Regioselective Hydrogenation of α,β-Unsaturated Ketones over Wilkinson's Catalyst

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Abstract: The reactivity of a variety of α,β-unsaturated acyclic and cyclic ketones towards regioselective hydrogenation in the presence of Wilkinson's catalyst was determined. Hydrogenation of sterically hindered α,β-unsaturated ketones proceeded at inefficient rates, if at all.

Key words: enones, regioselectivity, hydrogenation, Wilkinson's catalyst, flavonoids

The availability of a wide range of optically active monomeric flavonoids is crucial for the metabolic studies of such compounds. As current synthetic strategies are tedious and renowned for both low yields and enantiomeric excesses, the development of new strategies towards the synthesis of these monomers is crucial. Since most α,β-unsaturated flavonoids, such as flavones, isoflavones and flavonols, are easily obtainable from readily available starting materials, the aim of this study was to investigate the feasibility of the regioselective and future stereoselective hydrogenation of the 2,3-double bond in model α,β-unsaturated compounds with Wilkinson's catalyst [$(Ph_3P)_3RhCl$ (**1**), Figure 1]. Although the application of Wilkinson's catalyst (**1**) in the hydrogenation of α,β-unsaturated systems is, to the best of our knowledge, unexplored, rhodium catalysts are renowned for their high selectivity towards the hydrogenation of olefinic double bonds in the presence of carbonyl groups.[1] Furthermore, Wilkinson's catalyst (**1**) is reported to catalyze the hydrogenation of internal alkenes, including stilbenes, in high yield.[2] In order to facilitate stereoselectivity during these hydrogenation reactions, numerous modifications to the basic metal system have also been documented.[1,3]

As two types of flavonoids, acyclic and cyclic, occur naturally, initial studies focused on acyclic model compounds **4a–f**, where after the focus shifted to the more relevant cyclic models **2a–c** and **6a**,**b**.

In an attempt to gather as much data as possible with the equipment at hand, two different reactor systems were used in the investigation. The first reactor system, mainly used for the volatile substrates **4a–f** and **6a**,**b**, allowed the monitoring of the reaction by hydrogen consumption as a function of time under isobaric conditions. Products were identified by GC-MS after completion of the reaction. In the second and larger reactor,[4] sampling of the reaction mixtures was possible, so reactions could be followed and products identified by ^1H NMR spectroscopy. This setup was used for the nonvolatile substrates. Due to the different diameters (30 mm vs 50 mm for reactor 1 and 2, respectively) and therefore capacities of the two reactors (30 mL vs 50 mL), as well as the cost of chemicals, reactions were performed under more dilute conditions in reactor 2 and experimental data obtained in one reactor could therefore not be linearly extrapolated to the other.

All hydrogenations were performed in the noncoordinating solvent, dichloromethane.[5] This solvent proved to be superior to acetone and tetrahydrofuran in the selective hydrogenation of chromone (**2a**, Scheme 1) with yields of 46.2%, 7.8% and 14.3%, respectively, being obtained for the different solvents after a reaction time of 24 hours.

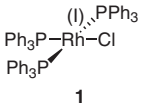

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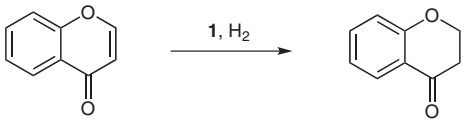
Figure 1



2a 3a

Scheme 1 Hydrogenation of chromone (**2a**) to chromanone (**3a**)

The effect of substitution around the double bond was subsequently investigated. According to the turnover frequency (TOF; product/catalyst molar ratio per hour), the addition of a substituent to the β-carbon dramatically decreased the reaction rate, which is also reflected in the turnover number (TON; product/catalyst molar ratio) and the yield (Table 1, entries 1 and 2). This result corresponds to the sluggish $(Cy_3P)_2Ru(CO)(Cl)H$ catalyzed hydrogenation of internal alkenes.[6] No hydrogenation was observed upon the addition of another substituent to either the α- or β-carbon (Table 1, entries 3 and 4). Aromatic substitution as in the case of *trans*-chalcone (**4e**) had an even larger negative effect on hydrogenation as is corroborated by TOF, TON and yield values considerably lower than those of pent-3-en-2-one (**4b**) (Table 1, entries 2 and

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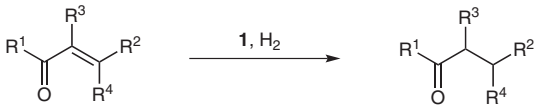
Table 1 Hydrogenation of Linear Substrates **4a–f**



4 **5**

Entry[a]	Substrate	R^1	R^2	R^3	R^4	Concn (M)	Temp (°C)	P (bar)	TON[b]	TOF[b] (h^{-1})	Yield[b] (%)
1	**4a**	Me	H	H	H	0.67	80	10	138	413	22
2	**4b**	Me	Me	H	H	0.57	80	10	29	88	4.8
3	**4c**	Me	Me	H	Me	0.49	80	10	–	–	–
4	**4d**	Me	Me	Me	H	0.50	80	10	–	–	–
5	**4e**	Ph	Ph	H	H	0.53	80	10	14	42	2.6
6	**4f**	H	Me	H	H	0.67	80	10	–	–	–
7	**4e**	Ph	Ph	H	H	0.53	80	10	141	443	19
8	**4e**	Ph	Ph	H	H	0.080	80	20	26	79	24
9	**4e**	Ph	Ph	H	H	0.16	80	20	96	286	43
10	**4e**	Ph	Ph	H	H	0.24	80	20	113	339	34
11	**4e**	Ph	Ph	H	H	0.32	80	20	153	460	35
12	**4e**	Ph	Ph	H	H	0.48	80	20	222	666	33
13[c]	**4e**	Ph	Ph	H	H	0.080	80	20	42	127	38

[a] Entries 1–6 were performed in reactor 1 and entries 7–13 in reactor 2.
[b] TON, TOF and yield were determined after 20 minutes.
[c] With additional triphenylphosphine.

5). The bulky and slightly electron-withdrawing phenyl substituents presumably influence alkene coordination to the rhodium complex both sterically and electronically in the rate-determining step.[7] Aldehydes like crotonaldehyde (**4f**) did not react under these conditions (Table 1, entry 6), most probably due to unfavorable electronic effects on the olefinic bond.

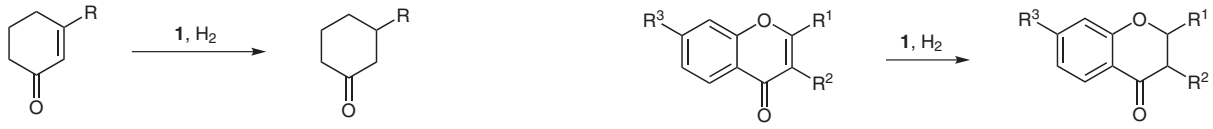
In switching from reactor 1 to 2, improved results were obtained for chalcone (**4e**) (Table 1, entries 5 and 7). This result is probably explicable in terms of improved mass transfer, including enhanced dissolution of hydrogen in the solvent due to the larger liquid surface area and/or better mixing in this reactor. For *trans*-chalcone (**4e**), both the TON and TOF increased with increasing chalcone concentration (Table 1, entries 8–12). Interestingly, the addition of triphenylphosphine to the reaction mixture increased the TON, TOF and yield (Table 1, entries 8 and 13), possibly due to additional stabilization of the catalyst, thus preventing fallout of rhodium black.

When the hydrogenation was extended to the simple cyclic substrate, cyclohex-2-enone (**6a**), TON, TOF and yield comparable to that of the β-substituted aliphatic enone, pent-3-en-2-one (**4b**), were obtained (Table 2, entry 1 and Table 1, entry 2), indicating similar accessibilities of the olefinic bond of these substrates to the catalyst.

Investigation of the effect of substitution in the cyclic substrate **6a** proved once again that the introduction of a substituent at the double bond has a significant effect on the TOF (44 h^{-1} vs 371 h^{-1} for **6b** and **6a**, respectively; Table 2, entries 8 and 2).

As an increase in hydrogen pressure from 10 bar to 20 bar proved to have a substantial effect on the TOF (Table 2, entries 1 and 2) and as no reaction could be obtained for flavone (**2b**) and 4′,7-dimethoxyisoflavone (**2c**) (*vide infra*), the effect of pressure and temperature on the reaction rate was subsequently fully investigated. The TOF of cyclohex-2-enone (**6a**) increased with an increase in pressure up to 30 bar, where after considerable fallout of rhodium black was encountered (Table 2, entries 1–4). The increased reaction rate at higher pressures might be explained by increased dissolution of hydrogen in the liquid phase, thus favoring the formation and stabilization of the active catalytic complex.[8] Subsequent investigation of the effect of temperature, by increasing the reaction temperature at 30 bar, revealed that the catalyst was rapidly deactivated at elevated temperatures as the reactions at 90 °C and 100 °C had stopped within 200 seconds and 150 seconds, respectively (Table 2, entries 5 and 6). The TONs after 100 seconds at 80 °C and 90 °C were comparable (Table 2, entries 3 and 5), whereas the reaction at 100 °C (Table 2, entry 6) initially proceeded more rapid-

Table 2 Hydrogenation of Cyclic Substrates **6a**,**b** and **2a–c**



Entry[a]	Substrate	R	R^1	R^2	R^3	Concn (M)	Temp (°C)	P (bar)	TON[b]	TOF[b] (h^{-1})	Yield[b] (%)
1	**6a**	H	–	–	–	0.58	80	10	26	78	4.9
2	**6a**	H	–	–	–	0.58	80	20	124	371	23
3	**6a**	H	–	–	–	0.58	80	30	139 (43)	418 (1543)	26
4	**6a**	H	–	–	–	0.58	80	40	43	130	8.1
5[c]	**6a**	H	–	–	–	0.58	90	30	(42)	(1498)	11
6[d]	**6a**	H	–	–	–	0.58	100	30	(63)	(2269)	14
7	**6a**	H	–	–	–	0.58	110	30	–	–	–
8	**6b**	Me	–	–	–	0.49	80	20	15	44	3.3
9	**2a**	–	H	H	H	0.080	80	20	1.6	4.9	1.5
10	**2b**	–	Ph	H	H	0.080	80	20	–	–	–
11	**2c**	–	H	PMP	OMe	0.080	80	20	–	–	–

[a] Entries 1–8 were performed in reactor 1 and entries 9–11 in reactor 2.
[b] TON, TOF and yield were determined after 20 minutes. The values in brackets were calculated after 100 seconds as the reactions in entries 5 and 6 had stopped within 200 seconds. Final yields are given for entries 5 and 6.
[c] Reaction had stopped after ca. 200 seconds.
[d] Reaction had stopped after ca. 150 seconds.

ly, but had stopped after 150 seconds with a yield of only 14% compared to 26% at 80 °C (Table 2, entry 3). As problems were also experienced with regard to repeatability at 30 bar, even at 80 °C, ensuing reactions were performed at 80 °C and 20 bar.

The hydrogenation of chromone (**2a**) proceeded sluggishly compared to that of *trans*-chalcone (**4e**) under similar conditions (Table 2, entry 9 and Table 1, entry 8). This is in stark contrast to the behavior of cyclohex-2-enone (**6a**) and pent-3-en-2-one (**4b**) (Table 2, entry 1 and Table 1, entry 2) and might be ascribed to the presence of the heterocyclic oxygen or the conformation of the heterocyclic ring. The lack of reactivity of flavone (**2b**) and 4′,7-dimethoxyisoflavone (**2c**) towards hydrogenation (Table 2, entries 10 and 11) corresponds with the above, as well as with the results encountered for **4a–d** (Table 1, entries 1–4) where steric hindrance by a substituent at either the α- or β-position had a negative effect on the reaction rate.

Thus, although it was established that Wilkinson's catalyst (**1**) in fact is able to regioselectively hydrogenate the olefinic bond of α,β-unsaturated ketones and though promising results were obtained for the reduction of *trans*-chalcone (**4e**), the regio- and stereoselective hydrogenation of flavonoid monomers with Wilkinson's catalyst does not seem to be a viable option for the synthesis of optically active monomeric flavonoids due to steric and electronic factors. Our results also indicate that higher electron density over the double bond seems to enhance binding of Wilkinson's catalyst to the olefin and therefore the selective hydrogenation of this functional group.

All chemicals were obtained from Sigma-Aldrich and used without further purification. Solvents were dried by standard methods and degassed three times with argon using standard Schlenk techniques. Catalyst solutions were degassed three times with argon and then flushed three times with H_2 prior to injection. The catalyst was presaturated with H_2 before the initiation of experiments. NMR spectroscopy was performed at 296 K in $CDCl_3$ on a Bruker AM-600 FT spectrometer. GC-MS analysis was performed on an HP 6890 GC instrument fitted with an HP 5973 mass selective detector (MSD), a National Institute of Standards and Technology (NIST) 98 library and a Supelco fused capillary column (30 m, 0.25 mm i.d., 0.25 μm film thickness). The temperature program was started at 50 °C (held for 4 min), ramped to 130 °C at 20 °C/min (held for 2 min) and ramped to 220 °C at 20 °C/min (held for 15 min) at a carrier gas flow rate of 1 mL/min.

Ketones 5 and 7; General Procedure for Liquid Substrates 4a–d,f and 6a,b in Reactor 1

For experiments in reactor 1 (Table 1, entries 1–6 and Table 2, entries 1–8), a soln of $(Ph_3P)_3RhCl$ (**1**; 9 mg, 0.01 mmol) in CH_2Cl_2 (9 mL) was charged to the reactor and the hydrogen ballast vessel was pressurized to a value of ca. 70 bar. The substrate, **4a–d**,**f** and **6a**,**b** (0.5 mL, 4.4–6.0 mmol depending on the substrate), was subsequently injected into the reactor and the regulator on the ballast ves-

sel set to maintain the pressure inside the reactor at the required constant level by feeding hydrogen from the ballast vessel into the reactor. Hydrogen gas consumption was recorded electronically as a function of time and the reaction products were identified by GC-MS upon completion of the reaction.

Procedure for Chalcone (4e) in Reactor 1

A soln of *trans*-chalcone (**4e**; 1.10 g, 5.3 mmol) in CH_2Cl_2 (1 mL) was injected into a soln of $(Ph_3P)_3RhCl$ (**1**; 9 mg, 0.01 mmol) in CH_2Cl_2 (9 mL) at 80 °C and 10 bar, and the mixture stirred at that temperature. As in the case of the liquid substrates, the progress of the reaction was monitored by hydrogen consumption, whereas the product was identified by GC-MS.

Ketones 3 and 5e; General Procedure for Solid Substrates 2a–c and 4e in Reactor 2

A soln of $(Ph_3P)_3RhCl$ (**1**; 20 mg, 0.022 mmol) in CH_2Cl_2 (5 mL) was injected into the substrate soln in CH_2Cl_2 (25 mL) at the temperature and pressure indicated in Tables 1 and 2, and the mixture stirred at that temperature. Samples of the reaction mixture were obtained at regular intervals and analyzed by ^{1}H NMR spectroscopy.

Chroman-4-one (3a)

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.88 (dd, *J* = 1.82, 7.87 Hz, 1 H, H-5), 7.45 (ddd, *J* = 1.82, 7.27, 8.28 Hz, 1 H, H-7), 6.99 (ddd, *J* = 0.81, 7.27, 7.87 Hz, 1 H, H-6), 6.95 (dd, *J* = 0.81, 8.28 Hz, 1 H, H-8), 4.52 (t, *J* = 6.46 Hz, 2 H, H-2), 2.79 (t, *J* = 6.46 Hz, 2 H, H-3).[9]

^{13}C NMR (150.9 MHz, $CDCl_3$): δ = 37.88, 67.10, 117.97, 121.45, 127.22, 136.04, 161.96, 191.85.

Dihydrochalcone (5e)

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.97–7.96 (m, 2 H, H-2′ and H-6′), 7.57–7.55 (m, 1 H, ArH), 7.47–7.44 (m, 2 H, ArH), 7.32–7.29 (m, 2 H, ArH), 7.27–7.26 (m, 2 H, ArH), 7.22–7.20 (m, 1 H, ArH), 3.31 (t, *J* = 7.74 Hz, 2 H, H-β), 3.08 (t, *J* = 7.74 Hz, 2 H, H-α).[10]

Procedure for Chalcone (4e) in Reactor 2 in the Presence of Triphenylphosphine

A soln of $(Ph_3P)_3RhCl$ (**1**; 20 mg, 0.022 mmol) and Ph_3P (3 mg, 0.01 mmol) in CH_2Cl_2 (5 mL) was injected into a soln of *trans*-chalcone (**4e**; 0.50 g, 2.4 mmol) in CH_2Cl_2 (25 mL) and the reaction was executed and followed as described previously.

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