Stereochemical aspects of the enantioselective hydrogenation of 2-pyrones

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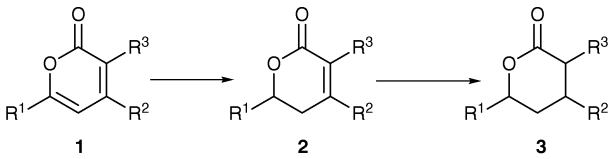
The highly enantioselective (86–98% ee) hydrogenation of 2-pyrones, using cationic ruthenium catalysts containing the (6,6′-dimethoxybiphenyl-2,2′-diyl)bis[3,5-di(*tert*-butyl)phenylphosphine] ligand, takes place either regioselectively at the 5,6 position or involves both double bonds in the ring, depending on the substitution pattern. Both steps show a *syn* stereochemistry. The diastereoselectivity of the double hydrogenation is high (*cis* : *trans* ⩾ 90 : 10). The second hydrogenation step shows kinetic resolution; however, when either enantiomeric catalyst was used essentially no double asymmetric induction effect was observed. The diastereoselectivity can be substantially reversed (*cis* : *trans* ≈ 12 : 88) when the alternative enantiomer of the diphosphine ligand is used for the second step.

The enantioselective hydrogenation of 2-pyrones (**1**, Scheme 1) is a matter of current interest.[1,2] The 5,6-dihydro-2-pyrones (**2**) produced may show interesting pharmaceutical properties[2] and serve as valuable synthetic intermediates, such as for the synthesis of tetrahydrolipstatin.[1] Furthermore, an exhaustive hydrogenation of the pyrone ring can lead to optically active δ-lactones (**3**) that are widely spread in nature.[1,2]

Some of us have reported that the hydrogenation of the 2-pyrone **1a** (Scheme 1), using the ruthenium catalyst precursors $[Ru(CH_3COO)_2(P\hat{}P)]$ in the presence of HBF_4 [where

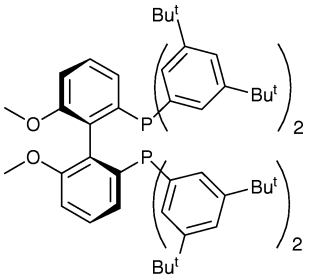


1 **2** **3**

a $R^1 = n\text{-}C_{11}H_{23}$-; R^2 = OH; $R^3 = n\text{-}C_6H_{13}$-
b $R^1 = CH_3$-; $R^2 = OCH_3$; R^3 = H
c $R^1 = R^2 = CH_3$-; R^3 = H

Scheme 1

P^P is MeO-biphep or related ligands and MeO-biphep represents (6,6′-dimethoxybiphenyl-2,2′-diyl)bis(diphenylphosphine)], results in a remarkable regioselectivity and enantioselectivity for the trisubstituted double bond.[1] The solvento-complex formed in the above reaction[3,4] was found to react with dihydrogen under pressure to give the species $[RuH(iso\text{-}C_3H_7OH)_2(P\hat{}P)](BF_4)$[5] {where P^P is (*S*)-(6,6′-dimethoxybiphenyl-2, 2′-diyl)bis[3, 5-di(*tert*-butyl)phenylphosphine] ((*S*)-**5**)}, similar to a previously reported hydrido-complex containing (*R*)-binap[binap = (1,1-binaphthyl-2,2′-diyl)bis(diphenylphosphine)].[6] Deuterium labelling has been widely used to obtain mechanistic information about the enantioselec-tive hydrogenation. For ruthenium systems containing atropisomeric ligands, however, only the neutral precursor $[Ru(OAc)_2(binap)]$ was investigated. This catalyst has been used mainly for the hydrogenation of unsaturated acids or their esters.[7–14] We report here an analogous investigation of the hydrogenation of 2-pyrones (**1**) using cationic systems prepared *in situ*. The investigation was undertaken not only to obtain information about the factors influencing the enantioselectivity for this important process, but also about the related complete hydrogenation of the 2-pyrone ring to the corresponding δ-lactones. The factors determining the final enantio- and diastereoselectivity of the latter reaction are also analysed.



(*S*)-**5**

Results and Discussion

Based on preliminary experiments, the substrates chosen for the labelling investigation were **1b** and **1c**. The catalyst was always formed *in situ* from $[Ru((S)\text{-}\mathbf{5})(OAc)_2]$ and HBF_4 (1 : 10 molar ratio) in 2-propanol as the solvent.[1,5] The use of stoichiometric amounts of acid as well as of $[RuH(iso\text{-}C_3H_7OH)_2(P\hat{}P)](BF_4)$ without any excess of acid results, in fact, in poor reproducibility of the reaction rate and low enantioselectivity.[4] Under the conditions used (60 bar H_2, 60 °C, 20 h, 6 μmol catalyst in 10 ml solvent, substrate to catalyst molar ratio ≈500), hydrogenation of **1b** stops at the level of the (*R*)-5,6-dihydro-2-pyrone **2b**, whereas that of **1c** proceeds to form lactone **3c** (*cis* : *trans* molar ratio = 11 : 1, *cf.* Scheme 2). The experiments were carried out using alternatively *iso*-C_3H_7OH–D_2 or *iso*-C_3H_7OD–H_2. The hydrogenation of **1b** to **2b** shows good enantioselectivity, the (*R*)-enantiomer being formed with ees (enantiometric excess) between 86% and 90%. During hydrogenation an extensive exchange of the label between the gas phase and the solvent takes place (Table 1). Control experiments showed that an equilibrium distribution of the label is rapidly achieved (less than 10 min compared with about 10 h hydrogenation time). Various ruthenium

Table 1 Deuterium distribution between the gas phase and the solvent before and after hydrogenation of **1b**

Run[a,b]	Solvent *iso*-PrOH	Gas phase *iso*-PrOD	H_2	HD	D_2
1 (i)	1.00	0	0	0	1.00
(f)	0.26	0.74	0.31	0.47	0.22
2 (i)	0	1.00	1.00	0	0
(b)	0.33	0.67	0.61	0.33	0.06

[a] Reaction conditions: 6 μmol [Ru((*S*)-**5**)$(OAc)_2$]–HBF_4 (1 : 10 molar ratio) as the catalyst precursor, substrate to catalyst ratio: (S/C) = 500, pH_2 = 60 bar; 10 ml 2-propanol; T = 60 °C; t = 20 h. [b] (i) Initial and (f) final distribution of deuterium label (expressed as molar fraction).

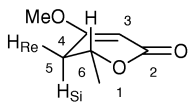
Table 2 Deuterium distribution for (*R*)-**2b**

Run[a]	d_0	d_1	d_2	MDN[d]
1[b]	0.24	0.48	0.28	1.04
2[b]	0.37	0.47	0.15	0.77
	H_{5Re}	H_{5Si}	H_6	
1[c]	0.38	0	0.58	0.96
2[c]	0.25	0	0.46	0.71

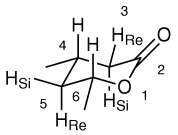
[a] For reaction conditions see Table 1. [b] Molar fraction of the differently labelled species from MS. [c] Deuterium content in the various positions from ^1H NMR, with OCH_3 signal intensity taken as the reference. [d] MDN = mean deuterium number (average number of deuterium atoms per molecule).

complexes were already observed to catalyse this exchange reaction, even if sometimes more slowly,[15–19] and possible mechanistic pathways were proposed.[18–20] The deuterium distribution for **2b**, as calculated by ^1H NMR and mass spectroscopy, is shown in Table 2. Comparison of the mean deuterium number per molecule (MDN), calculated from the two analytical methods, gives a clue about the limits of the determination. The relative concentrations of the various labelled species (Table 3), the formation of which is qualitatively evident from the ^{13}C NMR signals of the C5 and C6 carbon atoms, were calculated using both sets of data in Table 2. In fact, the overlapping of the ^1H NMR signals of the various isotopomers, even for H5, does not allow us to evaluate precisely these ratios based only on NMR.

However, despite the formation of different isotopomers of (*R*)-**2b**, only the positions H_{5Re}[21] and H_6 were found to contain the label, thus showing that the stereochemistry of the addition of the two hydrogen atoms is *syn*, in spite of the ionic nature of the catalyst and that a monohydridic species is probably involved in the catalytic cycle.



(*R*)-**2b**

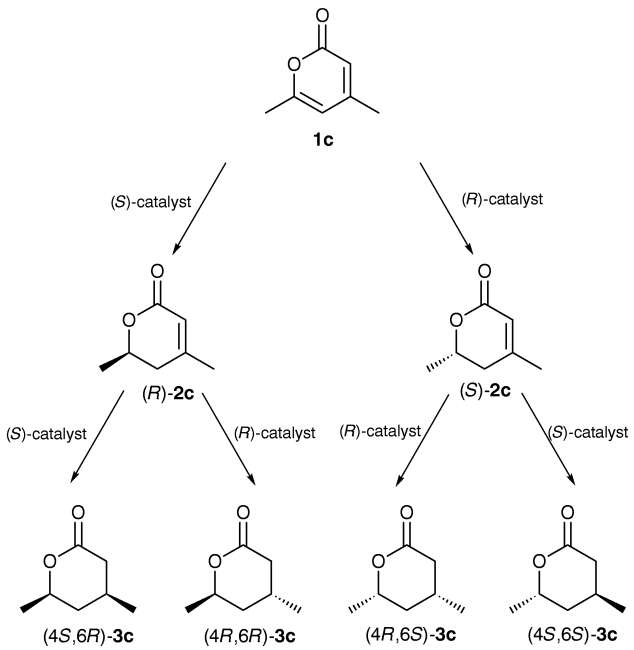


cis-(4*S*,6*R*)-**3c**

Similar results were obtained for the hydrogenation of unsaturated acids with the [$Ru(OAc)_2$(binap)] catalytic system.[7,8,10] From the data in Table 2 it is seen that position 6 in **2b** contains more deuterium than position 5 (0.58 *vs.* 0.38 and 0.46 *vs.* 0.25 for the two experiments, respectively). Moreover, in both experiments, as a consequence of the scrambling of the label, we find more deuterium [expressed as the fraction of deuterium atoms with respect to the total number of atoms, *i.e.*, D/(H + D)] in the solvent than in the gas phase (0.74 *vs.* 0.46 for run 1 and 0.67 *vs.* 0.23 for run 2). This distribution might be interpreted as a consequence of olefin insertion leading to an intermediate in which the carbon atom that is the most substituted [*i.e.*, C(6)] is bound to the ruthenium; this is followed by metal-mediated protonation[10] to bring about the larger deuterium content at C(6). Due to the mechanistic complexity of the catalytic system and to possible overlapping isotope effects in the various steps[22] this interpretation is probably premature, even if a highly regioselective (if not regiospecific) insertion of the ruthenium hydride into the double bond of (*Z*)-methyl α-acetamidocinnamate

Table 3 Relative concentrations (molar fractions) of the various labelled species (*R*)-**2b**

Run				
1	0.23	0.16	0.34	0.27
2	0.35	0.16	0.35	0.14



Scheme 2 Prevailing reaction pathway of the hydrogenation of **1c**. (*S*)- and (*R*)-catalyst stand for [Ru((*S*)-**5**)$(OAc)_2$]–HBF_4 and [Ru((*R*)-**5**)$(OAc)_2$]–HBF_4, respectively

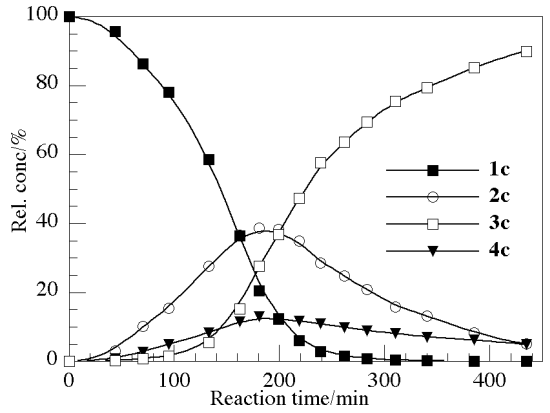


Fig. 1 Time-dependent concentrations of the various species during the hydrogenation of **1c** using [Ru((*R*)-**5**)$(OAc)_2$]–HBF_4 (5 bar H_2, 40 °C)

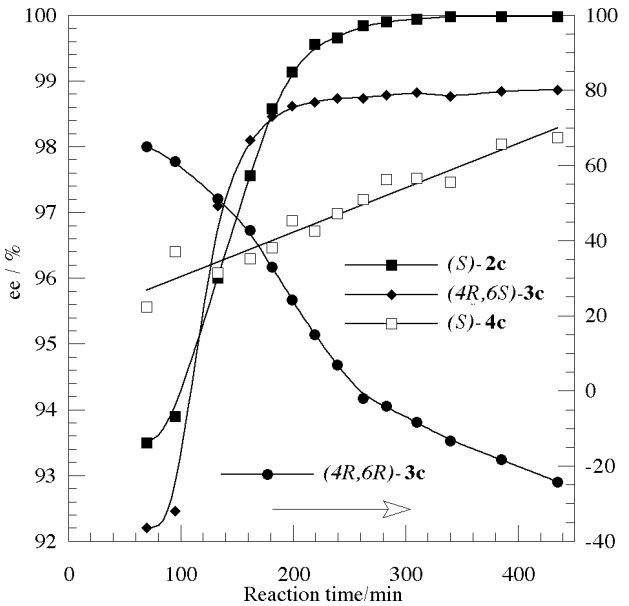


Fig. 2 Time-dependent enantioselectivity in the formation of the different species arising from the hydrogenation of **1c** with [Ru((*R*)-**5**)-$(OAc)_2$]–HBF_4 (*trans*-**3c** refers to the right ordinate)

was recently observed with the aforementioned binap system.[6,23]

Under the reaction conditions used for **1b**, the hydrogenation of 4,6-dimethyl-2*H*-pyran-2-one, **1c**, with [Ru((*S*)-**5**)$(OAc)_2$]–HBF_4 does not stop at the level of the (*R*)-5,6-dihydropyrone **2c** (Scheme 2). Only the fully hydrogenated δ-lactone **3c** was obtained in a diastereomeric excess of 84% in favour of the *cis*-(4*S*,6*R*) diastereomer. The diastereoselectivity is lower than that observed in the corresponding heter-

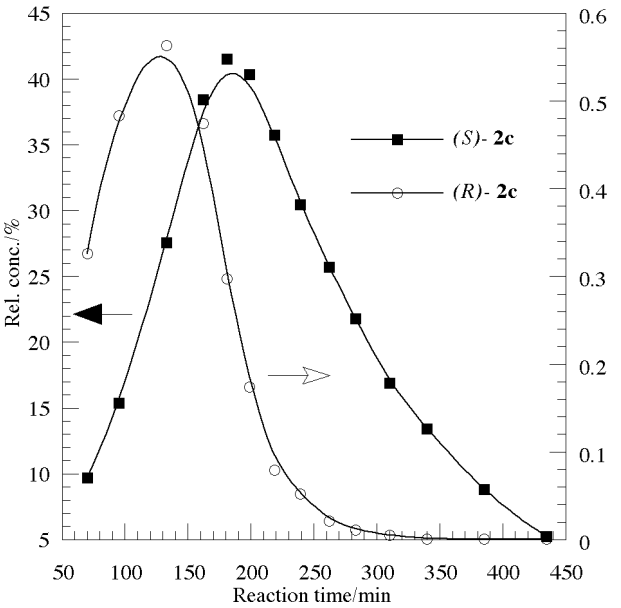


Fig. 3 Time-dependent relative concentrations of (*S*)- and (*R*)-**2c**

ogeneous hydrogenation with Pd/C, which gave quantitatively the *cis* diastereomer (see experimental). The enantioselectivity determined for the *cis*-lactone **3c** was close to 98% ee. As a consequence of the aforementioned scrambling of the label between the gas phase and the solvent, formation of molecules containing 0 to a maximum of 4 deuterium atoms takes place (Table 4). Nevertheless, NMR analysis (Table 4) shows that in positions 5 and 3 only one of the two diastereotopic atoms is labelled. This again indicates that both hydrogenation steps have a *syn* stereochemistry. As expected, a control experiment carried out using labelled solvent and deuterium gas showed complete deuterium incorporation at the previously mentioned carbon atoms and positions (compare Table 4).The reasons for the different amounts of deuterium incorporation in the hydrogenation of the two different double bonds are not clear.

The configuration of the asymmetric carbon atom in position 6 is the same in **3c** and in **2b**; moreover, the deuterium distribution at positions 5 and 6 is similar. This suggests that hydrogenation of **1c** could take place stepwise with the intermediate formation of **2c**. In order to prove this hypothesis, we carried out the asymmetric hydrogenation of **1c** using [Ru((*R*)-**5**)$(OAc)_2$]–HBF_4 as the catalyst under lower temperature and pressure (40 °C and 5 bar H_2). Indeed, we observed the formation of (*S*)-**2c** with an initial enantiomeric excess of about 93%. Moreover and rather unexpectedly, we have also identified the formation of the corresponding (*S*)-3,6-dihydro-4,6-dimethylpyrone **4c** with an initial ee of about 95% (Fig. 1 and 2). Hydrogenation of (*R*)-**2c** of 99.2% ee (isolated by chromatography from a reaction mixture of an

Table 4 Deuterium distribution for *cis*-(4*S*,6*R*)-**3c** formed from **1c** using [Ru((*S*)-**5**)$(OAc)_2$]–HBF_4

Run[a]	d_0	d_1	d_2	d_3	d_4	MDN[d]	
3[b]	0.08	0.24	0.30	0.26	0.12	2.10	
4[b]	0.17	0.34	0.31	0.14	0.04	1.54	
	H_{3Si}	H_{3Re}	H_4	H_{5Re}	H_{5Si}	H_6	MDN
3[c]	0	0.61	0.64	0	0.36	0.69	2.30
4[c]	0	0.40	0.53	0	0.31	0.57	1.81

[a] For reaction conditions see Table 1. Run 3: $Pr^iOH–D_2$; run 4: $Pr^iOD–H_2$. [b] Molar fraction of the differently labelled species from MS. [c] Deuterium content in the various positions from ^1H NMR, with the OCH_3 signal intensity taken as the reference. [d] MDN = mean deuterium number (average number of deuterium atoms per molecule).

experiment similar to that mentioned above at incomplete substrate conversion) using [Ru((*S*)-**5**)$(OAc)_2$]–HBF_4 led to the corresponding lactones **3c** also favouring the *cis*-diastereomer, but with lower selectivity (*cis* : *trans* = 80 : 20) when compared with the direct hydrogenation of **1c** (*cis* : *trans* = 92 : 8 to 90 : 10). Moreover, hydrogenation of (*S*)-**2c** (enantiomeric purity 99.6%), under the same conditions using the opposite catalyst enantiomer, [Ru((*S*)-**5**)$(OAc)_2$]–HBF_4, led to (4*S*,6*S*)-**3c** (*cis* : *trans* = 12 : 88). The prevailing pathways showing the dependence upon the absolute configuration of the catalyst precursor are summarized in Scheme 2.

The time behaviour of the concentration of the various reaction products reported in Fig. 1, after an initial period probably influenced by the formation of the active catalytic species, can be simulated (Micromath Scientist 2.0) by assuming first-order reactions. The relative overall rate constants show that the formation of **2c** from **1c** is 6 times faster then that of **4c** from **1c**. The first hydrogenation step (**1c** to **2c**) is also about 1.7 times faster then the following step (**2c** to **3c**). In Fig. 2 the enantiomeric excess of **2c**, *cis*- and *trans*-**3c** and **4c** during the reaction is shown. Kinetic resolution effects relative to the intermediates **2c** and **4c** can be recognized. The concentration of (*R*)-**2c** (minor enantiomer) decreases much faster (see Fig. 3) then that of the corresponding enantiomer, thus leading to an increase in the enantiomeric purity of **2c** (up to $\approx$100%, Fig. 2). The *trans*-lactone (4*R*,6*R*)-**3c** (Fig. 4) forms faster in the beginning than (4*S*,6*S*)-**3c**. With the progress of the reaction the amount of (4*S*,6*S*)-**3c** increases, thus causing a decrease in the enantiomeric purity of the *trans*-lactone (Fig. 2). The increasing enantiomeric purity of **2c** during the reaction also explains the increasing enantiomeric purity of the *cis*-lactone (4*R*,6*S*)-**3c** (Fig. 2). Fig. 5 shows the concentration changes of the intermediate **4c**. (*R*)-**4c** is hydrogenated faster then the (*S*)-enantiomer, again leading to an increase of the enantiomeric purity of **4c** during the reaction.

To summarize, the addition of hydrogen with the catalyst used is *syn* and takes place for all three substrates (**1a–c**) on the same enantioface of the C6=C5 double bond. As found for the 2-pyrone **1a**, the ruthenium-catalysed hydrogenation of **1b** to the dihydropyrone **2b** is highly regio- and enantioselective. Also, the hydrogenation of **1c** to **2c** is largely enantioselective; however, intermediate **2c** eventually leads to lactone **3c**. The diastereoselectivity of the second hydrogenation step (*i.e.*, the diastereoface selection) at the level of the intermediate **2c** is overwhelmingly determined by the chirality of the catalyst with a minor (if any) influence of the centre of asymmetry present in the substrate. This can be probably understood by looking at the conformation of **2c**, which was obtained by minimization of the free energy of a single molecule (using the molecular modelling program Cerius,[2] version 3.5). The conformation having the methyl group in an equatorial orientation has a 2.15 kcal mol^{-1} lower energy than the one with the methyl group in an axial position. It appears that (Fig. 6) the oxygen and the C(2) to C(4) atoms of the ring lie approximately in one plane.

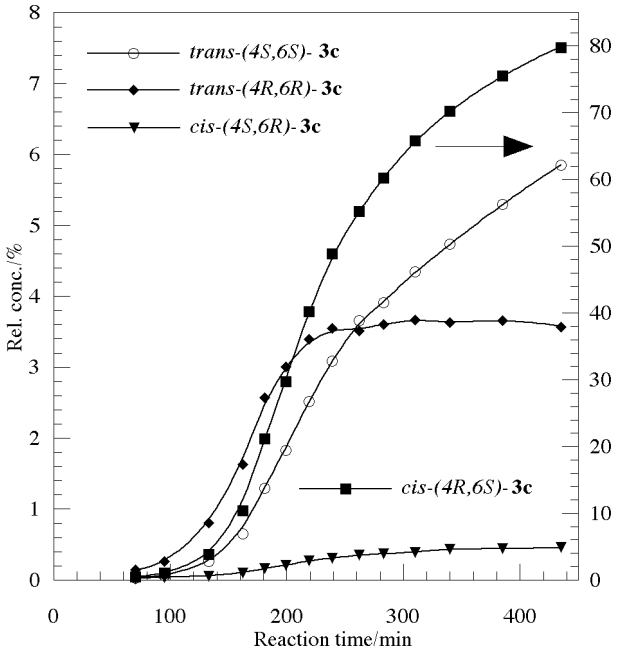


Fig. 4 Time-dependent relative concentrations of various species of **3c**

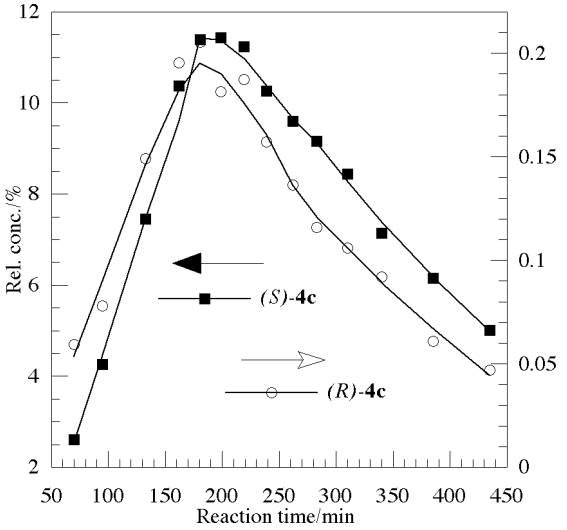


Fig. 5 Time-dependent relative concentrations of (*S*)- and (*R*)-**4c**

Thus, C(6) is forced into a position above the plane, hindering the hydrogenation of the remaining double bond from the Si enantioface [referred to C(4)], which leads to the *cis*-lactone. Hydrogenation from the Re enantioface to the *trans*-lactone is on the other side sterically hindered by the methyl-group. The labelling of the product at the C(3)—C(4) bond gives no information about the possible regioselectivity of insertion. Rather puzzling is the formal 1,4-hydrogenation of **1c** with formation of the 3,6-dihydropyrone **4c**, which also takes place with a large enantioselectivity. As a matter of fact, it could be the result of the existence of different catalytic species or of different reaction pathways at the level of the substrate–catalyst complex. Also, this intermediate eventually converts to the lactone **3c**.

The reason for the complete hydrogenation of compound **1c** may be due both to electronic as well as to steric effects. For compound **2b** the π-donor ability of the *O*-substituent in position C(4) may lead to a loss of the double bond character and, therefore, to a decrease of the stability of the intermediate substrate–catalyst complex, the formation of which would be necessary for further hydrogenation. It is noteworthy that dihydropyrone **2a** in chloroform is preferentially present in the

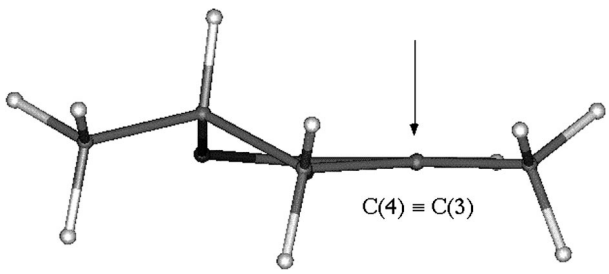


Fig. 6 Free energy minimized structure of the single molecule (*S*)-**2c** [viewed along the C(4)—C(3)-bond]

keto but not in the enol form, as shown in Scheme 1. Further hydrogenation of the keto group at position C(4) probably does not take place because of the steric hindrance of the alkyl group at position C(3). Electronic effects in this case are less probable due to the fact that hydrogenation of 4-hydroxy-2-pyrones (as 6-hexyl-4-hydroxy-2*H*-pyran-2-one or 4-hydroxy-6-methyl-2*H*-pyran-2-one) under the same conditions leads to the fully hydrogenated lactones, with almost no diastereoselectivity. A full account of the investigation of the scope of the asymmetric hydrogenation of 2-pyrones is in preparation.

Experimental

General

All hydrogenation reaction solutions were prepared and filled in the autoclave in a MBraun MB 150B-G-I glove box under nitrogen (<1.5 ppm oxygen). For homogeneous hydrogenation reactions, a 60 ml steel autoclave with a mechanical stirrer was used. Solution NMR spectra were measured using Bruker AM-300, AMX-400 or AMX-500 spectrometers with a TMS internal reference. IR spectra of solutions were measured using a Mattson Instruments 6020 Galaxy Series FT-IR. Optical rotations were measured with a Perkin Elmer Polarimeter 241. Analysis of the gas phase was conducted using a Leybold PGA 100 quadrupole mass spectrometer with a multiplier sensing head. Gas chromatographic analyses were conducted on a Hewlett Packard 5890 II GC equipped with a flame ionization detector on a Restek Rtx 200 capillary column (25 m). The enantiomeric excess was determined by gas chromatography using a Lipodex C (50 m) column or a column with heptakis (6-*O*-TBDMS-2,3-*O*-methyl)-β-cyclodextrin as the stationary phase. Helium was used as the carrier gas. EI-MS measurements were performed in the analytical laboratories of the ETH in Zurich. GC-MS analyses were conducted on a Hewlett Packard 5890 II GC equipped with a quadrupole mass spectrometer. For minimization and calculation of the free energy of **2c**, a consistent-valence forcefield[24] was applied using the program Cerius[2] (version 3.5). Simulation of the kinetics was conducted by using Micromath Scientist 2.0.

Starting materials. Fluoroboric acid solution (50% in water), palladium on activated charcoal and 2-propanol were purchased from Fluka. 2-Propanol was distilled under argon atmosphere prior to use. O-Deuterated 2-propanol (98% isotopic purity) was purchased from Dr. Glaser AG, Basel and deoxygenated by three freeze-thaw cycles. Hydrogen gas (purity 99.9999%) and deuterium gas (purity 99.8%) were used. 4,6-Dimethyl-2*H*-pyran-2-one[25] and 4-methoxy-6-methyl-2*H*-pyran-2-one[26] were prepared according to published methods and purified by crystallization under an argon atmosphere prior to use.

Hydrogenation of 4,6-dimethyl-2*H*-pyran-2-one (1c) with hydrogen in 2-propanol

In an N_2 atmosphere in the glove box 1.5 ml of a solution of fluoroboric acid in 2-propanol [351 mg HBF_4 (50% in water) in 50 ml 2-propanol] was added to a solution of 7.5 mg (0.006 mmol) of [Ru((*S*)-**5**)$(OAc)_2$] in 3.5 ml of 2-propanol. The solution was stirred for 1.5 h. 4,6-Dimethyl-2*H*-pyran-2-one (**1c**) (372.4 mg, 3 mmol) was weighed into the glass insert of the autoclave, the catalyst solution was added and the solution filled up to 10 ml with 2-propanol. The autoclave was closed and pressurized with 60 bar of H_2 and heated to 60 °C. After 20 h the autoclave was cooled to room temperature and the residual gas released. To determine the product distribution of the reaction a gas chromatographic analysis was carried out immediately. After removing the solvent from the reaction mixture, Kugelrohr distillation of the crude product gave 310 mg (81% yield) of a colourless liquid (92% purity), (4*S*,6*R*)-4,6-dimethyl-3,4,5,6-tetrahydro-2*H*-pyran-2-one, **3c**. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 1.13 [d, 3H, J = 6.3, 4-CH_3], 1.20 [ddd, 1H, J = 13.8, 11.2, 10.3, H_{Re}—C(5)], 1.37 [d, 3H, J = 6.3, 6-CH_3], 1.93 [dddd, 1H, J = 13.8, 3.2, 3.0, 1.9, H_{Si}—C(5)], 2.02 [dd, 1H, J = 16.6, 10.8, H_{Si}—C(3)], 2.07 [m, 1H, J = 11.2, 10.8, 6.3, 4.7, 3.0, H—C(4)], 2.67 [ddd, 1H, J = 16.6, 4.7, 1.9, H_{Re}—C(3)], 4.42 [m, 1H, J = 10.3, 6.3, 3.2, H—C(6)]. ^{13}C NMR (125.76 MHz, $CDCl_3$, 25 °C): 21.63 [q, 4-CH_3], 21.87 [q, 6-CH_3], 26.81 [d, C(4)], 37.81 [t, C(3)], 38.85 [t, C(5)], 77.00 [d, C(6)], 171.52 [s, C(2)]. EI-MS: 128 (3%, M^+), 113 (5), 84 (18), 69 (38), 56 (100), 42 (97). Anal. calcd for $C_7H_{12}O_2$ (128.17): C 65.60, H 9.44; found C 65.49, H 9.40. $[\alpha]_D^{25} = +6.6$ (c = 0.562, methanol). {Lit.:[25] $[\alpha]_D = +6.15$ [methanol)}.

Isolation and identification of 3,6-dihydro-4,6-dimethyl-2*H*-pyran-2-one (4c). In a similar experiment as described above carried out at 5 bar hydrogen pressure and 40 °C, at about 80% conversion (referring to **1c**) a small amount of **4c**[27] was isolated as a colourless liquid by column chromatography (hexane–ethyl acetate = 2:3). ^{1}H NMR [200 MHz, $CDCl_3$, 25 °C): 1.42 [d, 3H, J = 6.7, 6-CH_3], 1.78 [s, 3H, 4-CH_3], 2.95 [m, 2H, CH_2—C(3)], 5.02 [m, 1H, CH—C(6)], 5.53 [m, 1H, CH—C(5)]. ^{13}C NMR (50.32 MHz, $CDCl_3$, 25 °C): 21.41 [CH_3], 21.93 [CH_3], 34.40 [C(3)], 75.76 [C(6)], 121.81 [C(5)], 129.93 [C(4)], 169.72 [C(2)]. EI-MS: 126 (1%, M^+), 111 (4), 98 (9), 83 (16), 67 (14), 55 (18), 43 (100).

Isolation and identification of 5,6-dihydro-4,6-dimethyl-2*H*-pyran-2-one (2c). Similarly to the above procedure a small amount of **2c**[28] was isolated through column chromatography (hexane–ethyl acetate = 2 : 3). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): 1.43 [d, 3H, J = 6.3, 6-CH_3], 1.98 [s, 3H, 4-CH_3], 2.17–2.36 [2 × dd, 2H, CH_2—C(5)], 4.47–4.58 [m, 1H, CH—C(6)], 5.81 [s, 1H, CH—C(3)]. ^{13}C NMR (75.48 MHz, $CDCl_3$, 25 °C): 20.67 [CH_3], 22.92 [CH_3], 36.35 [C(5)], 73.62 [C(6)], 116.45 [C(3)], 156.93 [C(4)], 165.32 [C(2)]. EI-MS: 126 (4%, M^+), 111 (6), 82 (100), 67 (5), 54 (35), 39 (56). Anal. calcd for $C_7H_{10}O_2$ (126.15): C 66.65, H 7.99; found C 66.10, H 7.24. (*S*)-**2c**: $[\alpha]_D^{25} = +161.8$ (c 0.343, methanol).

Isolation and identification of *trans*-(4*S*,6*S*)-4,6-dimethyl-3,4,5,6-tetrahydro-2*H*-pyran-2-one (3c). The hydrogenation of (*S*)-**2c** using [Ru((*S*)-**5**)$(OAc)_2$]–HBF_4 as the catalyst precursor under the same conditions as described for the hydrogenation of **1c** gave as main product the *trans*-lactone (4*S*,6*S*)-4,6-dimethyl-3,4,5,6-tetrahydro-2*H*-pyran-2-one **3c** (85% purity). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): 1.09 [d, 3H, J = 6.6, 4-CH_3], 1.37 [d, 3H, J = 6.4, 6-CH_3], 1.57–1.81 [2 × m, 2H), 1.9–2.1 (m, 1H), 2.1–2.3 (m, 1H), 2.6 (m, 1H), 4.59 [m, 1H, CH—C(6)]. ^{13}C NMR (125.76 MHz, $CDCl_3$, 25 °C): 21.32 (q), 21.34 (q), 23.70 [d, C(4)], 36.61, 37.29, 73.58 [d, C(6)], 171.52 [s, C(2)]. $[\alpha]_D^{25} = -67.6$ (c = 0.074, methanol). {Lit.:[25] $[\alpha]_D = -62.7$ (methanol)}.

Hydrogenation of 4-methoxy-6-methyl-2*H*-pyran-2-one (1b) with hydrogen in 2-propanol.

The procedures were the same as described above for hydrogenation, starting with 420 mg (3 mmol) of the substrate **1b**, 7.5 mg of [Ru((*S*)-**5**)$(OAc)_2$] (0.006 mmol) and 1.5 ml of a solution of fluoroboric acid in 2-propanol [351 mg HBF_4 (50% in water) in 50 ml 2-propanol]. To determine the product distribution of the reaction, gas chromatographic analysis was carried out immediately after the reaction. The crude product was purified by column chromatography using a 1 : 1 mixture of hexane and ethyl acetate followed by sublimation[21] to give 280 mg (66%) of (*R*)-5,6-dihydro-4-methoxy-6-methyl-2*H*-

pyran-2-one (**2b**) as a colourless solid, mp 60–61 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 1.44 [d, J = 6.3, 6-CH_3], 2.31 [dd, J = 17.1, 4.1, H_{Re}—C(5)], 2.47 [ddd, J = 17.1, 11.5, 1.6, H_{Si}—C(5)], 3.75 [s, OCH_3], 4.53 [qdd, J = 11.5, 6.3, 4.1, H—C(6)], 5.14 [d, J = 1.6, H—C(3)]. ^{13}C NMR (125.76 MHz, $CDCl_3$, 25 °C): 20.54 [q, 6-CH_3], 34.58 [t, C(5)], 55.98 [q, OCH_3], 72.24 [d, C(6)], 90.23 [d, C(3)], 167.34 (s), 172.24 (s). Typical ^{13}C NMR signals of a mixture of partly deuterated **2b**: 34.58 [*C*(5)H—C(6)H], 34.46 [*C*(5)H—C(6)D], 34.27 [$^2J(^2H, ^{13}C) = 20.3$ Hz], 34.15 [$^2J(^2H, ^{13}C) = 20.1$], 72.29 [C(5)D-*C*(6)H], 72.25 [C(5)H-*C*(6)H], 71.91 [$^2J(^2H, ^{13}C) = 22.6$], 71.87 [$^2J(^2H, ^{13}C) = 22.6$]. Typical ^{1}H NMR signals of a mixture of partly deuterated **2b**: ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 2.306 [d, J = 17.1, H_{Re}—C(5)—C(6)D], 2.310 [dd, J = 17.1, 4.1, H_{Re}C(5)—C(6)H]. $[\alpha]_D^{25} = -122.7$ [methanol). {Lit.:[21] $[\alpha]_D = +256°$ [methanol) for the (*S*)-enantiomer}. Since **2b** shows 89% ee, the reason of the discrepancy of the optical activity is unclear.

Deuteration experiments

The same conditions were applied as in the above-mentioned hydrogenation using *O*-deuterated 2-propanol instead of normal 2-propanol or deuterium instead of hydrogen gas. After the autoclave had cooled down following the reaction a sample from the gas phase was taken to determine the amount of D_2, HD and H_2 present at the end of the reaction. For this purpose a gas reserve with about a 5 ml volume and equipped with a leak valve was connected *via* a pressure reducer to the autoclave. The system was evacuated and then filled with the gas from the autoclave. The gas reserve was connected to a quadrupole mass spectrometer and the relative contents of D_2, HD and H_2 were determined. To determine the percentage of *O*-deuterated 2-propanol after the reaction a 2 ml sample of the solvent was taken immediately after opening the autoclave. The sample was distilled in an argon atmosphere and analyzed using IR spectroscopy. The deuterium content could be determined by integrating the O—D stretch vibration at about 2488 cm^{-1}, taking the C—H stretch vibration at 2970 cm^{-1} as the internal reference. The integral areas were compared to that of 98% *O*-deuterated 2-propanol and 2-propanol. From the isolated and purified products, ^{1}H and ^{2}H NMR spectra as well as mass spectra were measured to determine the degree of deuteration of the products.

Heterogeneous hydrogenation of the substrates.

Small amounts of racemic 5,6-dihydro-6-methoxy-4-methyl-2*H*-pyran-2-one[29] (**2b**) and *cis*-4,6-dimethyl-3,4,5,6-tetrahydro-2*H*-pyran-2-one[30] (**3c**) were prepared from 4-methoxy-6-methyl-2*H*-pyran-2-one (**1b**) and 4,6-dimethyl-2*H*-pyran-2-one (**1c**) by hydrogenation on palladium on activated charcoal as the catalyst, according to published methods. Hydrogenation of 4,6-dimethyl-2*H*-pyran-2-one yielded preferentially the *cis* diastereomer (99%).

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