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Asymmetric Transfer Hydrogenation of Benzaldehydes

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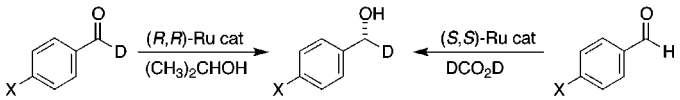
ABSTRACT



X = H, CH_3, OCH_3, Br, CF_3
Ru cat = RuCl[(*R*,*R*)- or (*S*,*S*)-NTsCH(C_6H_5)CH(C_6H_5)NH_2](η^6-arene)

A combined system of RuCl[(*R*,*R*)-YCH(C_6H_5)CH(C_6H_5)NH_2](η^6-arene) (Y = $NSO_2C_6H_4$-4-CH_3 or O) and *t*-C_4H_9OK catalyzes the asymmetric transfer hydrogenation of various benzaldehyde-*1-d* derivatives with 2-propanol to yield (*R*)-benzyl-*1-d* alcohols in 95–99% ee and with >99% isotopic purity. Reaction of benzaldehydes with a DCO_2D-triethylamine mixture and the *R*,*R* catalyst affords the *S* deuterated alcohols in 97–99% ee.

Chiral deuterated benzyl alcohol and its derivatives serve as useful probes in stereochemistry and mechanistic organic chemistry.[1] Although various asymmetric metal hydride reductions of benzaldehydes are known,[2] more useful hydrogenative methods have yet to be developed. Currently, the best methods[3] for asymmetric hydrogenation of aromatic ketones saturate benzaldehydes with only moderate enantioselectivity. For example, hydrogenation of benzaldehyde-*1-d* (**1a**) with $RuCl_2$[(*S*)-tolbinap][(*S*)-daipen][4] and *t*-C_4H_9OK yielded (*S*)-benzyl-*1-d* alcohol [(*S*)-**2a**] in 46% ee,[5] while a reaction with $Ru(OCOCH_3)_2$ [(*R*)-binap] under acidic conditions produced (*S*)-**2a** in 65% ee.[6] Other chiral Ru and Rh complexes exhibit even less satisfactory stereoselectivity and/or catalytic activity. In the present study, we disclose the first highly enantioselective catalytic transfer hydrogenation of benzaldehydes utilizing a chiral diamine-based or amino alcohol-based Ru(η^6-arene) catalyst and 2-propanol or formic acid as a hydrogen donor.[7−9]

When a 0.1 M solution of **1a** in 2-propanol containing RuCl[(*R*,*R*)-tsdpen](η^6-*p*-cymene) [(*R*,*R*)-**3a**][8,10] and *t*-C_4H_9-OK (aldehyde:Ru:base = 200:1:5) was mixed in an atmosphere of Ar at 22 °C for 30 min, (*R*)-**2a** was obtained in 98% ee[11] and in 100% yield. The formation of d_0 and d_2 products was negligible. Unlike reduction of aromatic ketones

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(10) TsDPEN = anion of *N*-tosyl-1,2-diphenylethylenediamine, [$N(SO_2$-C_6H_4-4-CH_3)CH(C_6H_5)CH(C_6H_5)NH_2]$^-$.

(11) The ee value of the alcohols was determined by 500 MHz ^{1}H NMR analysis of the MTPA esters. The inherent errors are considered to be within ±1%. Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512−519.

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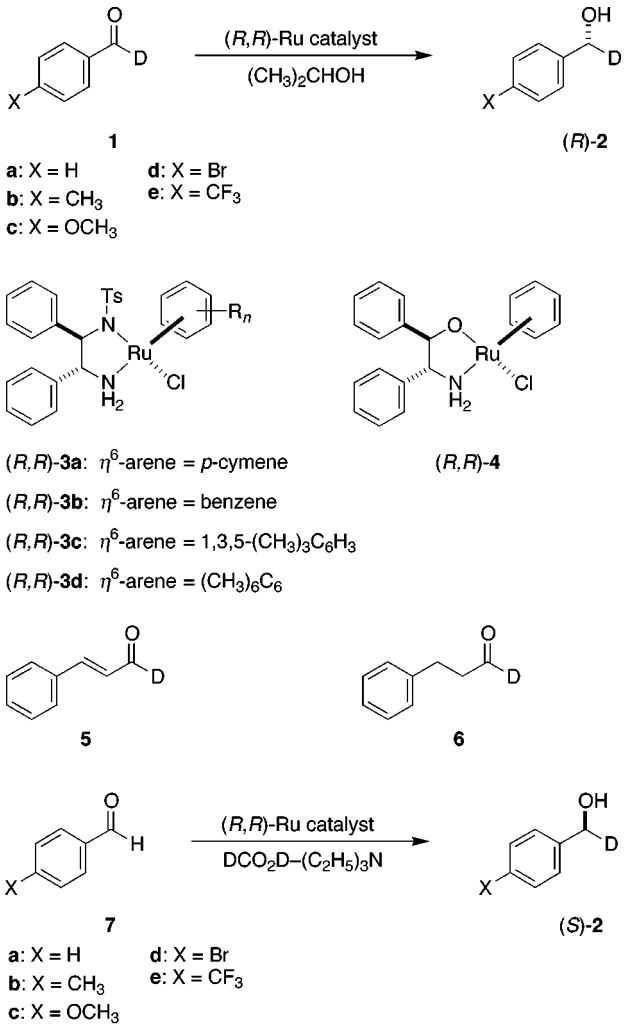

in which enantiomeric purity of the alcoholic products deteriorates as the reaction proceeds,[7,8] the reaction of benzaldehyde and its derivatives **1a**−**e** showed a consistently high enantioselectivity throughout the reaction. This was due to the favorable alcohol/carbonyl thermodynamic balance.[12] However, unnecessary prolonged standing after 100% conversion should be avoided to preserve a high degree of kinetic stereoselection.

Table 1 lists some examples of the reactions. The diamine-based Ru complexes (*R*,*R*)-**3b**−**d** possessing an η^6-benzene, -mesitylene, or -hexamethylbenzene ligand can also be used. A gram-scale reaction was performed with high reproducibility without any special techniques.[13] An Ru catalyst generated in situ from [RuCl$_2$(η^6-arene)]$_2$, *N*-monotosylated (*R*,*R*)-1,2-diphenylethylenediamine, and KOH afforded a similar result. Thus, this asymmetric catalysis provides a convenient way to obtain chiral deuterated benzyl alcohols. Nonaromatic aldehydes provide a lower enantioselectivity. For example, reaction of *trans*-cinnamaldehyde-*1-d* (**5**) catalyzed by (*R*,*R*)-**3b** produced (*R*)-cinnamyl-*1-d* alcohol in 72% ee, while dihydrocinnamaldehyde-*1-d* (**6**), an alkanal, with (*R*,*R*)-**3a** afforded the *R* alcohol in only 24% ee.

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Table 1. Asymmetric Transfer Hydrogenation of Benzaldehydes Using 2-Propanol[a] or Formic Acid[b]

				alcohol **2**[d]	
aldehyde	Ru(II) cat.	hydrogen source	time (h)	convn[c] (%)	% ee[e] (config)
1a	(*R*,*R*)-**3a**	(CH$_3$)$_2$CHOH	0.5	100	98 (*R*)
1a[f]	(*R*,*R*)-**3a**	(CH$_3$)$_2$CHOH	0.8	100	96 (*R*)
1a	(*R*,*R*)-**3b**	(CH$_3$)$_2$CHOH	0.5	100	97 (*R*)
1a	(*R*,*R*)-**3b**[g]	(CH$_3$)$_2$CHOH	0.33	97	96 (*R*)
1a	(*R*,*R*)-**3c**	(CH$_3$)$_2$CHOH	0.75	98	95 (*R*)
1a	(*R*,*R*)-**3d**	(CH$_3$)$_2$CHOH	7	99	96 (*R*)
1b	(*R*,*R*)-**3a**	(CH$_3$)$_2$CHOH	1	99	98 (*R*)
1c	(*R*,*R*)-**3a**	(CH$_3$)$_2$CHOH	1	87	99 (*R*)
1d	(*R*,*R*)-**3a**	(CH$_3$)$_2$CHOH	1	97	96 (*R*)
1e	(*R*,*R*)-**3a**	(CH$_3$)$_2$CHOH	1	98	96 (*R*)
5[h]	(*R*,*R*)-**3b**	(CH$_3$)$_2$CHOH	0.25	97	72 (*R*)
6	(*R*,*R*)-**3a**	(CH$_3$)$_2$CHOH	0.1	90	24 (*R*)
7a[i]	(*R*,*R*)-**3a**	DCO$_2$D	4	93	98 (*S*)
7b	(*R*,*R*)-**3a**	DCO$_2$D	4	92	98 (*S*)
7c	(*R*,*R*)-**3a**	DCO$_2$D	14	97	99 (*S*)
7d	(*R*,*R*)-**3a**	DCO$_2$D	6	99	99 (*S*)
7e	(*R*,*R*)-**3a**	DCO$_2$D	2	95	97 (*S*)

[a] The reaction was carried out at room temperature using a 0.1 M solution of **1** (1.0 mmol) in 2-propanol (**1**:Ru:*t*-C$_4$H$_9$OK = 200:1:4). [b] The reaction was carried out at 28 °C using an acetonitrile solution of **7** (10 mmol) (**7**:Ru:DCO$_2$D:(C$_2$H$_5$)$_3$N = 200:1:200:200). [c] Determined by GLC analysis. The value is close to yield; no byproduct was detected. [d] The d_1 content was >99%. [e] Determined by ^{1}H NMR analysis of the corresponding MTPA ester. [f] Reaction using 10 mmol of **1a**. [g] The Ru catalyst was generated in situ from [RuCl$_2$(η^6-benzene)]$_2$, (*R*,*R*)-HTsDPEN, and KOH (0.5:1:5). [h] **5**:Ru:*t*-C$_4$H$_9$OK = 100:1:6. [i] Reaction using 1.0 mmol of **7a**.

When [RuCl(η^6-benzene)]$_2$ was mixed with (*R*,*R*)-1,2-diphenylethanolamine[9] and *t*-C$_4$H$_9$OK in a 0.5:1:1 molar ratio in 2-propanol at 28 °C for 1 h, RuCl[(*R*,*R*)-OCH(C$_6$H$_5$)CH(C$_6$H$_5$)NH$_2$](η^6-benzene) [(*R*,*R*)-**4**] was generated, as substantiated by electrospray ionization mass analysis showing an [M + 1]$^+$ peak at 428.[14] Reaction of [RuCl(η^6-benzene)]$_2$, (*R*,*R*)-1,2-diphenylethanolamine, and triethylamine (0.5:1:7 molar ratio) in 2-propanol at 90 °C also produced (*R*,*R*)-**4** in 93% yield. A systematic investigation using this simple η^6-benzene−Ru complex and a series of *para*-substituted benzaldehyde-*1-d* derivatives (**1**:**4**:*t*-C$_4$H$_9$OK = 200:1:4, [**1**] = 0.1 M in 2-propanol, 28 °C, 0.5−6 h) provided interesting information, albeit with moderate enantioselectivity. The % ee of the *R* product and the relative rates of reduction (in parentheses) were *p*-CH$_3$O, 61% (0.55); *p*-CH$_3$, 49% (0.95); H, 45% (1.0); *p*-Br, 37% (1.5); *p*-CF$_3$, 20% (1.6).[15] The

(13) Transfer hydrogenation of **1a** in 2-propanol catalyzed by (*R*,*R*)-**3a**: A mixture of **1a** (1.07 g, 10.0 mmol), **3a** (31.8 mg, 50 μmol),[8b] and 1.0 M *t*-C$_4$H$_9$OK in *t*-C$_4$H$_9$OH (50 μL, 0.05 mmol) in 2-propanol (100 mL) was stirred at 22 °C for 50 min. After dilution with water, the product was extracted with ethyl acetate, and the organic layer was washed with an aqueous NaHCO$_3$ and brine, dried over Na$_2$SO$_4$, and concentrated. Bulb-to-bulb distillation at 100−101 °C/15 mmHg afforded (*R*)-**2a** (1.00 g, 92% yield) in 96% ee.[11] ^{1}H NMR of benzylic proton of (*R*)-MTPA ester: *S* isomer, δ 5.31; *R* isomer, δ 5.36.

(14) ^{1}H NMR (CDCl$_3$): δ 4.41 (m, 1, CHO), 4.75 (m, 1, CHN), 5.30 (br s, 6, η^6-C$_6$H$_6$), 5.36 (m, 1, NH), 5.49 (m, 1, NH), 6.9−7.5 (m, 10, C$_6$H$_5$). For a similar complex, see: Hennig, M.; Püntener, K.; Scalone, M. *Tetrahedron: Asymmetry* **2000**, *11*, 1849−1958. Structural determination by ESI mass spectroscopy: Kenny, J. A.; Versluis, K.; Heck, A. J. R.; Walsgrove, T.; Wills, M. *Chem. Commun.* **2000**, 99−100.

presence of an electron-withdrawing group in the aromatic ring has been found to facilitate the hydrogen transfer reaction, in accordance with the hydridic nature of the reducing species involved in the metal−ligand bifunctional catalysis.[7,8c,16,17] The ee value of the chiral alcohols increased from 20% for the *p*-CF_3 derivative to 61% for the *p*-CH_3O derivative. Under such conditions, the olefinic and saturated aldehydes, **5** and **6**, again yielded a near-racemic alcohol (<5% ee).

Formic acid serves as an exellent hydrogen donor. This transfer hydrogenation forming CO_2 occurs irreversibly to completion under truly kinetic control.[7,8b] By reversing the isotope labeling pattern in the substrate and hydrogen donor, another efficient asymmetric method has been developed. For example, when an acetonitrile solution of the *p*-methoxybenzaldehyde (**7c**), chiral catalyst (*R*,*R*)-**3a**, and a 1:1 mixture of DCO_2D and triethylamine (aldehyde:Ru:formic acid = 200:1:200 molar ratio) was stirred at 28 °C for 14 h, (*S*)-**2c** was obtained in 99% ee and with a 97% conversion.[18] The *p*-methoxy alcohol with a low oxidation potential[12] did not cause any ee erosion under such conditions. Examples are given in Table 1. The d_1 content in the benzyl alcohols is >99%. The benefit of this procedure is the need for only a stoichiometric amount (not in excess) of the deuterium source with respect to the substrate (1−2 g), because deuterated 2-propanol as a reducing agent must be used as a solvent.

Overall, these Ru-catalyzed reactions serve as efficient hydrogenative methods of converting benzaldehydes to chiral deuterated alcohols with a high enantiomeric and isotopic purity.

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Supporting Information Available: Procedures for the transfer hydrogenation of benzaldehydes, GC behavior of products, and $[\alpha]_D$ values and NMR data of chiral alcohols. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) The enantioselectivity was kinetically determined with a conversion of 22−65%.[11]

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(18) Transfer hydrogenation of **7c** with DCO_2D catalyzed by (*R*,*R*)-**3a**: A mixture of **7c** (1.37 g, 10.0 mmol), (*R*,*R*)-**3a** (32 mg, 0.05 mmol), DCO_2D (0.48 g, 10 mmol), and $(C_2H_5)_3N$ (1.01 g, 10 mmol) in acetonitrile (10 mL) was magnetically stirred at 28 °C for 14 h. The mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with an $NaHCO_3$ solution and brine, dried over Na_2SO_4, and concentrated. Bulb-to-bulb distillation of the residue afforded (*S*)-**2c** (1.329 g, 96% yield) in 99% ee.[11] ^{1}H NMR of benzylic proton of (*S*)-MTPA ester: *S* isomer, δ 5.28; *R* isomer, δ 5.26.