Hydrogenation of α-Keto Ethers: Dynamic Kinetic Resolution with a Heterogeneous Modified Catalyst and a Heterogeneous Base

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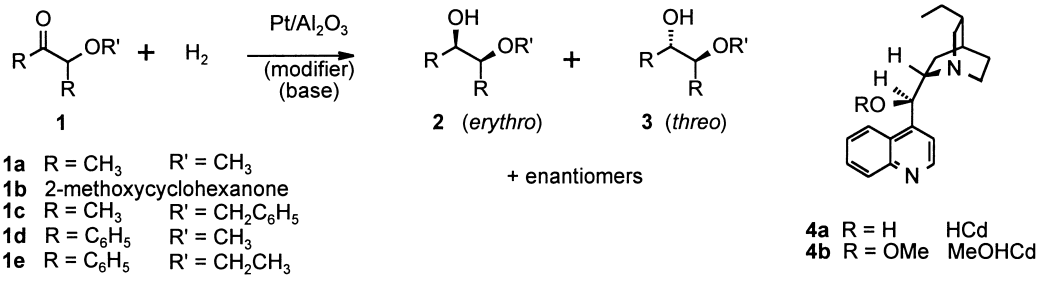
Abstract: The first successful example of the asymmetric hydrogenation of substituted α-keto ethers with *Cinchona*-modified Pt/Al_2O_3 is reported. In the absence of an additional base, kinetic resolution of the racemic starting material was observed with high diastereoselectivity and ee's up to 98% at conversions of <50%. Addition of KOH gave a strong reaction acceleration but racemic product. Immobilization of OH^- on solid ion exchangers resulted in the desired dynamic kinetic resolution, and ee's of >80% were obtained at >95% conversion. These effects are rationalized on the basis of a simple kinetic and structural model.

Keywords: asymmetric hydrogenation; dynamic kinetic resolution; heterogeneous modified catalyst; α-keto ethers; ligand accelerated catalysis

Dynamic kinetic resolution is a powerful tool to obtain products with high enantioselectivity from racemic starting materials.[1] If the asymmetric reaction creates a second stereogenic center, the diastereoselectivity of the product can also be controlled. A synthetically interesting reaction of this type is the hydrogenation of α-keto ethers giving very high de and ee using homogeneous Ru catalysts in the presence of KOH.[2] Despite the good selectivity, this methodology suffers from a drawback because both the homogeneous catalyst and the base are not easily separated from the product after the reaction. An elegant solution for this problem would be the use of a heterogeneous catalytic system.

Cinchona-modified heterogeneous Pt catalysts are technically useful for the hydrogenation of a number of ketones. Despite considerable search efforts for suitable substrates, up to now only strongly activated ketones such as α-keto acid derivatives[3] and cyclic analogues thereof,[3b] certain trifluoromethyl ketones,[3c] α-keto acetals,[4] and α-diketones[5] can be hydrogenated with satisfactory selectivities. Intrigued by the results of the homogeneous catalysts, we investigated Pt-*Cinchona* catalysts for the enantioselective hydrogenation of α-keto ethers (Scheme 1). Here, we report the successful combination of a chiral heterogeneous Pt catalyst and an insoluble, strongly basic ion exchanger for the enantio- and diastereoselective hydrogenation of racemic α-alkoxy ketones with good yields and moderate to good stereoselectivities.

For a preliminary investigation, we chose a proven Pt/Al_2O_3 catalyst modified with HCd derivatives under reaction conditions optimized for α-keto esters. Table 1 shows the results using racemic substrates **1a–1e** at conversions between 7 and 53%. As expected, kinetic resolution took place. AcOH or toluene gave the highest ee's, and the diastereoselectivities were always very high, with *erythro*-(*R,S*)-**2**[6] as the major product. With the exception of **1c**, ee's of 90–98% were obtained. Compared to the unmodified systems, ligand-accelerated catalysis was observed in all substrates carrying an aliphatic R group (**1a**, **1b**, and **1c**, for details see below).



Scheme 1. Structures and naming of the starting materials, products and *Cinchona* modifiers.

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Table 1. Hydrogenation of various α-keto ethers.[a]

Substrate	Solvent	Modifier	Time [min]	Conversion [%]	**2** [%]	ee **2** [%]	**3** [%]	Initial Rate (mmol H_2/min × g)
1a	AcOH	**4b**	12	22	20	98	<1	2.1
1b	toluene	–	145	33	25	–	7	0.5
1b	toluene	**4a**	24	44	42	92	<1	2.4
1b	*i*-PrOH	**4a**	6	38	38	79	<1	n.a.
1b	AcOH	**4b**	16	54	52	88	2	13.7
1c	toluene	**4a**	54	7	5	75	2	0.2
1d	toluene	–	23	34	29	–	5	1.5
1d	toluene	**4a**	63	42	42	91	<1	0.7
1e	toluene	**4a**	13	10	10	90	<1	1.0

[a] Reaction conditions: 1–2 g **1**, 20–25 mL solvent, 50–100 mg 5% Pt/Al_2O_3, 5–10 mg modifier, 25 °C, 60 bar.

With all substrates, the addition of the chiral modifier led to significantly higher diastereoselectivity. These finding are in contrast to results obtained with methoxyacetone where only 12% ee and a very low activity was observed.[7]

The effect of the modifier on the course of the reaction was investigated in detail for the cyclic **1b**. As a comparison of Figures 1a and 1b shows, the modifier causes an acceleration of the overall reaction by a factor of *ca.* 5 up to a conversion of 50% and then a significantly slower reaction – a clear sign for a kinetic resolution. The *cis/trans* ratio **2b**/**3b** increased from 4 to >30 in the presence of the modifier (**3b** not shown in Figure 1b). Similar effects were observed for all aliphatic ketones whereas a slight deceleration of the overall reaction was noticed for the aromatic ketones in the presence of the modifier (see Table 1). The course of the reactions (lines in Figures 1–3) was modeled by applying a simple

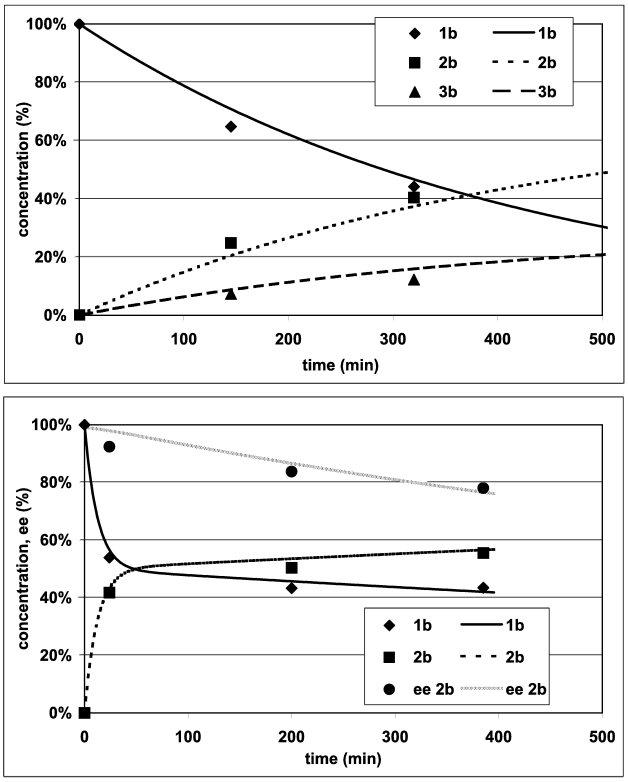


Figure 1. Hydrogenation of **1b** in toluene. Reaction conditions see Table 1. **a**) upper panel, no modifier, **b**) lower panel, HCd.

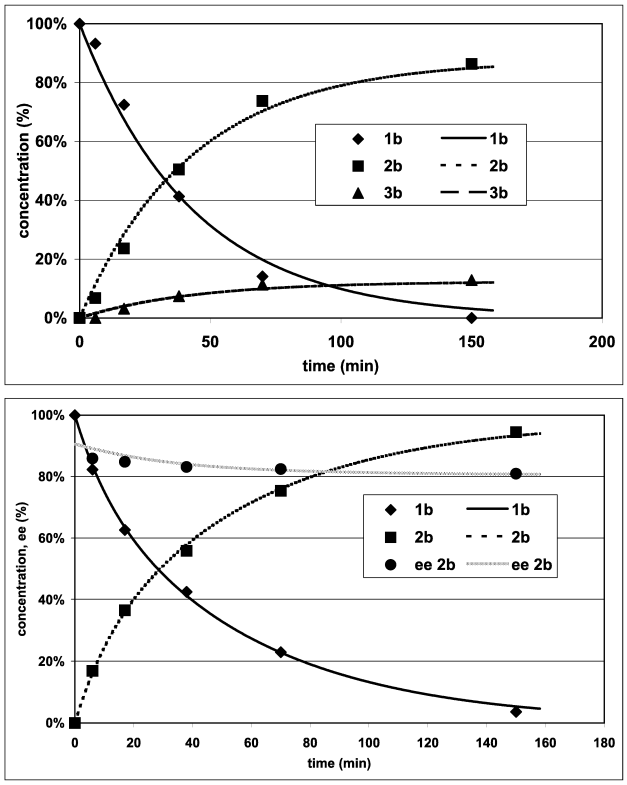


Figure 2. Hydrogenation of **1b** in the presence of ion exchanger. **a**) upper panel, no modifier, 1.0 g **1b**, 100 mg 5% Pt/Al_2O_3, 25 mL toluene, 1.6 g Amberlite IRA-900 OH^- activated, 60 bar, 25 °C. **b**) lower panel, with 10 mg HCd. Reaction conditions as in **a**).

kinetic model as shown in Scheme 2 and discussed below.

While the very high initial ee's were impressive, it was also clear that this method with yields of $<50\%$ and gradually decreasing ee's is of little preparative value. The obvious solution would be dynamic kinetic resolution as reported for the homogeneous system.[2] In fact, with >5 mM KOH in *i*-PrOH a very high rate was obtained for **1b** (100% conversion in 6 min!) but the ee was 0%. Obviously, something dramatic had happened to the modified catalyst. One possible explanation is that the adsorbed chiral modifier is displaced by OH^-, another one that the strong base interfered with the interaction of the modifier with the adsorbed ketone which is thought to occur via an H-bridge (see below).

We speculated that a solid base could still racemize the keto ether but would not disturb the chirally modified surface on the Pt due to physical separation by the support. To test this idea, we screened a number of strongly basic anion exchangers and solid bases. With OH^- activated Amberlite IRA-402 (gel type) and Amberlite IRA-900 (macroreticular), dynamic kinetic resolution was indeed observed in *i*-PrOH, the optimal solvent for the homogeneous system.[2] (*R,S*)-**2b** was obtained with ee's of up to 56% at $>95\%$ conversion. MgO on silica, sepiolite, or hydrotalcite had no effect, either because these materials were not basic enough or because the concentration of basic sites was too low. In toluene, even higher ee's of $>80\%$ at $>95\%$ conversion with less than 1% of **3b** were obtained but, in this solvent, only macroreticular ion exchangers showed the desired effect. Similar experiments were conducted with **1d** and an ee of 90% was achieved at 88% conversion.

Typical concentration profiles observed for **1b** and **1d** in the presence of OH^- activated Amberlite IRA-900 are depicted in Figures 2 and 3. The kinetic data were analyzed for **1b** and **1d** using the reaction scheme shown in Scheme 2 (for the non-dynamic case $k_{rac}=0$ was assumed). It is clear that for a rigorous analysis, a Langmuir-Hinshelwood approach would be necessary as, e.g., carried out for the hydrogenation of ethyl pyruvate with the same catalytic system.[8] However, for a simplified analysis, we decided to lump all kinetic and adsorption terms into pseudo-first-order rate constants k_{XY}, as already done for α-diketones.[5] As an additional

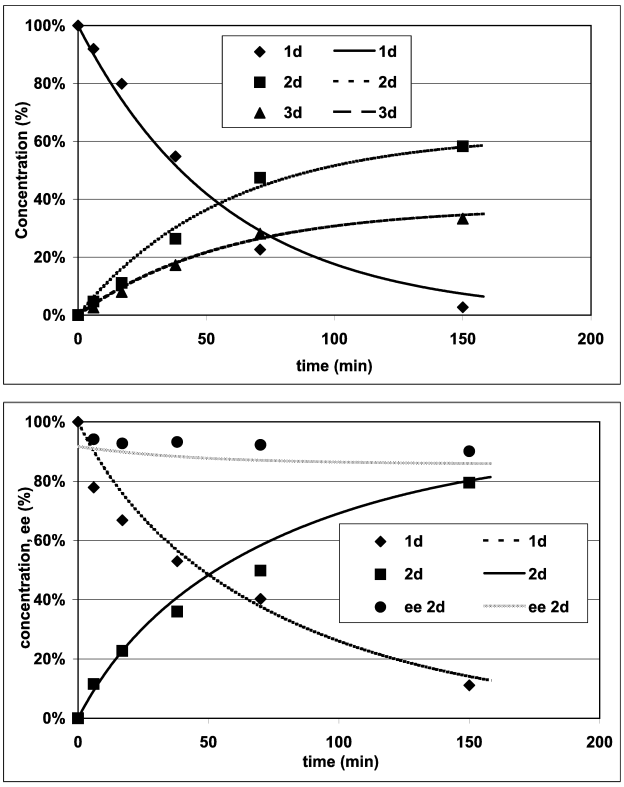
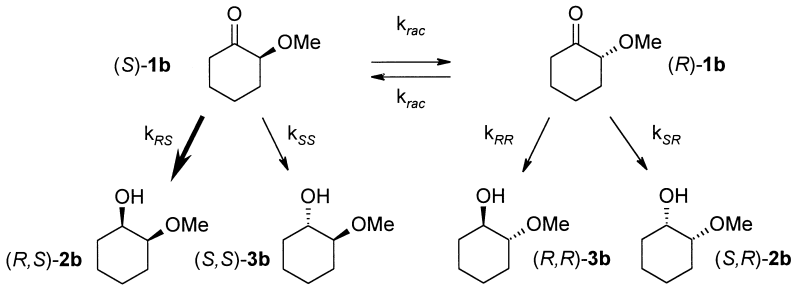


Figure 3. Hydrogenation of **1d** in the presence of ion exchanger. **a**) upper panel, no modifier. 2.0 g **1d**, 200 mg 5% Pt/Al_2O_3, 25 mL toluene, 1.6 g Amberlite IRA-900 OH^- activated, 60 bar, 25 °C. **b**) lower panel with 20 mg HCd. Reaction conditions as in **a**).

simplification, the very small k_{SS} and k_{RR} were assumed to be equal ($k_{RR}/_{SS}$). This model[6] has only three (no ion-exchanger) or four adjustable parameters (with ion-exchanger). The values for the various constants for **1b** and **1d** are summarized in Table 2. The surprisingly good fit (data for **1b** shown in Figures 1–3) makes us confident that our major conclusions are real and not artifacts of the simplifications.

Table 2 shows the effect of the modifier and/or the ion exchanger on the various rate constants and hence on the selectivity for the hydrogenation of **1b** and **1d**. With both substrates, addition of the modifier (with and without OH^-) led to a moderate to very strong increase



Scheme 2. Possible reaction pathways for the hydrogenation of **1b.**

Table 2. Pseudo first order rate constants[a] for **1b** and **1d**.

Substrate	Modifier	Base[b]	k_{RS}	k_{SR}	$k_{RR/SS}$	Σk	k_{rac}
1b	No	No	2.0	2.0	0.9	5.8	–
1b	Yes	No	94	0.5	0.1	95	–
1b	No	Yes	6.1	6.1	0.9	13	–[c]
1b	Yes	Yes	18	0.9	0.1	19	6.8
1d	No	No	9.4	9.4	1.7	23	–
1d	Yes	No	13	0.6	0.2	14	–
1d	No	Yes	6.5	6.5	3.9	21	–[c]
1d	Yes	Yes	20	0.9	0.5	22	11

[a] h^{-1}/g catalyst, see also Experimental Section.
[b] OH^- bound on Amberlite IRA-900.
[c] Cannot be obtained from our experimental data.

of k_{RS} and a notable decrease of all other rates. Whereas the overall reaction was significantly faster for aliphatic keto ethers (ligand accelerated catalysis[3a]), the aromatic ketones **1d** and **1e** showed a lower rate in presence of HCd. Because the k_{rac} values are smaller than k_{RS}, the ee decreases slowly during the reaction (see Figures 2b and 3b).

While there is still considerable debate on the detailed mode of action of *Cinchona*-modified catalysts, there is little doubt that the enantioselective reaction occurs on an active site formed by a number of surface Pt atoms and one adsorbed modifier.[3] Obviously, free OH^- ions can either displace the chiral modifier or deprotonate the complex shown in Scheme 3, giving strongly activated sites with no induction. Some mobile OH^- ions might also be responsible for the slightly lower initial ee's observed for the OH^- loaded ion exchanger.

The observed stereoselectivities can be rationalized by applying a variant of the model proposed by Pfaltz and Baiker[3] (Scheme 3). The most important feature is a hydrogen bond between the quinuclidine of the *Cinchona* molecule and one or two O atoms of the concomitantly adsorbed ketone. For the hydrogenation of α-keto esters only one N-H-O-C hydrogen bond was proposed. However, a second interaction would explain the positive effect of an α-oxygen in a *cis* position to the C = O group. It also rationalizes the preferred formation of the (*R,S*)-**2** isomers due to the steric effect of the methyl group in the adsorbed state. This means that the electronegative α-substituent not only activates the keto group but interacts with the modifier *via* a hydrogen bridge as well. Our model has obvious limits because it certainly does not explain why methoxyacetone gives such a low ee.

In conclusion, we have shown that substituted aliphatic and aromatic α-keto ethers are suitable substrates for the enantioselective hydrogenation catalyzed by *Cinchona*-modified Pt catalysts and that both kinetic resolution and dynamic kinetic resolution is possible. At conversions of < 50%, ee's of up to 98% were obtained when starting with a racemic substrate (kinetic resolution). With the addition of KOH, a strong acceleration of the reaction but 0% ee were observed, most likely because the chirally modified surface was disturbed/displaced. In order to get dynamic kinetic resolution the OH^- ions had to be immobilized on a solid ion exchanger, and ee's of > 80% were obtained at > 95% conversion.

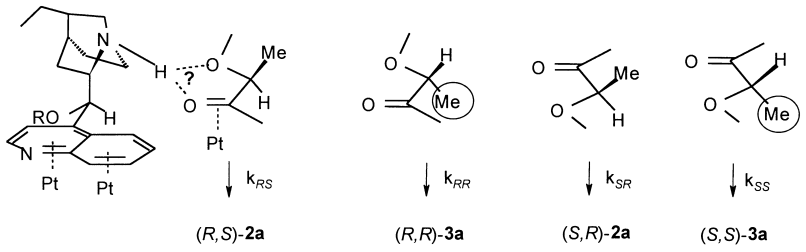
Experimental Section

Materials

All materials used were commercially available or synthesized according to literature methods. NMR analysis was done in $CDCl_3$ on a Bruker 300 MHz instrument equipped with an autosampler. The ee's of the products were determined on a chiral GLC column (hydrogen carrier gas, Beta-dex 110 column supplied from Supelco) or on HPLC (see below).

Typical Hydrogenation Experiment of 1d

10 mg dihydrocinchonidine (HCd, **4a)** were placed in a 50-mL pressure autoclave equipped with a magnetic stirring bar and baffles. 100 mg catalysts (JMC 94, Batch 14017/01, Supplier: Johnson Matthey, pretreated 2 h at 400 °C under a flow of hydrogen) were suspended in 2 mL toluene and transferred to the autoclave. 1 g **1d** was dissolved in 18 mL toluene and also transferred to the autoclave. After sealing, the autoclave was purged three times with argon and three times with hydrogen and then pressurized with hydrogen to 60 bar. The reaction was started by turning the magnetic stirrer on, and the temperature was kept constant at 25 °C with the help of a cryostat. The pressure in the autoclave was kept constant at 60 bar during the reaction by the use of a pressure transducer. The hydrogen consumption was measured by the pressure drop in a reservoir



Scheme 3. Artists view of the adsorbed reaction intermediates.

with a known volume. After 63 minutes, a sample of approximately 0.5 mL was withdrawn from the solution. After 128 min, the reaction was stopped, the pressure was released, and the autoclave was purged with argon for three times. The catalyst was filtered off and the reaction mixture was evaporated to dryness; yield: 0.85 g (85%). HPLC analysis was carried out on an HP 1100 with a Chiracel® OD (Daicel) column of 0.46×25 cm and hexane/isopropanol (98:2) as eluent and detection at 210 nm. Retention time: (*S*)-**1d** 12.2 min, (*R*)-**1d** 20.3 min, and for the *erythro* product 24.3 min for (*S,R*)-**2d** and 30.6 min for (*R,S*)-**2d** were measured. For the *threo* diastereomers (*S,S*)-**3d** and (*R,R*)-**3d**, 15.8 and 18.7 min were measured, but no assignment of the absolute configuration was possible for the *threo* diastereomers (below 2% for all systems containing modifier).

Dynamic Kinetic Resolution

1.6 g Amberlite IRA-900 (strongly basic anion exchanger, converted to the OH^- form by washing with 0.1 M NaOH until chloride free) were added after the substrate. The rest of the experiment was carried out as described above.

Determination of the Absolute Configuration of 2d and Related *erythro* Isomers

For analysis, an isolated mixture was chromatographed on silica gel (Merck 60 F 254) with ethyl acetate/hexane (15/85) as eluent. By comparison to the NMR spectra of the starting material, the earlier eluting material was identified as starting material. The later eluting fraction was identified as **2d** [*erythro* mixture of (*R,S*)- and (*S,R*)-enantiomers, 81% ee according to HPLC) by comparison to the ^{1}H NMR reported in the literature.[9] For the determination of the absolute configuration of the major product in **2d**, $[\alpha]_D$ of the purified sample was measured to be $= +18.85^\circ$ (DIP 181 polarimeter, 5 cm cuvette, *c* 4.2, in $CHCl_3$). The positive sign of the optical rotation confirmed the expected preferential formation of (*R,S*)-**2d** and the ee calculated by comparison with the literature value[9] was 81%, the same as determined by HPLC. For the hydrogenation of **1a – 1c** and **1e**, the main product was identified to be the *erythro* product by comparison of the ^{1}H NMR with known spectra. In analogy to **1d**, the absolute configuration of the main product was assumed to be always (*R,S*). This is also in accord with the fact that in the hydrogenation of all known activated ketones, cinchonidine derivatives such as **4a** an **4b** induce the (*R*)-alcohols.

Kinetic Model Used

For the determination of the rate constants we assumed that the reactions of **1** were first order in substrate and in catalyst, leading at constant hydrogen pressure to the following equations:

$$
\begin{aligned}
d[(R,S)\text{-}\mathbf{2}]/dt &= [cat](k_{RS}[(S)\text{-}\mathbf{1}]) \\
d[(S,S)\text{-}\mathbf{2}]/dt &= [cat](k_{SS}[(S)\text{-}\mathbf{1}]) \\
d[(S,R)\text{-}\mathbf{2}]/dt &= [cat](k_{SR}[(R)\text{-}\mathbf{1}]) \\
d[(R,R)\text{-}\mathbf{2}]/dt &= [cat](k_{RR}[(R)\text{-}\mathbf{1}]) \\
-d[(R)\text{-}\mathbf{1}]/dt &= [cat][(R)\text{-}\mathbf{1}](k_{SR} + k_{RR}) \\
-d[(S)\text{-}\mathbf{1}]/dt &= [cat][(S)\text{-}\mathbf{1}](k_{RS} + k_{SS})
\end{aligned}
$$

In case of dynamic resolution (ion exchanger present), the equations for (R)-**1** and (S)-**1** were modified to

$$
\begin{aligned}
-d[(R)\text{-}\mathbf{1}]/dt &= [cat]([(R)\text{-}\mathbf{1}](k_{SR} + k_{RR} + k_{rac}) - [(S)\text{-}\mathbf{1}]\, k_{rac}) \\
-d[(S)\text{-}\mathbf{1}]/dt &= [cat]([(S)\text{-}\mathbf{1}](k_{SS} + k_{RS} + k_{rac}) - [(R)\text{-}\mathbf{1}]\, k_{rac})
\end{aligned}
$$

The time-dependent concentration of all species was calculated by numerically integrating these equations. The values of the rate constants were determined by a least square fit of the calculated and measured values (Microsoft EXCEL).

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