Facile Preparation of Chiral 1,3-Diols via Stereoselective Transfer Hydrogenation of 1,3-Diones

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Asymmetric reduction of 1,3-diones catalyzed by (*S*,*S*)-TsDPEN-Ru(II) complex in a mixture of formic acid-triethylamine proceeded with a substrate/catalyst molar ratio of 100 to give (*S*,*S*)-1,3-diols with excellent diastereomeric (98.6% *de*) and enantiomeric purities (>99% *ee*). Other C_2-symmetric diols were also obtained in almost quantitative yields with high diastereomeric (80.0%—84.2% *de*) and enantiomeric purities (>99% *ee*).

Keywords Asymmetric transfer hydrogenation, ruthenium complex, chiral 1,3-diols

Introduction

C_2-Symmetric diols have been widely employed as chiral ligands and auxiliaries in a broad range of asymmetric transformations. The preparations as well as applications in stereoselective syntheses of chiral 1,2- and 1,4-diols, which can be easily obtained from tartrate sources or other reliable procedures, have been extensively studied.[1] On the other hand, 1,3-diols are much less explored. There is an increasing interest on the preparation of the chiral C_2-symmetric 1,3-diols.[2]

Asymmetric reduction of the readily available 1,3-diones to chiral 1,3-diols would be a promising and straightforward approach, but only a few practical reduction systems have been reported.[3] Oxazaborolidine catalyzed reduction with borane/methyl sulfide gave the chiral diols contaminated with a significant amount of *meso* isomers.[1(e)] Some improvements were reported recently using β-ketoiminato Co(II) complexes catalyzed reduction with $NaBH_4$[4] or asymmetric hydrogenation catalyzed with chiral ferrocenyl diphosphorus ligand.[5] However, transfer hydrogenation utilizing stable organic hydrogen donors would be a more attractive alternative in view of the less hazardous properties of the reducing agents and operation simplicity. In the past years asymmetric transfer hydrogenation of simple or functionalized aromatic ketones has been well studied.[6] Herein we would like to report the successful application of this methodology to synthesize optically pure C_2-symmetric 1,3-diols.

Results and discussion

Several excellent chiral catalytic systems, combining a ruthenium, rhodium or iridium precursor with chiral bidentate[7] or multidentate ligands,[8] have been reported for transfer hydrogenation of ketones. Noteworthy

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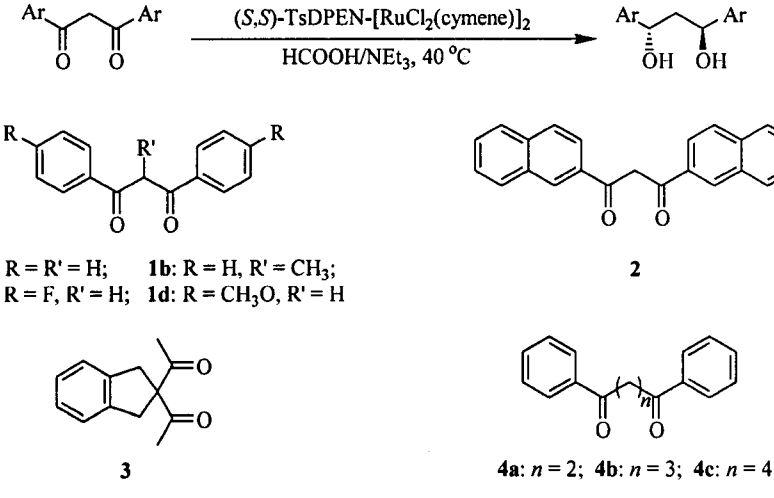
among these top ligands are (*S*,*S*)-*N*-(*p*-tolylsulfonyl)-1,2-diphenylethylenediamine[(*S*,*S*)-TsDPEN],[9] (1*R*,2*S*)-*N*-benzylnorephedrine[10] and (*S*,*S*)-*N*-(*p*-tolylsulfonyl)-1, 2-diaminocyclohexane [(*S*, *S*)-TsCYDN].[11] Our initial screening with dibenzoyl- methane (**1a**) as substrate demonstrated that (1*R*,2*S*)-*N*-benzylnorephedrine-[$RuCl_2(\eta^6\text{-cymene})]_2$,[10] (*S*, *S*)-TsDPEN-[$RuCl_2(\eta^6\text{-cymene})]_2$[12] and (*S*,*S*)-TsCYDN-[$RhCl_2Cp^*]_2$[11] in 2-propanol/KOH system were not favorable catalysts. No diol was detected with a molar ratio of substrate and catalyst (S/C) of 100 at 40℃ for 24 h. Fortunately, asymmetric reduction of **1a** catalyzed by the complex of (*S*,*S*)-TsDPEN and $[RuCl_2(\eta^6\text{-cymene})]_2$ proceeded very smoothly at 40℃ with a S/C of 100 in 2 mol/L DMF solution, using formic acid/triethylamine as hydrogen source.[1(d),9] (*S*,*S*)-1, 3-Diphenyl-1, 3-propanediol was obtained almost quantitatively with excellent diastereomeric (*dl* : *meso* = 98.9 : 1.1) and enantiomeric purities (>99% *ee*) (Table 1, Entry 1). While the molar ratio of S/C was raised to 200. the selectivity was not changed but the reactivity slightly decreased (Entry 2). Nevertheless, the S/C ratio of 500 would dramatically decrease the reactivity. Although the diol was formed with 43% yield using (*S*,*S*)-TsCYDN-$[RuCl_2(\eta^6\text{-cymene})]_2$ as a catalyst (Entry 3), no product was tested in formic acid/triethylamine mixture with (*S*,*S*)-TsCYDN-$[RhCl_2Cp^*]_2$. Various 1,3-propanediones (**1**—**3**) were also reduced to chiral 1,3-diols with high stereoseletivities in good yields (Scheme 1).

As reported in Table 1, 2-substituent of dibenzoylmethane (**1b**) would lower both selectivity and reactivity (Entry 4). *para* - Electron - withdrawing substituent on

Scheme 1



aromatic ring **1c** tended to slightly decrease the diastereoselectivity (Entry 5), while dione **1d** with *para*-electron-donating substituent was reduced with much lower reactivity (Entry 6). Furthermore, 1,3-di(β-naphthyl)-1,3-propanedione (**2**) with a larger arene ring was reduced to chiral 1, 3-diol with the best diastereoseclectivity (Entry 7).[4] 2, 2-Diacetylindane (**3**), an aliphatic dione, which failed to give good selectivities via borane reduction catalyzed by stoichiometric oxazaboralidine,[1(e),2(b)] was rapidly reduced with high diastereoselectivity (96% *de*), and *dl* isomer of the 1,3-diol freed from *meso* isomer was obtained by silica gel chromatography in >99% *ee* and 73% yield (Eentry 8).

Other C_2-symmetric diols **4** could be prepared utilizing this reduction system too. For example, chiral 1, 4-diphenyl-1, 4-butanediol, 1, 5-diphenyl-pentanediol and 1, 6-diphenyl-1, 6-hexanediol were obtained in almost quantitative yields with high enantiomeric (>99% *ee*) and diastereomeric purities (80.0%, 83.2% and 84.2% *de*, respectively) (Entries 9, 10 and 11).

Although pyridyl ketones have been reported to be stereoselectively reduced to pyridyl alcohols catalyzed by RuCl[(*S*,*S*)-TsDPEN](η^6-cymene) in formic acid/triethylamine mixture,[13] our attempts to reduce 2,2′-pyridil and 1,3-di(2′-pyridyl)-1,3-propanedione failed to give any expected alcohol. This was possibly due to replace-

Table 1 Asymmetric transfer hydrogenation of 1,3-propanediones

Entry	Substrate	Time (h)	Yield (%)[a]	*dl*:*meso*[b]	*ee* (%)[b]	Config.[c]
1	**1a**	40	96	98.9:1.1	>99	*S*,*S*
2[d]	**1a**	40	87	98.9:1.1	>99	*S*,*S*
3[e]	**1a**	45	43	94.2:5.8	>99	*S*,*S*
4	**1b**	65	27	96.6:3.4	98.6	-,[f]
5	**1c**	40	95	95.2:4.8	>99	-,[f]
6	**1d**	96	51	97.4:2.6	>99	-,[f]
7[g]	**2**	72	92	99.3:0.7	>99	-,[f]
8	**3**	40	73[h]	98.0:2.0[i]	>99	*S*,*S*
9	**4a**	60	99	90.0:10.0	>99	*S*,*S*
10	**4b**	40	99	91.6:8.4[j]	>99	*S*,*S*
11	**4c**	40	98	92.1:7.9	>99	*S*,*S*

[a] Isolated yields, and ^{1}H NMR data consistent with the structures; [b] Unless otherwise noted, *dl*/*meso* and *ee* values were determined by HPLC analysis using a Daicel Chiralcel OB, OD, OJ, ChiralPak AD column; [c] Unless otherwise noted, determined from the sign of rotation of the isolated product; [d] S/C = 200; [e] (*S*, *S*)-TsCYDN as the catalyst; [f] Absolute configuration was not determined yet, but their sign of the rotation was the same as that of other products; [g] In 1 mol/L HMPA solution; [h] Yield of isolated *dl* isomer; [i] Calculated from isolated *dl* and *meso* isomers; [j] Determined on HPLC with Silica Gel column, the *meso*-isomer and the (*R*, *R*)-form of *dl*-isomer overlapped on the chiral column.

ment of the chiral diamine ligand by the pyridyl alcohol produced to give an inactive catalyst as the release of CO_2 gas was only detected at the initial stage of the reaction.

In conclusion, this paper presented a facile access to the enantioselective synthesis of the symmetric 1,3-diols via transfer hydrogenation of the corresponding 1,3-diones catalyzed by diamine-based Ru(II)-arene complex. Other C_2-symmetric diols could also be prepared with good selectivities comparable to the borane reductions catalyzed by stoichiometric oxazaborolidine.[1(e)] Since optically pure 1,3-diols have been readily converted to 1,3-diamines and other derivatives[2(a),4] without any loss of optical purity, the study of these chiral compounds as potential ligands or synthons in asymmetric synthesis is currently in progress in our laboratory.

Experimental

General

DMF was dried with $MgSO_4$ and distilled under reduced pressure. The diones, formic acid-triethylamine azeotrope and RuCl[(*S*, *S*)-TsDPEN](η^6-cymene)[7(a)] were prepared according to literature methods.

General procedure for asymmetric transfer hydrogenation of diones catalyzed by RuCl[(*S*, *S*)-TsDPEN](η^6-cymene)

To a mixture of 1, 3-diphenyl-1, 3-propanedione (90 mg, 0.4 mmol) and the preformed RuCl[(*S*, *S*)-TsDPEN](η^6-cymene) (2.6 mg, 0.004 mmol) in dry DMF (0.2 mL) was added an azeotrope of formic acid-triethylamine (0.2 mL) under argon. The mixture was stirred at 40℃ and monitored by TLC. After 40 h, the mixture was diluted with ethyl acetate and washed with brine, dried over Na_2SO_4, and concentrated. Flash chromatography with EtOAc-petroleum ether (1:4) gave pure 1,3-diol (88 mg, 96% yield). ^{1}H NMR ($CDCl_3$) δ: 7.38—7.28 (m, 10H), 5.01 (t, J = 6.0 Hz, 2H), 2.23—2.19 (m, 2H). The *ee* (>99%) and *de* (97.8%) were determined by HPLC on a chiralcel OD column [hexane/2-propanol (9/100), 1.0 mL/min, $t_{(S,S)}$ = 12.1 min, $t_{(R,R)}$ = 14.3 min, t_{meso} = 17.5 min]. $[\alpha]_D^{20}$ - 68.2 (*c* 1.0, EtOH) [Lit.[2(a)] $[\alpha]_D$ - 67.5 (*c* 0.3, EtOH)].

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