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Highly enantioselective catalytic hydrogenation of a 5-amino-3,5-dioxopentanoic ester

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ABSTRACT

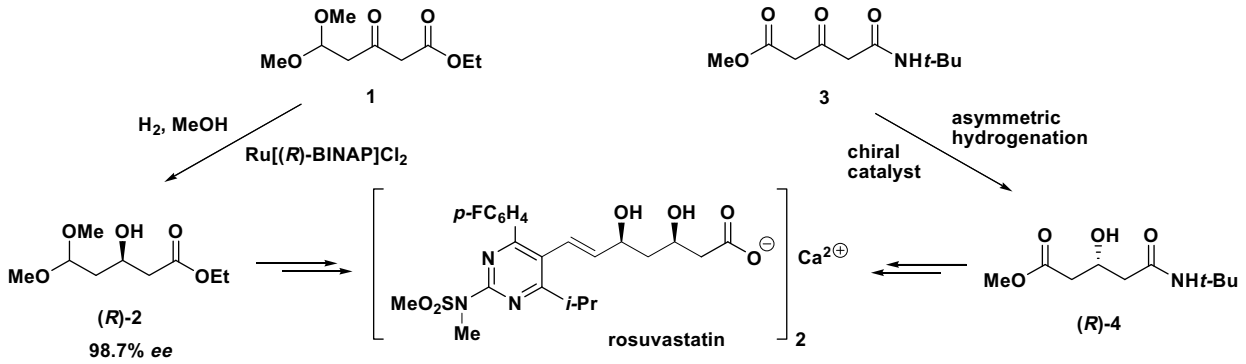
The highly enantioselective hydrogenation of methyl 4-*tert*-butylcarbamoyl-3-oxo-butyrate to the corresponding secondary alcohol, representing an interesting chiral building block, for example, for the synthesis of statins, has been investigated in the presence of homogeneous chiral Rh(I) and Ru(II) complexes bearing phosphine ligands. The highest enantioselectivity (up to 96%) was achieved with a [Ru((*R*)-BINAP)(*p*-cymene)Cl]Cl complex (sub./cat. ratio 100:1, 5 bar H_2, rt, MeOH).

Transition metal-catalyzed asymmetric reactions represent one of the most powerful tools for the synthesis of enantiomerically pure compounds in academia and industry.[1,2] In particular, the enantioselective hydrogenation can be conducted on a large scale by use of hydrogen as a cheap reducing agent.[3,4] During the last 40 years an enormous number of trivalent phosphorus ligands have been developed for different types of homogeneous asymmetric hydrogenations using 'soft' metals like rhodium, ruthenium, iridium, and palladium.[5]

Recently, we reported on the preparation and highly enantioselective hydrogenation of ethyl 3-hydroxy-5,5-dimethoxypentanoate (**1**),[6] which presents a key intermediate on the way to the chiral side chain of pharmaceutically important statins (Scheme 1). It was shown that homogeneous hydrogenation of **1** proceeds with highest enantioselectivity (up to 98.7%) in the presence of [Ru((*R*)-(BINAP))Cl]$_2$ as a pre-catalyst and a sub./cat. ratio by up to 20,000:1 at 50 bar and 50 °C in MeOH. In turn chiral building block (*R*)-**2** was successfully employed for the total synthesis of rosuvastatin.[7]

From retrosynthetic analysis, shown in Scheme 1, it follows that the chiral side chain of rosuvastatin can also be generated starting from *N*-*tert*-butyl-3-oxoglutarate (**3**) via enantioselective hydrogenation provided a chiral catalyst can be identified to differentiate between the two rather similar enantiotopic faces of the prochiral ketone. Besides the targeted application in statin synthesis, the chiral product represents an interesting building block for the construction of other highly functionalized compounds.

In our first attempt, the substrate **3** required for hydrogenation was prepared by mono-amidation of dimethyl acetone-1,3-dicarboxylate (**5**) with *tert*-butylamine according to Helmchen's



Scheme 1. Alternative pathways for the total synthesis of rosuvastatin with enantioselective hydrogenations as key step.

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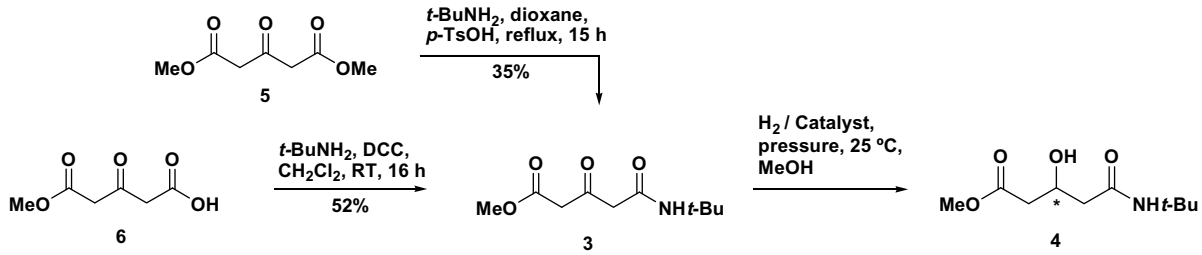


Scheme 2. Synthesis and enantioselective hydrogenation of methyl *N*-*tert*-butyl-3-oxoglutarate (**3**).

procedure (Scheme 2).[8] The reaction was performed by addition of *tert*-butylamine to the boiling mixture of **5** in dioxane in the presence of a catalytic amount of *p*-toluenesulfonic acid. Slow addition of *tert*-butylamine is essential for the success of the reaction. Refluxing of the reaction mixture was continued for further 15 h. Product **3** was crystallized from CH_2Cl_2 in an ice-bath and after additional purification by column chromatography (silica gel, eluent: hexane/EtOAc = 2:3) it was obtained with a yield of 35% only.

In order to optimize the reaction we found that acylation of *tert*-$BuNH_2$ by acetonedicarboxylate mono-methyl ester (**6**) in the presence of dicyclohexyl carbodiimide (DCC) in CH_2Cl_2 at room temperature improved the conversion up to 75% (52% yield).

Results of the enantioselective hydrogenation[9] of **3** are summarized in Table 1. Hydrogenations using commercial pre-catalysts [Ru((*S*)-BINAP)(*p*-cymene)Cl]Cl and [Ru((*R*)-BINAP)(*p*-cymene)Cl]Cl proceeded smoothly at 25 °C and an initial H_2-pressure of 50 bar in MeOH (substrate concentration 0.001 mmol/ml) affording methyl 5-(*tert*-butylamino)-3-hydroxy-5-oxopentanoate (**4**) with enantioselectivities of 84% (entry 1) and 83% (entry 2), respectively.[10] The reaction was complete within 4 h at a ratio of sub./cat. = 100. Similar activity (>99% of conversion in 4 h) and enantioselectivity (82%) were achieved using [Ru((*R*)-BINAP)]Cl_2 × ImH × DMF pre-catalyst (entry 3) or commercial [Ru((*R*)-BINAP)]Cl_2 (dimer) (entry 4).[11] Tests of other chiral Ru-complexes, for example, [Ru((*R,R*)-**7**)]Cl_2 × Et_3N × DMF (entry 5) in the same conditions, showed only moderate enantioselectivity (54%).

Homogeneous Ru-complexes are not the only metal catalysts able to mediate the hydrogenation of ketones. For example, Togni et al. reported the highly enantioselective reduction of β-keto esters (up to 97% ee) catalyzed by a rhodium complex based on Josiphos as a chiral ligand under mild conditions (rt, 20 bar, 15 h).[12] Therefore, we screened also a set of analogous Rh-complexes with several commercially available chiral diphosphines (see Table 1, entries 6–12). The activity of all tested Rh-complexes was nearly similar to that noted with Ru-complexes. The reaction was complete within 4–6 h at a ratio of sub./cat. = 100; however, the ee-values were disappointingly low—in the range of 22–46%. The best enantioselectivity (46%) among all tested Rh-complexes was achieved with [Rh((*R,R*)-**8**)(COD)]BF_4 (entry 7).

A decrease of the initial H_2-pressure from 50 to 25 bar caused an increase of the enantioselectivity. For example, the application of [Ru((*R,R*)-**7**)]Cl_2 × Et_3N × DMF as pre-catalyst at 25 bar showed complete conversion after 9 h and 66% ee (compare entries 5 and 14). Commercial BINAP complexes, like [Ru((*S*)-BINAP)(*p*-cymene)Cl]Cl, or [Ru((*R*)-BINAP)(*p*-cymene)Cl]Cl and [Ru((*R*)-BINAP)]Cl_2 (dimer) showed the same activity (>99% conversion within ca. 9 h and enantioselectivities of ~90%) (entries 15–17).[12]

The asymmetric hydrogenation of **3** at 25 °C and an initial H_2-pressure of 25 bar in MeOH using Noyori-type Ru-complexes like (*R,R*)-**9** (entry 18) and (*R,R,R*)-**10** (entry 19), showed high activity (>99% of conversion after 9 h) with 91% ee and 88% ee, respectively.

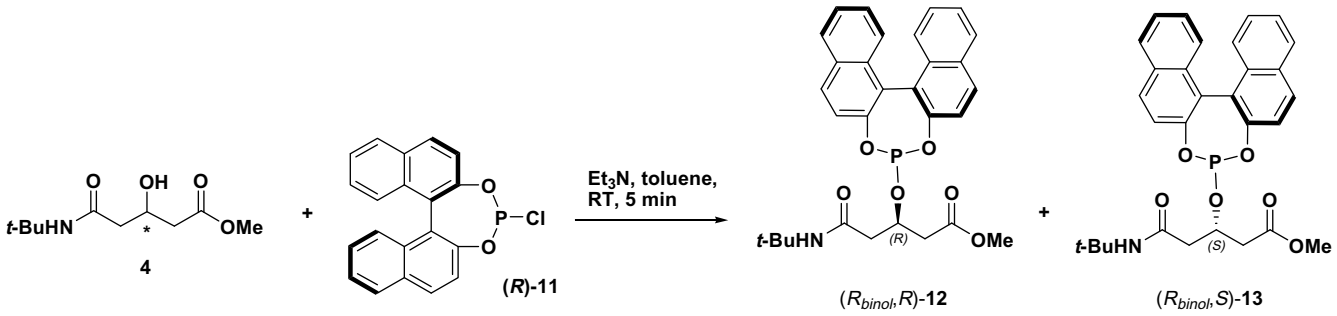
As expected the hydrogenation at 10 and 5 bar in MeOH at 25 °C proceeded much slower and complete conversion was possible only between 12 and 24 h. Thus, BINAP-cymene complexes, like [Ru((*S*)-BINAP)(*p*-cymene)Cl]Cl and [Ru((*R*)-BINAP)(*p*-cymene)-Cl]Cl induced enantioselectivities of 90% at 10 bar (entries 20 and 21) and up to 96% at 5 bar of initial H_2-pressure, respectively.

It is interesting to note that employment of [Ru((*R*)-BINAP)]Cl_2 (dimer) gave in the hydrogenation of **3** at 10 bar higher enantioselectivity (93%, entry 22) than [Ru((*R*)-Tol-BINAP)]Cl_2 (dimer) (87%, entry 23). Both Ru-complexes (*R,R*)-**9** and (*R,R,R*)-**10** showed a similar tendency, and 95% ee and 88% ee were achieved (entries 24 and 25). A decrease of the H_2-pressure from 10 bar to 5 bar led to a significant deceleration of the reaction rate (for complete conversion ⩾24 h of reaction time), but the enantioselectivity remained at the same high level (entries 26–28).

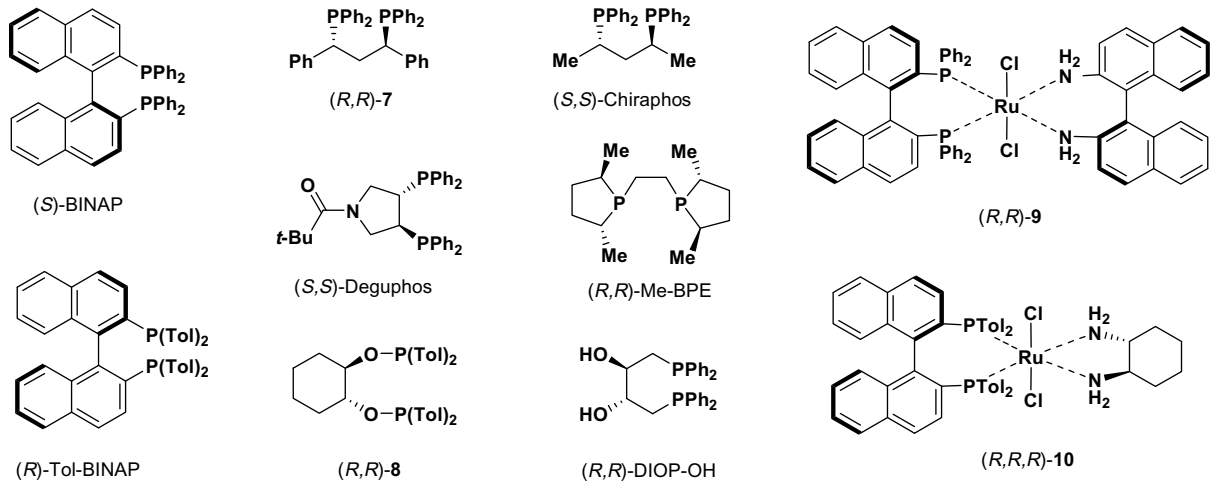
Table 1
Asymmetric hydrogenation of methyl *N*-*tert*-butyl-3-oxoglutaramate (**3**) in MeOH at 25 °C (sub./cat. = 100)[a]

Entry	Pre-catalyst	pH_2 [bar]	ee[b] (%) (conf.)
1	[Ru((*S*)-BINAP)(*p*-cymene)Cl]Cl	50[c]	84 (+)
2	[Ru((*R*)-BINAP)(*p*-cymene)Cl]Cl	50[c]	83 (−)
3	[Ru((*R*)-BINAP)]Cl_2 × ImH × DMF	50[c]	82 (−)
4	[Ru((*R*)-BINAP)]Cl_2 (*dimer*)	50[c]	82 (−)
5	[Ru((*R,R*)-**7**)]Cl_2 × Et_3N × DMF	50[c]	54 (+)
6	[Rh((*R*)-BINAP)(COD)]BF_4	50[c]	24 (−)
7	[Rh((*R,R*)-**8**)(COD)]BF_4	50[c]	46 (−)
8	[Rh((*R,R*)-Me-BPE)(COD)]OTf	50[c]	30 (−)
9	[Rh((*R*)-Tol-BINAP)(COD)]BF_4	50[c]	40 (−)
10	[Rh((*S*)-BINAP)(COD)]BF_4	50[c]	22 (+)
11	[Rh((*S,S*)-Chiraphos)(NBD)]BF_4	50[c]	41 (−)
12	[Rh((*S,S*)-Deguphos)(COD)]BF_4	50[c]	31 (−)
13	[Ru((*R,R*)-DIOP-OH)(COD)]BF_4	25[d]	8 (−)
14	[Ru((*R,R*)-**7**)]Cl_2 × Et_3N × DMF	25[d]	66 (+)
15	[Ru((*S*)-BINAP)(*p*-cymene)Cl]Cl	25[d]	90 (+)
16	[Ru((*R*)-BINAP)(*p*-cymene)Cl]Cl	25[d]	89 (−)
17	[Ru((*R*)-BINAP)]Cl_2 (*dimer*)	25[d]	89 (−)
18	(*R,R*)-**9**	25[d]	91 (−)
19	(*R,R,R*)-**10**	25[d]	88 (−)
20	[Ru((*S*)-BINAP)(*p*-cymene)Cl]Cl	10[e]	90 (+)
21	[Ru((*R*)-BINAP)(*p*-cymene)Cl]Cl	10[e]	90 (−)
22	[Ru((*R*)-BINAP)]Cl_2 (*dimer*)	10[e]	93 (−)
23	[Ru((*R*)-Tol-BINAP)]Cl_2 (*dimer*)	10[e]	87 (−)
24	(*R,R*)-**9**	10[e]	95 (−)
25	(*R,R,R*)-**10**	10[e]	88 (−)
26	[Ru((*S*)-BINAP)(*p*-cymene)Cl]Cl	5[f]	96 (+)
27	[Ru((*R*)-BINAP)(*p*-cymene)Cl]Cl	5[f]	95 (−)
28	(*R,R*)-**9**	5[f]	96 (−)

[a] Reactions were run till completion. Conversion was analyzed by ^1H NMR spectroscopy.
[b] Ratio of enantiomers was estimated by quantitative ^{31}P NMR spectroscopy using enantiopure phosphite, prepared from (*R*)-BINOL and PCl_3 according to Scheme 3.
[c] 4–6 h.
[d] 9–10 h.
[e] 12–24 h.
[f] ⩾24 h, reaction time.



Scheme 3. Formation of two diastereomeric phosphites by reaction of methyl 5-(*tert*-butylamino)-3-hydroxy-5-oxopentanoate (**4**) and chlorophosphite (*R*)-**11**, prepared from (*R*)-BINOL and PCl_3.



An increase of the sub./cat. ratio to 500 led to a drastic decrease of the rate and the enantioselectivity was much lower. For example, with (*R,R*)-**9** as catalyst applying 50 bar and 25 bar of H_2-pressure at 25 °C in MeOH ee-values of 26% and 40% were achieved. The reason for the decrease of the ee is not clear up to now.

Unfortunately, several trials to analyze the hydrogenation product **4** by gas chromatography using various chiral GC-columns failed. As a successful alternative revealed the derivatization reaction with the enantiopure chlorophosphite (*R*)-**11**, prepared from (*R*)-BINOL and PCl_3 and subsequent NMR-analysis (Scheme 3).[7,13] The chlorophosphite reacted quantitatively with the alcohol **4** to give diastereomeric phosphites (R_{binol},*R*)-**12** and (R_{binol},*S*)- **13**.[14]

The ^{31}P NMR spectra of both compounds were characterized by signals separated till the base line (δ_P 152.5 ppm and 154.9 ppm), therefore it was possible to determine precisely the enantiomeric composition of the hydrogenation product.[15]

Acknowledgments

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9. *General procedure for catalytic hydrogenation of keto ester* **3**: Pre-catalyst [Ru((*R*)-BINAP)(*p*-cymene)Cl]Cl (6.7 mg, 0.008 mmol) was placed in a 12 ml-autoclave under argon, followed by the addition of a solution of keto ester **3** (172.2 mg, 0.8 mmol) in abs MeOH (8 ml). The mixture was pressurized with hydrogen to 50 bar and stirred at 25 °C until the H_2 consumption ceased (~4 h). Evaporation of the solvent in vacuum gave 4-*tert*-butylcarbamoyl-3-hydroxy-butyrate (**4**) as yellowish oil in quantitative yield. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.30 (s, 9H, $C(CH_3)_3$), 2.16–2.42 (m, 4H, CH_2CO_2Me and $CH_2C(O)NH$-*tert*-Bu), 3.25 (s, 3H, CO_2CH_3), 3.48 (br s, 1H, OH), 4.38–450 (m, 1H, CHOH).
10. Enantioselectivities at higher temperatures (50 °C) for Ru-complexes with BINAP as ligand were slightly lower, but still above 80% ee in all trials. A decrease of the reaction temperature to 10 °C led to a dramatic deceleration of the reaction rate. Only ca. 50% of conversion was achieved within 69 h, but the enantioselectivity was not affected (84%). MeOH was found to be the solvent of choice, since the reaction rates dropped significantly when the reactions were performed in CH_2Cl_2, EtOH, *i*-PrOH or ethyl acetate.
11. Ru-complexes with BINAP as a ligand induced slightly lower ee-values at 50 °C and an initial H_2-pressure of 25 bar in comparison with the reaction at 25 °C, but still above 85% ee.
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14. *The determination of the enantiomeric composition of alcohol* **4** *was conducted following the general procedure (according to Scheme 3)*: A 10% solution of (*R*)-11 (0.5 mL, 0.14 mmol) in dry benzene, the alcohol **4** (21 mg, 0.10 mmol), abs Et_3N (20 mg, 0.19 mmol), and dry benzene-d_6 (0.1 ml) were mixed together in a vial. The resultant pale solution was immediately transferred into an NMR-tube under argon, and then the ^{31}P NMR spectrum was recorded. Two singlet peaks at δ_P 152.5 ppm and 154.9 ppm separated till the baseline correspond to compounds (R_{binol},*R*)-**12** and (R_{binol},*S*)-**13**, respectively. The enantiomeric excess of alcohol 4 was calculated from the integral intensities of the peaks.
15. The specific rotation was determined to be $[\alpha]_D^{24}$ +1.7 (*c* 8.0, MeOH) of product **4**, which was prepared by hydrogenation of carbonyl compound **3** using [Ru((*S*)-BINAP)(*p*-cymene)Cl]Cl complex as pre-catalyst at 5 bar of initial hydrogen pressure and obtained with an enantioselectivity of 96% ee (Table 1, entry 26).