*Asymmetric Reduction*

# Enantioselective Reduction of Aromatic and Aliphatic Ketones Catalyzed by Ruthenium Complexes Attached to β-Cyclodextrin**

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Molecular recognition of substrates by cyclodextrins is made possible by noncovalent interactions in the hydrophobic cavity of the water-soluble, cyclic sugar oligomers. Inclusion complexes of cyclodextrins[1] and their reactions constitute one of the earliest examples of supramolecular chemistry.[2] As a result of these unique features, cyclodextrins can be used to mediate regioselective reactions[3] and in particular for preparing enzyme models.[4,5]

In this context, the binding properties of β-cyclodextrins have been complemented with chemically reactive subunits,

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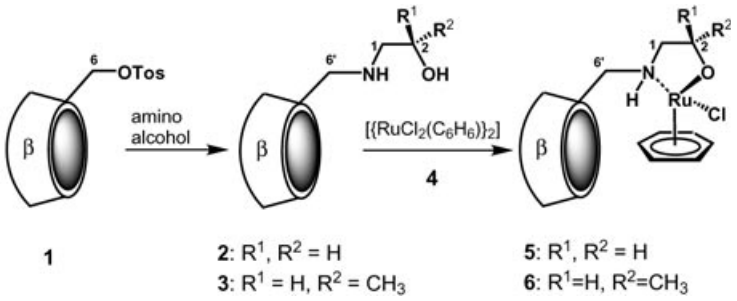
either by attaching functional groups such as acid–base catalysts[3] or by linking β-cyclodextrins to metal complexes.[4,5] In most cases superb reactivity and a very high degree of regioselectivity were observed. In contrast, enantioselective reactions with β-cyclodextrin (β-CD) as the only chiral subunit of the catalyst in general gave products with *ee* values well below 50%. For example, the highest enantiomeric excess reported for a product of $NaBH_4$ reduction of an aromatic ketone in the presence of β-cyclodextrin was 24% *ee*.[6] Additives, such as amines[7] or aminoboranes, [8] improved the enantioselectivity, but only at the expense of the yield. We report herein our results on the first ruthenium–arene complexes of β-cyclodextrin-modified amino alcohols and their use in asymmetric hydrogenation reactions of prochiral ketones.

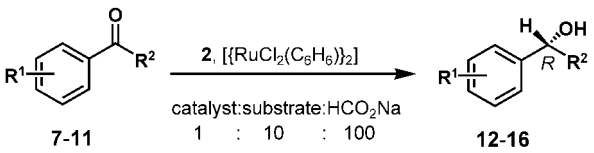
Mono(*O*-6-tosyl)-β-cyclodextrin (**1**, β-CD-Tos) is commercially available and can also be prepared by the tosylation of β-CD on a large scale.[9] The amino alcohol linked β-cyclodextrins **2** and **3** were obtained in good yields as crystalline compounds by the treatment of **1** with an excess of the amino alcohol. [{$RuCl_2(C_6H_6)$}$_2$] (**4**) was prepared by a literature procedure.[10] The formation of Ru complexes of **2** and **3** (Scheme 1) was shown to be quantitative by $^1$H NMR




***Scheme 1.*** Synthesis of Ru complexes of the amino alcohol β-cyclodextrins **2** and **3**. The structures of **5** and **6** are tentatively assigned.

spectroscopic studies (600 MHz, $D_2O$). For example, significant chemical-shift changes are observed between **2** and **5**: The doublets assigned to the two H atoms at C6′ of **2** shift downfield by 0.56 ppm, and the triplet assigned to the H atoms at C1 of **2** shifts downfield by 0.49 ppm. The formation of the Ru complex **6** from **3** leads to the following chemical-shift changes: The signals for the two H atoms at C6′ shift downfield by 0.56 ppm and 0.51 ppm, and those for the H atoms at C1 shift downfield by 0.36 ppm and 0.54 ppm.

For catalytic reactions, the Ru complexes were formed in situ and treated with ketones at room temperature under an argon atmosphere in the presence of excess sodium formate as the hydrogen source (Scheme 2). Even with β-cyclodextrin




***Scheme 2.*** Asymmetric reduction of ketones in water.

as the only chiral unit of the Ru complex the alcohol products are formed with remarkable enantioselectivity, predominantly with the *R* configuration (Table 1). Evidently the observed *ee* values correlate with the binding constants of the ketones to β-cyclodextrin,[1] thus reflecting the preorganization of substrates such that *Si* addition of the hydride to the carbonyl group is preferred in the reactive complex.[11]

***Table 1:*** Enantioselective reduction of ketones **7**–**11** with the catalyst **2**+**4** (10 mol%).

| Ketone | $R^1$ | $R^2$ | Alcohol[a] | Yield [%][b] | *ee* [%][c] |
|---|---|---|---|---|---|
| **7** | H | $CH_3$ | (*R*)-**12** | 81 | 12 |
| **8** | H | $C_2H_5$ | (*R*)-**13** | 61 | 6 |
| **9** | *p*-$CH_3$ | $CH_3$ | (*R*)-**14** | 67 | 31 |
| **10** | *p*-Cl | $CH_3$ | (*R*)-**15** | 93 | 47 |
| **11** | *p*-*t*Bu | $CH_3$ | (*R*)-**16** | 64 | 47 |

[a] Absolute configuration based on optical rotation. [b] Yields based on GLC analysis and isolated material. [c] Enantiomeric excess determined by $^1$H NMR spectroscopy (Eu(tfc)$_3$) (tfc = 3-(trifluoromethylhydroxymethylene)-D-camphorate) and HPLC analysis (chiracel OD-H).

Since it is known from work by other research groups[12] that asymmetric reduction catalyzed by Ru/amino alcohol complexes lacking a cyclodextrin unit is largely dependent on the chirality at the carbinol carbon atom (C2), we prepared **3** by the condensation of (*S*)-(+)-1-amino-2-propanol and β-CD-Tos (**1**). Ligand **3** was isolated in 66% yield as a white solid and was subsequently characterized by high-field NMR spectroscopy, MS(ESI), and X-ray crystal-structure analysis (Figure 1). Initial experiments with the Ru complex of **3**

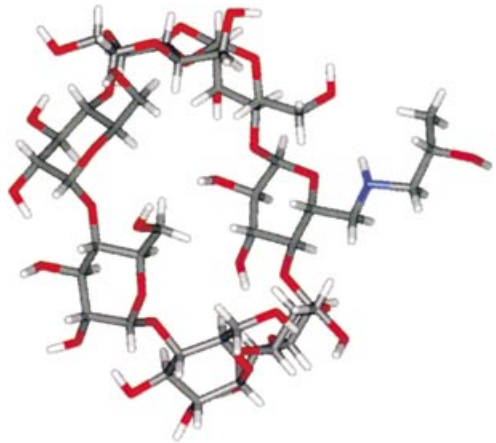


***Figure 1.*** Structure of ligand **3** derived from X-ray crystal-structure analysis.

revealed a solubility problem in water. To avoid rather dilute conditions the transfer-hydrogenation reactions with **3** were carried out in a mixture of $H_2O$/DMF (3:1; see Experimental Section; DMF = *N*,*N*-dimethylformamide).

When the β-CD derivative **3** was used, the products were obtained with *ee* values of up to 97% and in acceptable yields (Table 2). It is interesting to note that with **3** as a ligand for Ru, acetophenone (**7**) was reduced to (*S*)-**12** with 77% *ee*; in

***Table 2:*** Enantioselective reduction of ketones **7**–**11** with the catalyst **3**+**4** (10 mol%).

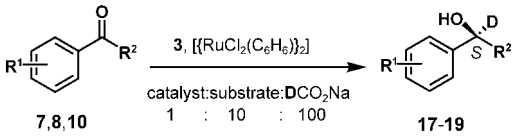
| Ketone | $R^1$ | $R^2$ | Alcohol[a] | Yield [%][b] | *ee* [%][c] |
|---|---|---|---|---|---|
| **7** | H | $CH_3$ | (*S*)-**12** | 90 | 77 |
| **8** | H | $C_2H_5$ | (*S*)-**13** | 63 | 80 |
| **9** | *p*-$CH_3$ | $CH_3$ | (*S*)-**14** | 69 | 94 |
| **10** | *p*-Cl | $CH_3$ | (*S*)-**15** | 77 | 87 |
| **11** | *p*-*t*Bu | $CH_3$ | (*S*)-**16** | 51 | 97 |

[a], [b], and [c]: see Table 1.

contrast, the Ru complex of (*S*)-1-amino-2-propanol lacking the β-cyclodextrin unit gave **12** in only ≈50% *ee* in favor of the *S* isomer.[13] Since we obtained *R* alcohols by using Ru complexes with ligand **2** and *S* alcohols with ligand **3** our results suggest a clear dominance of the chirality at C2 on the enantioselectivity.

The catalytic system described herein also enables the synthesis of $^2$H-enriched benzyl alcohols starting from ketones and with sodium [$D_1$]formate as a deuterium source for isotope labeling. Thus, ketones **7**, **8**, and **10** were reduced with 10% of **3**+**4** and $DCO_2Na$ (98% D) in a $H_2O$/DMF mixture (3:1, 500 μL) to give *S* deuterated alcohols **17**, **18**, and **19** in good yields and with enantioselectivities comparable to those observed with HCOONa. High-field NMR (600 MHz) spectroscopic measurements showed that $^2$H-labeling was as high as >97 atom% (Table 3).

***Table 3:*** Enantioselective reduction of ketones **7**, **8**, and **10** with the catalyst **3**+**4** (10 mol%) and $DCO_2Na$.

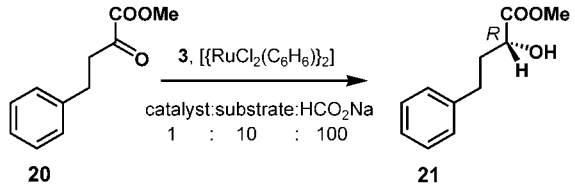



| Ketone | $R^1$ | $R^2$ | Alcohol[a] | Yield [%][b] | *ee* [%][c] |
|---|---|---|---|---|---|
| **7** | H | $CH_3$ | (*S*)-**17** | 79 | 77 |
| **8** | H | $C_2H_5$ | (*S*)-**18** | 53 | 76 |
| **10** | *p*-Cl | $CH_3$ | (*S*)-**19** | 70 | 87 |

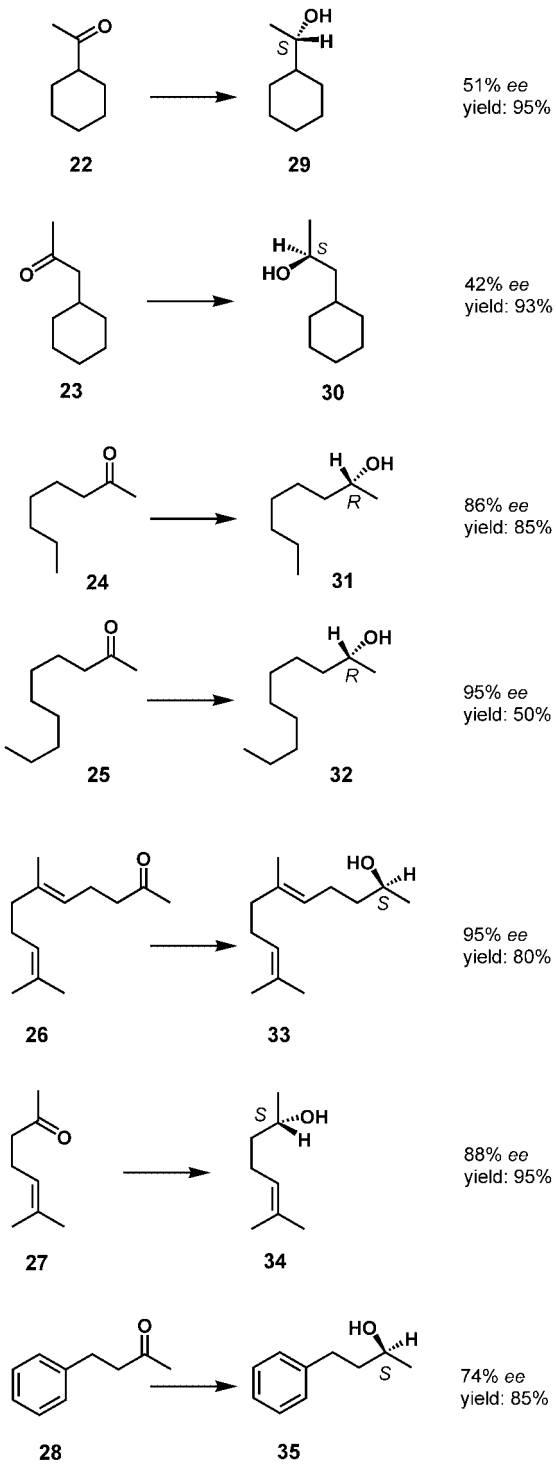
[a], [b], and [c]: see Table 1.

Further examples demonstrate the potential scope of the system. α-Ketoesters, such as **20**, are reduced quantitatively to the corresponding *R*-configured alcohols **21** with 57% *ee* (Scheme 3).

Also most promising were first reactions with aliphatic and unconjugated ketones. Thus, ketones **22**–**28** were reduced under the same conditions as described above to alcohols **29**–**35** in acceptable yields and with moderate to high enantioselectivity (Scheme 4).



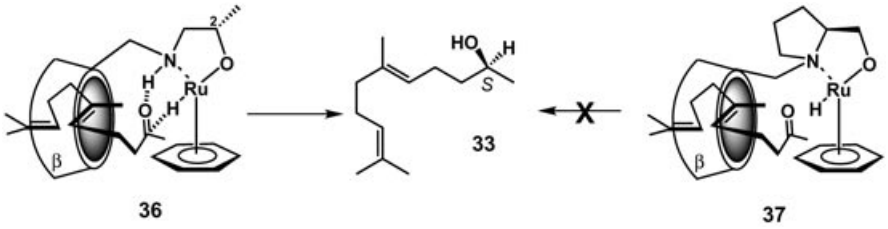

***Scheme 3.*** Reduction of the α-ketoester **20**.




***Scheme 4.*** Enantioselective reduction of aliphatic ketones under the conditions used for the reactions in Table 2.

The reaction mechanism of our transformations seems to resemble that suggested by Noyori and co-workers,[11] since in contrast to **36** the cyclodextrinyl–prolinol–Ru complex **37** was completely unreactive, thus indicating the significance of the N–H group for hydrogen transfer to the carbonyl group (Scheme 5).




***Scheme 5.*** Suggested hydrogen transfer (*Re* attack) from the Ru–hydride intermediate to geranyl acetone (**26**) encapsuled in β-cyclodextrin (see **36**); the reaction in **37** fails.

In summary, we have synthesized new water-soluble Ru complexes of β-cyclodextrin-modified amino alcohols **2** and **3** to serve as supramolecular catalysts in hydrogen-transfer reactions. Up to 97% *ee* and good to excellent yields were observed. In all cases, β-cyclodextrin plays an important role on the enantioselectivity through preorganization of the substrates in the hydrophobic cavity. This finding is particularly significant in the case of substrates such as **22**–**28**. Although a number of highly enantioselective Ru-based hydrogen-transfer catalysts are known,[14] including one example that functions in water,[15] none of these systems have been shown to reduce unconjugated ketones.

## Experimental Section

Synthesis of **2**: A neat solution of mono(*O*-6-tosyl)-β-cyclodextrin (265 mg, 0.20 mmol) and aminoethanol (960 mg, 15.7 mmol, 80 equiv) was stirred for 12 h at 70 °C. Water was then added (1.0 mL), and the resulting yellow solution was added dropwise to acetone (60 mL). The resulting white precipitate (245 mg) was filtered off and recrystallized from water to give pure **2** (140 mg, 59%). MS(ESI): *m*/*z* 1179 ($M^+$, 100), 612 ($[M+Na]^{2+}$, 72), 1201 ($[M+Na]^+$, 67); $^1$H NMR (600 MHz, $D_2O$): $\delta = 4.97$–$5.02$ (m, 7H), 3.79–3.86 (m, 8H), 3.68–3.77 (m, 19H), 3.44–3.50 (m, 13H), 3.33 (dd, $J = 9.60$, 9.60 Hz, 1H), 2.92 (d, $J = 10.86$ Hz, 1H), 2.69 (m, 1H), 2.54 ppm (m, 2H); m.p.: decomposition $> 275$ °C.

Synthesis of **3**: A neat solution of mono(*O*-6-tosyl)-β-cyclodextrin (300 mg, 0.23 mmol) and (*S*)-(+)-2-aminopropanol (1.4 g, 18.6 mmol, 80 equiv) was stirred for 12 h at 70 °C. Water (0.5 mL) was then added, and the resulting yellow solution was added dropwise to acetone (60 mL). The white precipitate (300 mg) was removed by filtration and recrystallized from water. The white crystals were washed with an ice-cold acetone/water mixture (1:1, 5 mL) to give pure **3** (181 mg, 66%). MS(ESI): *m*/*z* 1192 ($M^+$, 100), 618.5 ($[M+Na]^{2+}$, 85) 1214 ($[M+Na]^+$, 78); $^1$H NMR (600 MHz, $D_2O$): $\delta = 5.00$–$5.05$ (m, 7H), 3.87–3.94 (m, 8H), 3.76–3.85 (m, 19H), 3.48–3.63 (m, 13H), 3.38 (dd, $J = 9.60$, 9.60 Hz, 1H), 3.02 (d, $J = 10.86$ Hz, 1H), 2.79–2.82 (m, 1H), 2.54–2.57 (m, 2H), 1.09 (d, $J = 6.32$ Hz, 3H); m.p.: decomposition $> 275$ °C. Crystal data for **3**: $C_{45}H_{77}NO_{35}\cdot 16\,H_2O$, orthorhombic, $P2_1$, $a = 12.8092(4)$ Å, $b = 19.6407(5)$ Å, $c = 26.2645(5)$ Å, $\alpha = 90°$, $\beta = 90°$, $\chi = 90°$, $V = 6696.3$ Å$^3$, $Z = 4$, $\rho_{calcd} = 1.47$, 85399 reflections were measured, $T = 173$ K. Data were collected with $Mo_{K\alpha}$ radiation on a Bruker diffractometer (KAPPACCD and scantype PHIOMEGA).

**6** (formed in situ): MS (ESI): $m/z = 1191$ ([ligand **3**]$^+$, 100), 1371 ([**6**-Cl]$^+$, 11), 1406 ([**6**]$^+$, 18); UV/Vis ($H_2O$): $\lambda_{max} = 251$ nm.

General procedure:[16] Ligand **3** (0.01 mmol) was dissolved in $H_2O$/DMF (3:1, 0.5 mL), $[RuCl_2(C_6H_6)]_2$ (**4**, 0.005 mmol) was added, and the resulting mixture was stirred for 1 h at room temperature. HCOONa (1.0 mmol) was then added, and after further stirring for 10 min the ketone (0.1 mmol) was injected. The reaction was usually finished after 24 h at room temperature. The mixture was then extracted three times with hexane (5 mL), the combined hexane extracts were washed with water (6 mL) and dried over $Na_2SO_4$, and the product(s) were analyzed by GC/HPLC and/or purified by TLC. The *ee* values of the products were determined by HPLC on a chiral phase (chiracel OD-H), GC on a chiral phase (hydrodex 3P), and $^1$H NMR/$^{19}$F NMR spectroscopic studies of the corresponding Mosher esters.

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[16] The concentrations of the catalyst (10 mol%) and formate (excess) were adjusted to give a reasonable reaction time of approximately 24 h. Decreasing the catalyst and/or formate concentration led to unsuitably long reaction times. Preliminary experiments in which Ru–O was replaced by Ru–NTos revealed a sixfold increase in the rate of the reaction, thus allowing for lower catalyst loadings; results will be reported in a subsequent publication.

  