Enantioselective Syntheses of Nonracemic Benzyl-α-*d* Alcohols via Catalytic Transfer-Hydrogenation with Ru, Os, Rh, and Ir Catalysts

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*Summary: The synthesis of chiral benzyl-α-d alcohols via the reduction of benzaldehyde-α-d derivatives has been investigated with a series of catalysts that were derived in situ from (1R,2S)-(+)-cis-1-amino-2-indanol and the chloro-bridged dimers of p-cymeneRu, p-cymeneOs, Cp*Rh, or Cp*Ir. An unusual trend was observed in which substrates containing electron-withdrawing substituents led to greater enantioenrichment than those with electron-donating substituents. All four catalyst systems were found to produce benzyl-α-d alcohols with high conversion (>98%). Modest to good enantioselectivities (up to 68% ee) were observed.*

Introduction

Isotopically labeled, nonracemic compounds are powerful tools for mechanistic and structural applications in NMR, biochemical, organic, and organometallic investigations.[1−4] The syntheses of chiral deuterated benzyl alcohols[5−11] have involved various stoichiometric[5] and enzymatic[6] reductions of benzaldehyde-α-*d* derivatives, while only a handful of transition-metal-catalyzed examples have been reported.[7,8,10] Of these examples, perhaps the most successful catalytic transfer-hydrogenation system to date was pioneered by Noyori and co-workers,[8] who extended a system derived from $(ArRuCl_2)_2$/(*R*,*R*)-tsdpen, where tsdpen = *N*-toluenesulfonyl)-1,2-diphenylethylenediamine, (with 2-propanol or NEt_3/HCOOH as the reducing agents) to various substrates including aryl ketones, α,*β*-acetylenic ketones, imines, and most recently benzaldehyde-α-*d* derivatives.

Previously, Palmer et al.[12] reported that the catalyst derived in situ from $(p\text{-cymeneRuCl}_2)_2$ and (1*R*,2*S*)-(+)-*cis*-1-amino-2-indanol was effective for the enantioselective reduction of aryl alcohols, and we[13] reported that the system is highly effective for the kinetic resolution of racemic[14] and nonracemic[15] alcohols. Herein we report our findings on the asymmetric reduction of *ortho* and *para*-substituted benzaldehyde-α-*d* derivatives with four catalysts derived in situ from the amino indanol and *p*-cymeneRu, *p*-cymeneOs, Cp*Rh, or Cp*Ir chloro-bridged dimers.[16]

The substrates for this investigation were satisfactorily synthesized by reductive cleavage of the parent methyl esters or carboxylic acids with $LiAlD_4$ followed by Swern oxidation to the respective benzaldehyde-α-*d* derivatives as previously reported (>99% deuterium incorporation) (see Scheme 2).[7] We also found that the Moffat oxidation procedure was capable of yielding satisfactory results, although small amounts of dicyclohexylcarbodiimide (DCC) remained (however, it can be removed by column chromatography on silica gel). A third oxidation method employing pyridinium chlorochromate (PCC) was also investigated.[17] In our hands this method led to scrambling of the methylene deuterons with protons and thus an unsatisfactory degree of deuterium incorporation into the aldehyde functionality.

Catalysts were prepared by heating the desired organometallic dimer in 2-propanol for 20 min with 4 molar equiv of (1*R*,2*S*)-(+)-*cis*-1-amino-2-indanol (an excess is commonly used).[12−15] This solution was cooled to ambient temperature, followed by addition of the desired benzaldehyde-α-*d* derivative in 2-propanol. Once this solution had been cooled to the desired temperature (generally −78 °C), the reaction was initiated with the addition of a 0.1 M solution of ^{t}BuOK in 2-propanol and the solution was allowed to warm to room temperature. Once the reaction was complete (e.g., >98% conversion as determined by GC analysis), an aliquot of the catalytic solution was removed via syringe and was evaporated under reduced pressure. This material was subjected to flash chromatography and the eluate was evaporated under reduced pressure to yield clear oils or white powders. Scheme 3 illustrates that the ee's were determined by conversion of the chiral alcohols to diastereomeric esters with (*R*)-MTPA, (+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid. ^{1}H NMR spectral

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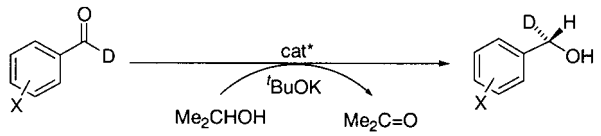
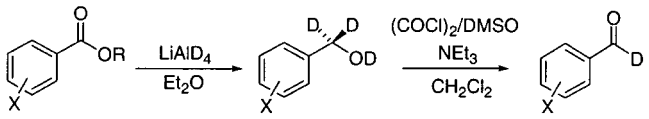
Scheme 1. Preparation of Nonracemic Benzyl-α-*d* Alcohols

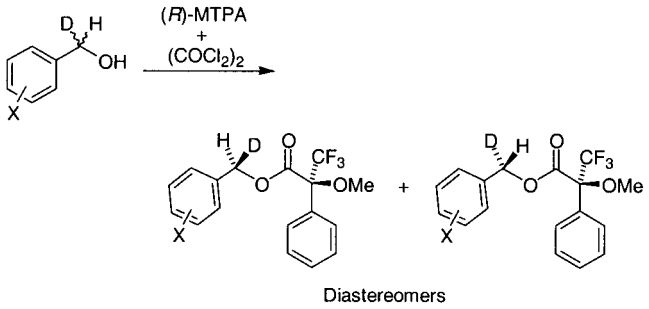


Scheme 2. Synthetic Approach for Benzaldehyde-1-*d* Substrates

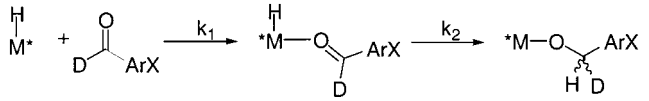


R = H, Me
X = *p*-CF_3, *p*-Br, *p*-Me, *p*-OMe, *o*-Me, *o*-CF_3

Scheme 3. Generation of Diastereomers from the Product Alcohols for Use in Determination of Enantiomeric Purity



Scheme 4. Substrate-Dependent Rate of Reduction for Various Substituted Benzaldehyde-α-*d* Derivatives



if $k_1 > k_2$ *then* e-donating is fastest

if $k_2 > k_1$ *then* e-withdrawing is fastest

X = *e*-donating or *e*-withdrawing substituent

analyses of the product alcohols were consistent with published work.[8]The catalytic results for the *para*-substituted substrates are shown in Table 1. Notably, an apparent trend was observed in which the electron-withdrawing substituents generally led to the greatest levels of enantioenrichment. One exception to this trend was observed for the reduction of *p*-trifluoromethylbenzaldehyde-α-*d* with the osmium catalyst. Overall, the rhodium catalyst performed the best in terms of enantioselectivity for substrates containing electron-withdrawing substituents (*p*-CF_3 and *p*-Br), yielding ee's of 67% and 68%, respectively. All of the catalysts reduced benzaldehyde-α-*d* with similar ee's (ranging from 54% to 63%). All catalysts performed similarly for the electron-donating substituents (*p*-Me and *p*-OMe). It should be noted that a decrease in conversion and ee was not observed when catalytic solutions were allowed to stand for an extended time period (∼1 week). This can be a source of enantiomeric purity and yield degradation with other systems (e.g., the aryl ketone/alcohol equilibrium).[13−15]

Table 1. Results for the Reduction of *para*-Substituted Benzaldehyde-α-*d* Derivatives to Form Chiral *p*-Benzyl-α-*d* Alcohols[a]

entry	substrate[b]	cat.[c]	% ee (config.)[d]
1	4′-CF_3	Ru	61 (*S*)
2	4′-Br	Ru	68 (*S*)
3	4′−H	Ru	63 (*S*)
4	4′-Me	Ru	55 (*S*)
5	4′-OMe	Ru	39 (*S*)
6	4′-CF_3	Os	49 (*S*)
7	4′-Br	Os	59 (*S*)
8	4′−H	Os	60 (*S*)
9	4′-Me	Os	51 (*S*)
10	4′-OMe	Os	44 (*S*)
11	4′-CF_3	Rh	67 (*S*)
12	4′-Br	Rh	68 (*S*)
13	4′−H	Rh	63 (*S*)
14	4′-Me	Rh	56 (*S*)
15	4′-OMe	Rh	31 (*S*)
16	4′-CF_3	Ir	67 (*S*)
17	4′-Br	Ir	57 (*S*)
18	4′-H	Ir	54 (*S*)
19	4′-Me	Ir	45 (*S*)
20	4′-OMe	Ir	33 (*S*)

[a] The catalysts were derived from chloro-bridged dimers [(*p*-cymeneRuCl_2)$_2$, (*p*-cymeneOsCl_2)$_2$, (Cp*RhCl_2)$_2$, or (Cp*IrCl_2)$_2$] and (1*R*,2*S*)-*cis*-1-amino-2-indanol (all catalysts were activated upon addition of ^{t}BuOK). All reactions were completed by allowing solutions to warm from −78 to +25 °C. In general, the reactions were complete within 4 h. All conversions were greater than 98%. [b] The reactions did not proceed until the reaction mixture had warmed to ∼+5 °C. [c] The catalyst loading was 3%, and the concentration of ^{t}BuOK was 0.006 M. This provides a base:metal ratio of 5:1. [d] The absolute configurations of the product alcohols were determined by comparison of ^{1}H NMR spectra of the (*R*)-MTPA esters with literature values.[8] In the instances where the alcohols were converted to the (*R*)-MTPA esters, the downfield resonances corresponding to the (*S*) alcohols had greater intensity except for those derived from 4′-CF_3 alcohols (see Supporting Information in ref 8).

Table 2. Results for the Reduction of *ortho*-Substituted Benzaldehyde-α-*d* Derivatives to Form Chiral *o*-Benzyl-α-*d* Alcohols[a]

entry	substrate[b]	cat.*	% ee (±rotation)
1	2′-Me	Ru	51 (−)
2	2′-CF_3	Ru	26 (−)
3	2′-Me	Os	33 (−)
4	2′-CF_3	Os	25 (−)
5	2′-Me	Rh	52 (−)
6	2′-CF_3	Rh	67 (−)
7	2′-Me	Ir	47 (−)
8	2′-CF_3	Ir	65 (−)

[a] The catalysts were derived from organometallic dimers [(*p*-cymeneRuCl_2)$_2$, (*p*-cymeneOsCl_2)$_2$, (Cp*RhCl_2)$_2$, or (Cp*IrCl_2)$_2$] and (1*R*,2*S*)-*cis*-1-amino-2-indanol (all catalysts were activated upon addition of ^{t}BuOK). All reactions were completed by allowing solutions to warm from −78 to +25 °C. In general, the reactions were complete within 4 h. All conversions were greater than 98%. [b] The reactions did not proceed until the mixture had warmed to ∼+5 °C. In the instances where the alcohols were converted to the (*R*)-MTPA esters, the downfield resonances of the diastereotopic methylene protons were of greater intensity.

Catalytic results for the *ortho*-substituted substrates are shown in Table 2. For the reduction of *o*-tolualdehyde-α-*d*, the series of catalysts performed similarly (47−52% ee). One exception is that the osmium catalyst displayed decreased enantioselectivity (33%). With 2′-trifluoromethylbenzaldehyde-α-*d* as a substrate, an improved enantiomeric purity was observed with the Rh and Ir catalysts (67% and 65% ee), and decreased ee's were observed for Ru and Os catalysts (26% and 25%

ee). The stark contrast in selectivity between group 8 and 9 catalysts confirms that both steric and electronic factors can affect the enantioselectivity in these reactions.

The correlation with electronic effects that we report has previously been observed in other systems.[18,19] In a separate investigation into the kinetic resolution of racemic alcohols with *p*-cymeneRuCl$_2$/aminoindanol, we observed that electron-donating substituents led to the highest enantioselectivities.[14] Yamada and Noyori have observed that electron-donating substrate substituents produce the highest ee's (benzaldehyde-α-*d* derivatives) with a catalyst system derived from RuCl$_2$(η^6-benzene)]$_2$/(*R*,*R*)-1,2-diphenylethanolamine.[8] As such, the variations in this electronic trend suggest that broad generalizations concerning trends with different catalysts may not be appropriate.

In a separate investigation into carbonyl reduction with oxazaborolidine catalysts, Corey and Helal suggested two mechanistic possibilities for similar results.[19] If ketone complexation is the turnover-limiting step, then the relative rates of reduction should be greater for the electron-donating substituents. However, in the case where hydride transfer is the turnover-limiting step, then the rate of reduction should be greatest for the electron-withdrawing substituents. It should be noted that these considerations ignore steric factors (which is a valid assumption in the case of *para*-substituents). Hence, as substrates change, the balance between factors that determine stereocontrol may be affected by change of relative rates and relevant transition states.

In conclusion, the asymmetric reduction of benzaldehyde-α-*d* derivatives with substituents having different electronic and steric properties has been investigated with a series of Ru, Os, Rh, and Ir catalysts. All four catalyst systems were found to rapidly produce chiral nonracemic benzyl-α-*d* alcohols with high conversions (>98%). A substrate-dependent electronic trend was observed wherein the highest levels of enantioenrichment were generally observed for the reduction of benzaldehydes containing electron-withdrawing substituents. Modest to good enantioselectivities (up to 68% ee) were observed.

Experimental Section

All synthetic manipulations were carried out using standard Schlenk techniques under an inert atmosphere. Reagent grade 2-propanol was distilled from CaH_2 and was degassed with freeze−pump−thaw cycles (3×) prior to use. Trifluoromethylbenzoic acid was obtained from Alfa-Aesar, and methylbenzoate derivatives, (1*R*,2*S*)-(+)-*cis*-1-amino-2-indanol, (Cp*IrCl$_2$)$_2$, $LiAlD_4$, and 99% ee (*R*)-MTPA = (+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid, were obtained from Aldrich; all were used without further purification. (*p*-CymeneRuCl$_2$)$_2$,[20] (*p*-cymeneOsCl$_2$)$_2$,[20] and (Cp*RhCl$_2$)$_2$[21] were prepared according to literature procedures. The percent conversion in each product was determined by GC analysis using a Hewlett-Packard 5890A gas chromatograph with a Cyclodex-B chiral column. The enantiomeric excess in each product was obtained by derivatization to the (*R*)-MTPA ester followed by ^{1}H NMR analysis of the diastereotopic methylene protons and comparison to previously published materials (*o*-methylbenzaldehyde-α-*d* and *o*-trifluoromethylbenzaldehyde-α-*d* are reported in the Supporting Information). Integration and peak fitting were performed using NUTS (NMR Utility Transform Software for Windows 95/NT) and the Jandel PeakFit program Version 4. Optical rotations were measured on a Perkin-Elmer model 341 polarimeter at 589 nm and 25.0 °C, using a 1 dm path length. ^{1}H NMR spectra were recorded on either a Bruker 500 MHz or a Bruker 400 MHz spectrometer, and chemical shifts were in ppm relative to residual solvent resonances (^{1}H).

Experimental Procedure for the Transfer-Hydrogenation of Benzaldehyde-α-*d* Derivatives to Chiral Benzyl-α-*d* Alcohols. A Schlenk flask equipped with a reflux condenser was charged with the desired organometallic dimer (0.0125 mmol), (1*R*,2*S*)-*cis*-1-amino-2-indanol (0.05 mmol), and a stir bar. The apparatus was evacuated and backfilled with nitrogen, followed by the addition of degassed 2-propanol (5 mL). The solution was heated under reflux for 20 min and was allowed to cool to ambient temperature. This solution was added via syringe to a flask containing a solution of degassed 2-propanol (15 mL) and the desired benzaldehyde-α-*d* (0.93 mmol) derivative.[7,22,23] The mixture was cooled to the desired temperature (generally −78 °C), and reaction was initiated by addition of 0.1 M ^{t}BuOK/2-propanol (1.25 mL). Conversions were determined by GC analysis, and the ee was determined by derivatization as the (*R*)-MTPA esters and integration of the diastereotopic methylene (C*H*D) resonances.[24]

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Supporting Information Available: Modified procedure for the preparation of Mosher's ester of chiral benzyl-α-*d* alcohol derivatives. Characterization of substrates and products including ^{1}HNMR, ^{2}DNMR, and GC retention times. This material is available free of charge via the Internet at http://pubs.acs.org.

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(24) It should be noted that there can be a reversal of chirality descriptor in MTPA derivatives even though the sense of chirality is the same. (*S*)-MTPA-Cl (acid chloride) is derived from (*R*)-MTPA owing to replacement of the carboxylic acid functionality with an acid chloride according to the Cahn−Ingold−Prelog rules. Therefore, (*R*)-MTPA yields the (*R*)-MTPA-ester, whereas the (*R*)-MTPA-Cl yields the (*S*)-MTPA-ester.