d* and its derivatives catalyzed by BINAP-Ru(II) complexes

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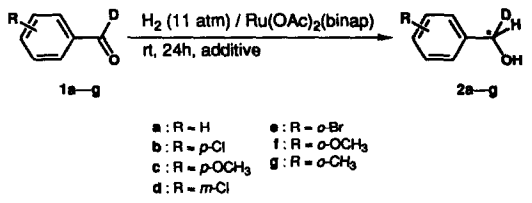
Abstract

Optically active benzyl-α-*d* alcohols have been synthesized in up to 89% ee by asymmetric hydrogenation of benzaldehyde-α-*d* and its derivatives catalyzed by BINAP-Ru(II) complexes. A remarkable enhancement in enantioselectivities has been observed for *o*-bromo- and *o*-methoxy-benzaldehyde-*d*, but moderate enantioselectivities for *o*-methyl and other *m*- and *p*-substituted derivatives.

Keywords: Ruthenium; Asymmetric hydrogenation; BINAP; Aldehyde; Catalysis; Chirality

1. Introduction

Isotopically labeled optically active primary alcohols, RCDHOH, are important compounds for the mechanistic studies of chemical and biochemical reactions [1]. Enantiomerically pure primary 1-deuterio alcohols have been obtained through catalytic processes by using enzymes. Though some chiral reducing agents have been reported to reduce aldehydes in excellent enantiomeric excesses [2,3], there exists only a few reports on the catalytic asymmetric synthesis of 1-deuterio alcohols by asymmetric hydrogenation of 1-deuterio aldehydes [4]. Here, we report a novel synthesis of alcohols of this type through asymmetric hydrogenation of benzaldehyde-α-*d* [5] and its derivatives catalyzed by BINAP-Ru(II) complexes which are known to be highly efficient catalysts for asymmetric hydrogenation of prochiral carbonyl compounds [3c,6,7]



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2. Experimental details and discussion

As catalysts, either a monomeric diacetate complex, $Ru(OAc)_2$(binap) [8], or a halogen-containing dimeric BINAP-Ru(II) complex, Ru_2Cl_4(binap)$_2$(NEt_3) [9], was used. The choice of catalyst was dependent upon the solvent used. The reaction was carried out at room temperature under a hydrogen pressure of 11 atm with the substrate : catalyst ratio (S : C) of 85-100. Some selected results are shown in Table 1. ^{1}H-NMR analysis showed that no loss of deuterium occurred during hydrogenation.

Reports on the hydrogenation of other carbonyl compounds [6,7] show that higher enantiomeric excesses were obtained from reactions in methanol as solvent (run 1) than in THF (29% ee). Interestingly, the use of a mixture of THF and methanol increased the yields and the rates of the hydrogenation without significant changes in enantioselectivity (run 1 vs. 2). For reactions in methanol or a mixture of methanol and THF, $Ru(OAc)_2$(binap) was the catalyst of choice because the halogen-containing catalyst Ru_2Cl_4(binap)$_2$(NEt_3) afforded mainly dimethylacetal of the starting aldehydes. The latter complex, however, was used as catalyst in aqueous THF (run 7). It is noteworthy that the addition of a small amount of 0.2 N HCl (ca. 5 equivs. to Ru) to the catalytic system in THF

Table 1
Asymmetric hydrogenation of **1** catalyzed by BINAP–Ru(II) complexes [1]

Run	Substrate	Catalyst	S:C	Solvent	Additive	Time (h)	Yield (%) [2]	ee (%) [3]	^{1}H-NMR of ArCD*H*OH [3]		
									Major, δ	Minor, δ	Config.
1	**1a**	$Ru(OAc)_2$((*R*)-binap)	85	MeOH	none	48	64	65	12.90	13.07	(*S*)-(+)
2	**1a**	$Ru(OAc)_2$((*R*)-binap)	90	THF/MeOH(1/1)	none	48	> 99	65	15.80	16.04	(*S*)-(+)
3	**1a**	$Ru(OAc)_2$((*R*)-binap)	100	THF	aq.HCl	24	> 99	65	15.15	15.37	(*S*)-(+)
4	**1b**	$Ru(OAc)_2$((*R*)-binap)	100	THF/MeOH(1/1)	none	23	40	38	21.48	21.73	–
5	**1b**	$Ru(OAc)_2$((*R*)-binap)	100	THF	aq.HCl	24	> 99	70	26.50	26.79	–
6	**1b**	$Ru(OAc)_2$((*R*)-binap)	100	THF	H_2O	24	26	–	–	–	–
7	**1b**	Ru_2Cl_4((*S*)-binap)$_2$(NEt_3)	100	THF	H_2O	24	> 99	70	15.56	15.39	–
8	**1c**	$Ru(OAc)_2$((*R*)-binap)	100	THF	aq.HCl	24	> 99	59	26.14	26.43	–
9	**1d**	$Ru(OAc)_2$((*R*)-binap)	100	THF	aq.HCl	24	67	73	13.41	13.65	–
10	**1e**	$Ru(OAc)_2$((*R*)-binap)	100	THF	aq.HCl	24	> 99	89	10.96	11.06	(*S*)-(+) [4]
11	**1f**	$Ru(OAc)_2$((*R*)-binap)	85	THF	aq.HCl	24	> 99	82	17.04	17.42	–
12	**2g**	$Ru(OAc)_2$((*R*)-binap)	85	THF	aq.HCl	24	> 99	70	19.80	20.13	–

[1] A solution of the substrate (1 mmol/5.0 mL) and the catalyst was stirred under H_2 (11 atm) at room temperature.
[2] Determined by ^{1}H-NMR analysis of the reaction mixture using tetramethylsilane as internal standard.
[3] Determined by ^{1}H-NMR spectroscopy in the presence of ca. 0.5 equiv. of tris[heptafluoropropylhydroxymethyllene-(+)-camphorato]europium, $Eu(hfc)_3$.
[4] The absolute configuration of **2e** was determined after reduction of **2e** to **2a** by $LiAlH_4$.

increased the ee values in some cases (runs 4-6). Some effects of the addition of aqueous HCl on catalytic activity and enantioselectivity were also found for the hydrogenation of ketones catalyzed by Ru_2Cl_4(binap)(NEt_3) [6c] and [RuCl(binap)(benzene)]Cl [6d].

Asymmetric hydrogenation of *o*-bromobenzaldehyde-*α-d* and *o*-methoxybenzaldehyde-*α-d* with hetero-atom substituents in the ortho position gave the corresponding benzyl-*α-d* alcohols **2e** and **2f** in 89% ee and 82% ee, respectively. Hydrogenation of *o*-methyl- and other meta- and para-substituted benzaldehyde-*α-d* derivatives proceeded in moderate enantioselectivities (59-73% ee). These results suggest that a hetero-atom located in a position near to the formyl group in the substrates exerts some directing influence on enantioselectivity through an interaction with the BINAP-Ru(II) catalytic center. Such a halogen atoms effect has been observed for asymmetric reduction of *o*-bromoacetophenone catalyzed by a similar catalytic system [6a]. Many functionalized olefins and ketones with hetero-atom substituents at neighboring positions have also been hydrogenated in high enantioselectivities by using BINAP-Ru catalysts [3c,7]. The bromine atom in the product (+)-**2e** was removed without racemization by treatment with $LiAlH_4$ to give (*S*)-**2a** [10]. Thus, the absolute configuration of (+)-**2e** was determined to be S. Hydrogenation of benzaldehyde-*α-d* (**1a**) by Ru$(OAc)_2$((*R*)-binap) also gave (*S*)-predominant benzyl-*α-d* alcohol [11], although the enantioselectivity was only moderate (runs 1-3).

Catalytic asymmetric deuteration of benzaldehydes was also carried out using a similar catalytic system. However, the deuteration of benzaldehydes in a methanol-containing solution was unsuccessful; it afforded, primarily, non-deuterated benzyl alcohols. This result suggests that the D-H exchange between the ruthenium-deuteride complex and methanol is rather fast compared with the rate of deuteration. Deuteration of benzaldehydes in CH_3OD was also unsuccessful becuase the reaction proceeded very slowly (40% conversion after 24 h) resulting in the formation of non-deuterated products (2-3%).

3. Conclusion

In conclusion, the asymmetric hydrogenation of benzaldehyde-*α-d* (**1a**) and its derivatives catalyzed by BINAP-Ru(II) complexes gave the corresponding benzyl-*α-d* alcohols in moderate to high enantioselectivities. In the case of *o*-bromobenzaldehyde-*α-d* (**1e**), the enantiomeric excess of the product **2e** reached 89%. This is, to our knowledge, the first example of the synthesis of optically active benzyl-*α-d* alcohols through asymmetric hydrogenation of the corresponding aldehydes-*α-d* catalyzed by chiral transition metal complexes. Further investigation to extend this method to the synthesis of optically active aliphatic primary alcohols-*α-d* is now under investigation.

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