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Alternative Hydrogen Source for Asymmetric Transfer Hydrogenation in the Reduction of Ketones

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cis-1,4-Butenediol is shown to be a highly active hydrogen source for asymmetric transfer hydrogenation in the reduction of ketones. With the use of a ruthenium catalyst, *cis*-1,4-butenediol is isomerised and subsequently oxidised to a lactone as an irreversible step, which provides the driving force for the asymmetric reduction of ketones.

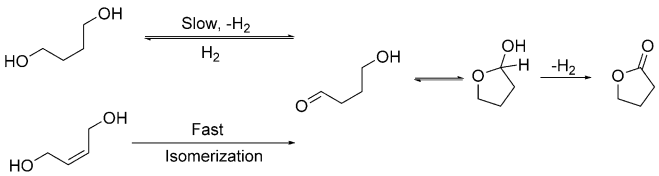
Catalytic transfer hydrogenation (TH) has been well reported in the literature, and the most prevalent sources of hydrogen are derived from either isopropanol or an azeotropic mixture of formic acid with triethylamine (5:2).[1] Catalyst systems that use a variety of metal centres, such as Al,[2] Ru,[3] Rh,[4] Ir[5] and Fe,[6] have been reported with improvements made to these systems.

Ru-catalysed asymmetric transfer hydrogenation (ATH) is a well-established protocol. Noyori and Hashiguchi used chiral Ru^{II} complexes with mono-tosylated diamines to catalyse the ATH of ketones.[3b] The most widely used derivative of the chiral catalyst is formed in situ from the reaction of the dichlororuthenium(II) *p*-cymene dimer and (1*S*,2*S*)-(+)-*N*-(4-toluenesulfonyl)-1,2-diphenylethylenediamine (TsDPEN) in the presence of a base, usually potassium hydroxide.

Modifications to the standard Noyori system have been reported,[3c] in particular Wills et al. reported the use of tethered Ru^{II} catalysts that have excellent stability and provide high levels of enantioselectivity.[7] Despite the advances of these catalyst systems, there are still issues with the use of either of the two most common hydrogen sources. For every molecule of isopropanol that is oxidised, acetone is produced, which is often reduced more easily by the catalyst than the substrate ketone. A large excess of isopropanol is, therefore, required to drive the reaction to near completion. The ubiquitous formic acid/triethylamine (5:2) azeotropic mixture, although it is efficient as a hydrogen source, produces a stoichiometric amount of CO_2.

Herein we describe a highly active prospective hydrogen source, *cis*-1,4-butenediol, which to the best of our knowledge has not been investigated in ATH reactions previously. The diol has been optimised for the asymmetric reduction of ketones using (*S*,*S*)-tethered-TsDPEN RuCl (Wills Catalyst) as a catalyst. *cis*-1,4-Butenediol is synthesised on an industrial scale from 2-butyne-1,4-diol and is important in the production of endosulfan[8] and Vitamins A and B[9] and is an additive in resin manufacturing.[10] 2-Butyne-1,4-diol is synthesised from the Reppe carbonylation of acetylene using formaldehyde as the carbonyl source, therefore, it is produced cheaply.[11] Lindlar's catalyst[12] as well as many supported Pd[9,13] and Ni catalysts[14] are able to hydrogenate butynediol to butenediol selectively. Therefore, this is considered a suitably cheap available hydrogen source for these investigations.

Previously, our group has shown that 1,4-butanediol can be used as a hydrogen source for TH reactions.[15] We wished to extend this methodology to the more commercially desirable ATH protocol. We proposed to investigate the difference between *cis*-1,4-butenediol and 1,4-butanediol on the basis that the slow oxidation step of 1,4-butanediol to form 4-hydroxybutanal could be circumvented by using *cis*-1,4-butenediol and selecting a catalyst that was efficient for the isomerisation of allylic alcohols (Scheme 1). *cis*-1,4-Butenediol was, therefore, chosen to be investigated given that the isomerisation of *cis*-1,4-butenediol to 4-hydroxybutanal is catalysed readily by Ru TH catalysts.[16]



Scheme 1. Possible pathways for hydrogen abstraction from 1,4-butanediol and *cis*-1,4-butenediol in the presence of $[Ru(p\text{-cymene})Cl_2]_2$.

Initial optimisation focused on the use of $[Ru(p\text{-cymene})Cl_2]_2$ in conjunction with KOH and (*S*,*S*)-TsDPEN. A solvent screen showed that toluene and THF gave the best conversions and maintained high enantioselectivities, so to ensure the ready solubility of the reagents THF was chosen. We used 10 mol% KOH and varied the concentration of 1,4-butanediol versus *cis*-1,4-butenediol and identified that 0.5 equivalents of 1,4-butanediol provided excellent enantioselectivity but poor conversion (Table 1, entry 4). However, the turnover for this pathway appears to become inhibited, which presumably confirms the pathway depicted in Scheme 1. Hence an increase of the amount of 1,4-butanediol in the reaction mixture results in small increases in conversion with the concurrent suppression of enantioselectivity (Table 1, entries 5–6). This reduction in se-

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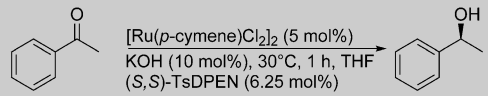
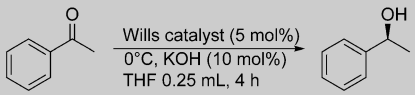
Table 1. Optimisation for [Ru(*p*-cymene)Cl_2]$_2$.



Entry[a]	Diol	Diol [equiv.]	Conv. [%][b]	*ee* [%][c]
1	*cis*-1,4-butenediol	1.1	36	88
2	*cis*-1,4-butenediol	2.0	44	91
3	*cis*-1,4-butenediol	4.0	44	90
4	1,4-butanediol	0.5	36	>99
5	1,4-butanediol	2.0	46	90
6	1,4-butanediol	4.0	53	84
7[d]	*cis*-1,4-butenediol	4×1.0	67	90
8[e]	*cis*-1,4-butenediol	4×1.0	75	92

[a] [Ru(*p*-cymene)Cl_2]$_2$ (5 mol%), (*S*,*S*)-TsDPEN (6.25 mol%), KOH (10 mol%), 1 mmol acetophenone, 0.25 mL of THF, 30 °C, reactions run under Ar in a sealed vessel. [b] Conversion into 1-phenylethanol calculated by analysis of ^{1}H NMR spectra. [c] Enantiomeric excess calculated using chiral HPLC after purification by column chromatography. [d] Reaction performed over 1.5 h using slow addition, 1 equivalent of diol was added every 30 min. [e] Reaction performed over 1.5 h using slow addition 1 equivalent of diol every 30 min, 1.1 equivalents of KOH.

Table 2. Diol comparison with Wills catalyst.



Entry[a]	Diol	Diol [equiv.]	Conv. [%][b]	*ee* [%][c]
1	1,4-butanediol	1.0	53	89
2	1,4-butanediol	2.0	67	86
3	1,4-butanediol	4.0	67	86
4[d]	*cis*-1,4-butenediol	1.0	88	94
5[e]	*cis*-1,4-butenediol	2.0	90	96
6[f]	*cis*-1,4-butenediol	2.0	85[g]	>99

[a] Wills catalyst 0.05 mmol, 1 mmol acetophenone, 0.25 mL of THF, 0 °C, reactions run for 4 h under Ar in a sealed vessel. [b] Conversion into 1-phenylethanol calculated by analysis of ^{1}H NMR spectra. [c] Enantiomeric excess calculated using chiral HPLC after purification by column chromatography. [d] Reaction run for 2 h. [e] Reaction performed at −10 °C for 6 h. [f] Reaction performed at −10 °C, using 20 mol% KOH. [g] Isolated yield [%].

lectivity could possibly be attributed to solubility issues observed in the viscous diol reagent. *cis*-1,4-Butenediol showed enantioselective reductions with around 90% *ee* regardless of concentration; slow addition of the diol provided a marked improvement in conversion. It is proposed that this is because the catalyst system initially isomerised the diol and that time was allowed for ATH to occur without isomerisation out-competing it, which thus improved turnover, although the increased reaction time could not be discounted. We anticipated that the addition of more KOH should provide a pathway for the lactone to be hydrolysed to the hydroxy acid and would then take no further part in the reaction. Indeed, an increase in conversion was observed if 1.1 equivalents of KOH were used (Table 1, entry 8).

Unfortunately, we were unable to improve on the results shown with this catalytic system (Table 1, entry 8). However, changes to the ligand resulted in improved conversions. Indeed, quantitative conversion became possible with an excess of ligand, an increased amount of base, an increase of 1,4-butanediol and the use of a more stable catalyst precursor, [Ru(Me_6C_6)Cl_2]$_2$. However, the total loss of stereochemical control was observed with this increased conversion.[17]

We attributed the loss of stereochemical control to the instability of the active form of the catalyst and so our investigations focused on the tethered Wills catalyst (Figure 1). As mentioned previously, we proposed that the faster isomerisation step to form the 4-hydroxybutanal from *cis*-1,4-butenediol would result in a greater turnover of the catalyst at lower temperatures to allow a greater enantioselectivity. Naturally, we compared *cis*-1,4-butenediol with 1,4-butanediol as the hydrogen source using the Wills catalyst, and the results are summarised in Table 2.

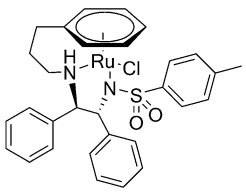


Figure 1. (*S*,*S*)-Tethered-TsDPEN RuCl (Wills Catalyst).

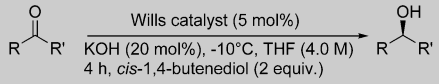
The use of the Wills catalyst at the lower temperature of 0 °C resulted in good conversions in just 4 h for both diols with superior conversions obtained for *cis*-1,4-butenediol as expected. It was pleasing to observe an improvement in the stereochemical control that accompanied the high conversion. An increase of the amount of diol did not impact the conversion or stereochemical control significantly if more than two equivalents were used.

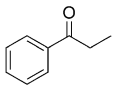
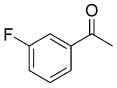
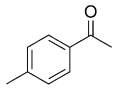
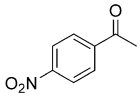
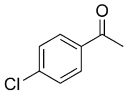
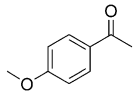
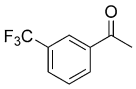
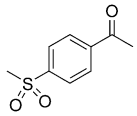
KOH was the best base, and an excess of base was not required, although the conversion was improved by the use of 20 mol% of KOH (Table 2, entry 6). An amount of 5 mol% of Wills catalyst was required to obtain high conversions and retain a high enantioselectivity. An extension of the reaction time further allowed the racemisation of the 1-phenylethanol product (Table 2, entry 5). Indeed, if the experiment was performed under the optimised conditions (Table 2, entry 6) with a substitution of enantiomerically pure (*R*)-1-phenylethanol in place of the acetophenone substrate, the *ee* of the alcohol decreased after 2 h at −10 °C.

With the optimised conditions in hand, we were able to look at the potential substrate scope as shown in Table 3. The method showed a good tolerance for electron-withdrawing and electron-donating groups around the aromatic ring. However, an increase in the alkyl chain length resulted in a requirement for extended reaction times, presumably the active site on the catalyst is sensitive to steric bulk in this position. We were able to obtain excellent enantioselectivities and good to excellent isolated yields.

In summary, we have developed a method that uses *cis*-1,4-butenediol as the hydrogen source for ATH. By using the lactone formation as an irreversible step, the reductions can be taken to very high conversions and retain enantioselectivity without the need to overcome the equilibrium issues associated with isopropanol.

Table 3. Substrate scope using Wills catalyst and *cis*-1,4-butenediol.



Entry[a]	Substrate	Isolated yield[b]	*ee* [%][c]
1		85	>99
2		51[d]	96
3		96	80[f]
4		96	>99
5		55(100)[e]	86
6		93	>99
7		99	96
8		59(100)[e]	93[f]
9		89	79
10		91	75[g]
11		80	99

[a] 1 mmol substrate, 20 mol% KOH, 2 mmol *cis*-1,4-butenediol, 0.25 mL THF, −10 °C, 4 h. [b] Product isolated by column chromatography. [c] Enantiomeric excess calculated using HPLC after purification by column chromatography. [d] Reaction time 16 h. [e] Conversion in parentheses calculated by analysis of ^{1}H NMR spectra. [f] Enantiomeric excess calculated using specific rotation. [g] Enantiomeric excess calculated using ^{1}H NMR spectroscopy and a chiral shift reagent.

Experimental Section

Typical procedure for the ATH of ketones: A mixture of KOH (0.2 mmol) and (*S,S*)-tethered-TsDPEN RuCl (0.05 mmol) was purged under Ar for 10 min and cooled to −10 °C in an ice/NaCl (3:1) bath. Ketone (1.0 mmol), *cis*-1,4-butenediol (2.0 mmol) and THF (0.25 mL) were added, and the reaction mixture was stirred at −10 °C for 4 h. The mixture was then warmed to RT, purification by silica gel column chromatography afforded the corresponding alcohol product, which was identified by comparison with authentic samples by ^{1}H NMR spectroscopy, and the enantioselectivity was determined by chiral HPLC.

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Keywords: hydrogen · hydrogenation · ketones · reduction · ruthenium

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[17] See Supporting Information.

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