Asymmetric Synthesis

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Efficient Enantioselective Synthesis of Optically Active Diols by Asymmetric Hydrogenation with Modular Chiral Metal Catalysts**

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The enantioselective hydrogenation of prochiral ketones is one of the most elegant and effective methods for the preparation of optically active secondary alcohols. With regard to the environment, asymmetric hydrogenations represent a highly efficient and atom-economical process. Multiple applications have been developed using chiral ruthenium complexes with atropisomeric ligands for the synthesis of optically active primary and secondary alcohols. The latter are important building blocks for the synthesis of natural products, pharmaceuticals and, agrochemicals.[1–3]

The development of a general and efficient enantioselective route to terminal, vicinal 1,2-diols still presents a great challenge. These compounds are important chiral building blocks for the synthesis of natural products such as macrodiolides,[4a,b] insect pheromones,[4c] β-lactone esterase inhibitors,[4d] δ-lactones,[4e] and many other biologically active substances.[4f,5] In the synthesis of the anti-HIV pharmaceutical Tenofovir and related pharmaceuticals the application of enantiomerically pure (*R*)-propane-1,2-diol is of critical importance.[6] A further application of terminal optically active 1,2-diols is the resolution of atropisomeric compounds.[7] The asymmetric dihydroxylation of terminal alkenes is the most common method for the preparation for this class of compounds. However, small sterically less demanding alkyl derivatives, such as propene, cannot be enantioselectively oxidized to the diol by asymmetric dihydroxylation, nor to the epoxide by asymmetric epoxidation.[8]

The difficulty in the highly enantioselective transformation of small alkyl derivatives arises from the similar steric demands of the two groups adjacent to the carbonyl functionality. The result is poor *Re* and *Si* face differentiation for the sterically less demanding alkyl derivatives; in contrast, the sterically more demanding aryl ketones can be readily differentiated (Figure 1).

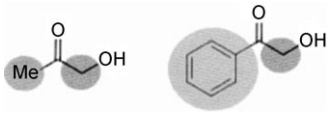
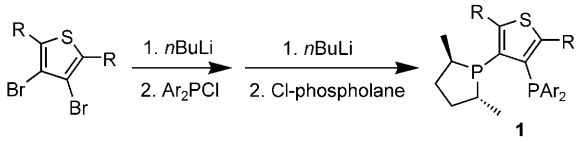


Figure 1. Comparison of the steric demand of alkyl- and aryl-substituted α-hydroxy ketones.

The hydrogenation of α-hydroxy ketones is one alternative for the generation of valuable optically active, terminal 1,2-diols. Good progress has been made in the hydrogenation of the sterically demanding α-hydroxy acetophenones using various ruthenium[9a-f] and iridium catalysts.[9g] Rhodium[10a] and ruthenium complexes[10b] were also successfully applied in asymmetric transfer hydrogenations. Further work concentrated on asymmetric enzymatic reductions.[11]

A general, reductive, and highly enantioselective synthesis of aliphatic 1,2-diols has not been reported previously. Therefore, we began our examination of the enantioselective synthesis of optically active diols with the application of a new class of modular diphosphane ligands **1**. Particular attention was given to nonsymmetric ligands as these were considered more suitable for the enantioface differentiation of the alkyl hydroxy ketones, which are more challenging substrates. Ligands **1** can be prepared simply in two steps on a large scale and are based on a 2,5-disubstituted thiophene core structure, a chiral phospholane unit,[12,13] and a readily variable diarylphosphino group (Scheme 1).



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Scheme 1. Synthesis of the modular diphosphane ligands.

Thus, we synthesized a series of ligands and tested them in the asymmetric ruthenium-catalyzed asymmetric hydrogenation of hydroxyacetone (**2a**), whereby 1,2-propanediol (**3a**) could be isolated in high enantiomeric excess (up to 96% *ee*) (Table 1). Other privileged ligands including various derivatives of binaphthyl, duphos, deguphos, and members of the catasium group generally resulted in lower reactivities and enantioselectivities. The best result with regard to the selectivity was obtained with the *o*-tolyl-substituted ligand **1d**, which provided the desired propane-1,2-diol in 96% *ee*.

To further optimize the reaction parameters we varied the hydrogen pressure, reaction temperature, and solvents.[14]

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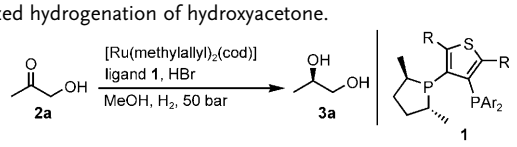
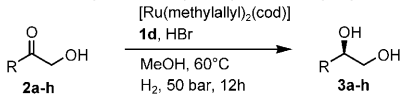
Table 1: Selected ligands employed in the asymmetric ruthenium-catalyzed hydrogenation of hydroxyacetone.

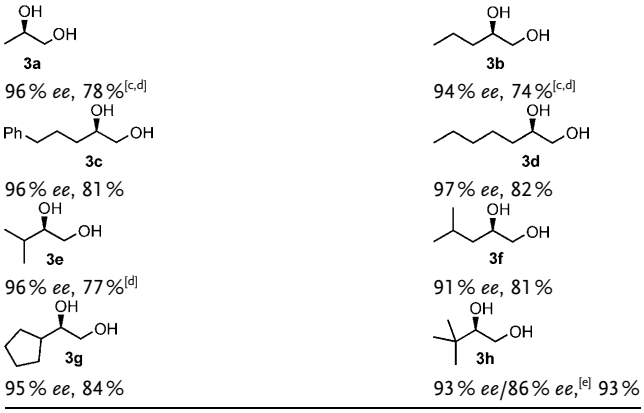


Entry[a]	R	Ar	L	*ee* [%][b]
1	Me		**1a**	70
2	Me		**1b**	80
3	Me		**1c**	79
4	Me		**1d**	96
5	Ph		**1e**	81

[a] Reaction conditions: Hydroxyacetone (**2a**), [Ru(methylallyl)$_2$(cod)] (1 mol%) (cod = cyclooctadiene), **1** (1.1 mol%), HBr (5 mol%) in 1 mL MeOH. [b] Determined by GC on a chiral stationary phase.

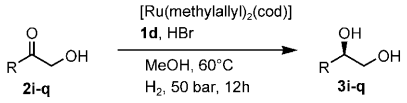
Table 2: Substituted aliphatic α-hydroxy ketones prepared.[a,b]





[a] Reaction conditions: **2a–h** (0.3 mmol), [Ru(methylallyl)$_2$(cod)] (1 mol%, **1d** (1.1 mol%), HBr (5 mol%) in 1 mL MeOH. [b] Yield after chromatography, enantioselectivities determined by GC analysis on a chiral stationary phase. [c] H_2 pressure of 80 bar. [d] Yield of doubly acylated product.[15] [e] Reaction time of 36 h.

Table 3: Aromatic α-hydroxy ketones prepared.



Entry[a]	R	**3**	Yield [%][b]	*ee* [%][c]
1	phenyl	**3i**	90	98
2	4-Me-C_6H_4	**3j**	86	98[d]
3	4-Et-C_6H_4	**3k**	99	98
4	4-Cl-C_6H_4	**3l**	80	99
5	4-Br-C_6H_4	**3m**	83	>99
6	2-naphthyl	**3n**	88	98
7	1-naphthyl	**3o**	66	91
8	2-Me-C_6H_4	**3p**	76[e]	94
9	3-OMe-C_6H_4	**3q**	55	98

[a] Reaction conditions: **2i–q** (0.3 mmol), [Ru(methylallyl)$_2$(cod)] (1 mol%), **1d** (1.1 mol%), HBr (5 mol%) in 1 mL MeOH. [b] Yield after chromatography. [c] Enantioselectivities determined by GC analysis on a chiral stationary phase. [d] H_2 pressure of 80 bar. [e] Reaction time of 36 h.

However, we observed that hydrogen pressure and reaction temperatures between 50 and 80 °C had negligible effect on the hydrogenation. The choice of solvent had a significant effect on the reaction. In methanol very good selectivities and yields were obtained while in other solvents, such as acetonitrile, 1,4-dioxane, dibutyl ether, and water, no reduction occurred. The reduction can also be conducted in aromatic solvents such as toluene; however, the yield is reduced.

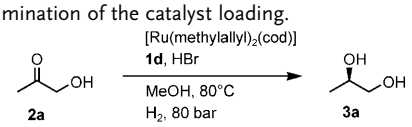
Using the optimized reaction conditions we examined the substrate spectrum of the asymmetric reduction by employing various aliphatic hydroxy ketones. For the first time a series of sterically less demanding 1,2-diols could be obtained in good yields and with excellent enantioselectivities (Table 2). In this manner it was not only possible to reduce linear substrates (**3a**–**3d**) but also branched substrates (**3e**–**3h**) in good yields and with excellent selectivities (up to 97% *ee*). It was even possible to obtain the sterically more demanding *tert*-butyl-substituted, terminal diol (**3h**) in very good enantioselectivities.

In addition to the reduction of aliphatic α-hydroxy ketones, we also examined the hydrogenation of the corresponding aromatic substrates. Utilizing the optimized reaction conditions we were able to obtain a series of terminal, aromatic diols with various substitution patterns as well as electron-donating and -withdrawing substituents on the arene in very good yields and with excellent enantioselectivities (Table 3). In comparison to all the previously reported chiral catalysts our newly developed, nonsymmetric ruthenium catalysts exhibits surprisingly high substrate scope, ranging from linear and branched aliphatic ketones to aromatic ketones.

In further experiments we concentrated on the application of the highly efficient enantioselective hydrogenation of α-hydroxy ketones. Thus we examined the reduction of hydroxyacetone with low catalyst loadings (Table 4). It was shown that with a substrate/catalyst ratio of 10000 the reduction to (*R*)-propane-1,2-diol could be conducted without loss of selectivity on a multigram scale.

In summary we have developed a highly efficient, enantioselective hydrogenation[16] for the synthesis of terminal 1,2-diols. Applying new, nonsymmetric diphosphine ligands, which are based on a chiral phospholane unit and a variable second donor function and which can be readily produced on a large scale, we were able to develop an asymmetric hydrogenation in which not only diverse aromatic

Table 4: Examination of the catalyst loading.



Entry[a]	S/C	*t* [h]	Yield [%][b]	*ee* [%][c]
1	1000	17	80	95
2	10000	48	85	94

[a] Reaction condition: [Ru(methylallyl)$_2$(cod)] (5 mg, 1 equiv), **1d** (7.5 mg, 1.1 equiv), 5 equiv HBr, hydroxyacetone (**2a**) in MeOH. [b] Yield after chromatography. [c] Determined by GC analysis on a chiral stationary phase.

but also aliphatic α-hydroxy ketones can be transformed into valuable 1,2-diols with excellent enantioselectivity.[17] Furthermore, the catalyst loading could be reduced to 0.01 mol% without loss of enantioselectivity. This underscores the preparative application of this methodology.

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[17] The modular catalysts can also be applied efficiently in the synthesis of 1,2-amino alcohols, α- and β-hydroxy esters, and amines. A manuscript regarding this work is in preparation.

