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Asymmetric Catalysis on Cinchonidine-Modified Pt/Al_2O_3: Kinetics and Isotope Effect in the Hydrogenation of Trifluoroacetophenone

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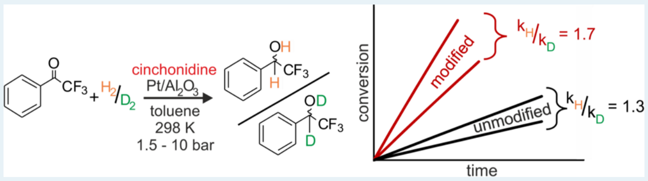
S *Supporting Information*



ABSTRACT: Kinetics and parametric sensitivity of the asymmetric hydrogenation and deuteration of the trifluoro-activated ketone, 2,2,2-trifluoroacetophenone (TFAP), to (*R*)-1-phenyl-2,2,2-trifluoroethanol have been studied on an alumina supported Pt catalyst modified by cinchonidine (CD). The observed catalytic behavior is explained by a reaction network consisting of three catalytic cycles which are mutually interconnected: asymmetric hydrogenation of TFAP on CD-modified sites (Pt-CD), asymmetric hydrogenation on Pt-CD sites interfering with the acidic product alcohol Pt-CD-P, and the racemic hydrogenation occurring on unmodified Pt sites. The contributions of these reaction cycles change with progress of TFAP conversion. The catalytic performance is shown to depend strongly on various factors such as the concentrations of ketone and modifier, catalyst amount, solvent, and hydrogen pressure. Depending on reaction conditions, addition of CD can induce considerable rate enhancement ($r_{\text{modified}} > r_{\text{unmodifed}}$). Particularly striking is the influence of hydrogen pressure (coverage) on enantioselection, as higher coverage diminishes the ee, which contrasts the corresponding behavior of α-ketoesters. The special role of hydrogen is investigated by substituting H_2 by its heavier isotope D_2. With the aid of time-resolved attenuated total reflection infrared spectroscopy the kinetic effects of the isotopic substitution along with other reaction parameters are studied and a kinetic isotope effect for unmodified and modified reactions is determined, which suggests that hydrogen is involved in the rate-determining step.

KEYWORDS: *asymmetric hydrogenation, chiral surface modification, cinchonidine, platinum, trifluoroacetophenone, kinetic isotope effect, rate enhancement*

■ INTRODUCTION

Heterogeneous asymmetric catalysis possesses several features which render it a promising future strategy for an efficient and sustainable production of pure enantiomers.[1] Among the various strategies for designing heterogeneous enantioselective noble-metal catalysts,[2] Pt modified by cinchona alkaloids offers strong stereoselective control combined with high activity in the hydrogenation of activated ketones. Enantioselectivity is simply achieved by addition of trace amounts of a chiral compound, the so-called chiral modifier, to the reaction mixture and its strong adsorption at the Pt surface creates the asymmetric catalytic sites.[3] It is the simplicity of the concept as well as the promising benefits with regard to separation, catalyst regeneration, and facile transfer to continuous mode operation[4] which make such a solid−liquid−gas system attractive for industrial exploitation. To date, the best modifier-substrate combinations achieve enantioselectivities similar to established industrial processes.[5]

However, the underlying reaction mechanism is still not fully understood, and the performance of the catalytic system is highly sensitive to the molecular structures of the chiral modifier and substrate.[2a] Without further improvement of the current mechanistic understanding of chirally modified metal catalysts, rational design of heterogeneous asymmetric hydrogenations will continue to be a very cumbersome empirical task.[6] Elucidating the enantiodifferentiating action at the catalytic solid−liquid interface has to take into account complex interactions between coadsorbed modifier and prochiral ketone which depend on various factors such as the heterogeneity of the Pt surface, the organic solvent, and hydrogen partial pressure (surface coverage). Regarding the current mechanistic understanding, a 1:1 type diastereomeric surface complex of prochiral ketone and modifier is thought of being responsible for imparting stereocontrol on the Pt surface.[2a] Recent in situ surface studies indicate an N−H−O type hydrogen bond interaction formed between the keto-group of TFAP and the tertiary amine functionality of coadsorbed cinchonidine (CD)[7] which can be protonated even in aprotic solvent by chemisorbed hydrogen/deuterium.[8] In contrast to the thoroughly investigated α-ketoesters, α-trifluoro ketones take a special role in the pool of structurally different ketones suitable for asymmetric hydrogenation catalyzed by the Pt-cinchona system. While also high substrate specificity is experienced with regard to the second substituent of the prochiral ketone,

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structural requirements in the chiral modifier deviate. Besides an anchoring moiety and specific stereogenic centers, not only the quinuclidine N atom of CD but also the C9-OH alcohol function is required, as methyl ether derivatives of CD lead to a loss in enantioselection.[9] Furthermore, the role of hydrogen in the enantiodifferentiation shows an unusual behavior. In contrast to general observations with most of the other suitable substrate classes, trifluoro-activated ketones are most enantioselectively hydrogenated at low hydrogen pressure.[10] While the right combination of substrate concentration, chiral modifier concentration, catalyst amount, and hydrogen partial pressure can lead to very high activity and ee, this substrate class is also highly sensitive toward reaction parameters like initial substrate concentration[11] and addition of achiral additives. Moreover, based on catalytic hydrogenations in which enantiopure product alcohol was added to the reaction solution the detrimental effect of the undesired (*S*)-alcohol on enantioselection was identified and a multiple cycle mechanism derived, involving CD-modified Pt as well as (*S*)-product as retardant and trifluoroacetic acid as additive.[12] Careful optimization including the addition of low amounts of trifluoroacetic acid can greatly enhance the performance to an enantiomeric excess (ee) up to 92%.[9]

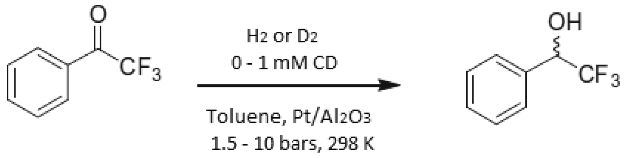
Herein, we study the kinetics of the hydrogenation of 2,2,2-trifluoroacetophenone (TFAP) to (*R*)-1-phenyl-2,2,2-trifluoroethanol ((*R*)-PTFE) on CD-modified Pt/Al_2O_3 by substituting hydrogen with its heavier isotope deuterium. The determination of the kinetic isotope effect (KIE), that is, a different rate constant for the isotopes can provide important mechanistic insight into the catalytic hydrogenation and reveal the rate-determining step. In general, a decrease of the vibrational frequency of the chemical bond in the heavier molecular isotope D_2 and the respective lower zero-point energy (ZPE) leads to a higher activation barrier for the hydrogenation if the bond is broken along the reaction coordinate. In the homogeneously catalyzed hydrogenations of acetophenone KIEs between 1.2 and 2.0 have been determined depending on the transition metal catalyst and reaction conditions, and the heterolytic splitting of dihydrogen was proposed to be the turnover-limiting step.[13]

In heterogeneous catalysis, isotopic studies on hydrogenations are rather scarce. Farkas et al. and Friedman et al. investigated the catalytic gas phase reduction of acetone on Pt with deuterium and from the d-product distribution they derived a ketonic hydrogenation mechanism via direct H_2 addition.[14] In the heterogeneous hydrogenation of cyclohexanone in liquid phase under elevated pressure, Tanaka et al. confirmed the direct addition of two deuterium atoms to the carbonyl bond over Os, Ir, and Pt catalysts.[15] KIE studies in heterogeneous catalysis have been reported for hydrogenations of hydrocarbons[16] and carbon oxides.[17] Because of the involvement of multiple surface steps and reaction intermediates in the catalytic cycle the interpretation of the overall measured isotope effect can be misleading as thermodynamic isotope effects and entropic contributions arising from surface concentrations of reaction intermediates also contribute and sometimes even compensate KIEs.[18] For hydrogenations on a catalytic surface, the measurable isotopic effect is determined by the activating dissociation of H_2/D_2 (ZPE difference of 1.8 kcal/mol) and the addition of chemisorbed hydrogen/deuterium to the activated ketone but also differences in ZPE related to formation of quasi-equilibrated intermediate surface species can be reflected as equilibrium isotope effect, partly canceling out ZPE differences in reactants. For instance, at equal pressures higher deuterium than hydrogen coverage on a Pt electrode was derived in an electrochemical study[19] and more stable half-hydrogenated transition-states can be formed with D.[18,20]

To the best of our knowledge, the following study represents the first investigation of the KIE for the liquid-phase hydrogenation of a ketone, in particular for heterogeneous asymmetric reactions on chirally modified Pt.

For the catalytic hydrogenation shown in Scheme 1, the influence of the concentrations of chiral modifier CD and TFAP, catalyst amount, and hydrogen partial pressure are thoroughly investigated. Time-resolved ATR-IR spectroscopic measurements of the liquid phase provide the experimental basis for the determination of rate constants using simple power rate law kinetics. KIEs are determined for unmodified and modified hydrogenations at several different $H_2(D_2)$-pressures and modifier concentrations.

Scheme 1. Hydrogenation of TFAP to the Corresponding Alcohol PTFE



EXPERIMENTAL SECTION

Materials. Cinchonidine, CD (Sigma-Aldrich, 96%), 2,2,2-trifluoroacetophenone, TFAP (Sigma-Aldrich, 99%), (*R*)-1-phenyl-2,2,2-trifluoroethanol, (Fluka, 99%, R:S 98:2) and (*S*)-1-phenyl-2,2,2-trifluoroethanol (Fluka, 99%, S:R 98:2), and toluene (Sigma-Aldrich, ≥99.9%) were used as received. The 5 wt % Pt/Al_2O_3 reference catalyst (BASF-Engelhard 4759) was purchased from BASF. Hydrogen (PanGas, Hydrogen 5.0, ≥ 99.999%) and deuterium (PanGas, enrichment ≥99.8%) were used as received.

Catalytic Hydrogenations and Deuterations. The 5 wt % Pt/Al_2O_3 catalyst was prereduced in a fixed-bed tubular reactor under flowing hydrogen for 1 h at 673 K, subsequently cooled down to room temperature for 30 min under flowing hydrogen and kept under flowing nitrogen before transfer to the autoclave. The characteristics for the as-prepared catalyst are a platinum dispersion of 0.22 and a mean platinum particle size of 4.5 nm.[21] For deuterations, the prereduction was also carried out under flowing hydrogen because preliminary experiments did not show any detectable deviations for the reaction rate or ee when prereducing it under flowing deuterium. For the in situ reduction the specific gas, H_2 or D_2, was used as described below.

Hydrogenations and deuterations of TFAP were carried out in a 60-mL Hastelloy steel jacketed-reactor connected to a multiposition valve (VICI) which allows for connecting the reactor to the hydrogen, deuterium, and nitrogen reservoirs, and to open it to the atmosphere. The hydrogen and deuterium pressures were controlled with a constant pressure regulator (Brooks 5688 Series). The standard reaction temperature (298 K) in the jacket was controlled with a Haake Phoenix (Thermo) water bath. To exclude external mass transfer limitation, reaction rates (and enantioselectivities) were determined for the faster hydrogenation (10 bar) at increasing stirring rates. At stirring rates above 500 rpm, no effect on the kinetics and enantioselectivities could be observed which is in line with the comprehensive study by Garland et al. covering potential internal and external mass transfer limitation in the much faster enantioselective hydrogenation of ethyl pyruvate.[22] Furthermore, for the same commercial Pt/Al_2O_3 which was applied in this study they confirmed the absence of internal mass transfer limitations. The general reaction procedure was the following: the prereduced catalyst was transferred to the reactor and reduced again in situ in 5 mL solvent at the reaction pressure (H_2 or D_2) and at the reaction temperature for 1 h. After the in situ reduction, the stirrer was switched off, and a mixture consisting of ketone (and also CD in case of modified reaction) in 5 mL of solvent was added. After flushing the reactor three times with pure H_2 or D_2, the semibatch reactor was pressurized to the reaction pressure, and the stirrer was switched on again. Under standard conditions 50 ± 0.5 mg, 0.2 M (2 mmol) or 1.0 M (10 mmol) TFAP, 0−1 mM CD (0−0.01 mmol) in 10 mL of toluene at 298 K were stirred mechanically (750 rpm).

The conversion and enantioselectivity in the hydrogenation and deuteration of TFAP were determined by gas chromatography (GC), using an Agilent Technologies 7890A gas chromatograph equipped with a flame ionization detector (FID). Samples were injected with a split ratio of 20:1 at an injector temperature of 250 °C. For GC separation, a chiral capillary column (CP-Chirasil-Dex CB, 25 m length, 0.25 mm internal diameter, 0.25 μm film thickness) was used. The temperature program started at 120 °C, held for 1 min, increased to 130 °C at 1 °C min^{-1}, held for 1 min, increased to 140 °C at 10 °C min^{-1}, held for 1 min, increased to 150 °C at 1 °C min^{-1}, held for 1 min, and then increased to 180 °C at 40 °C min^{-1}. The FID was operated at 300 °C with constant flows of hydrogen as fuel gas (30 mL/min) and air as oxidant (400 mL/min). Nitrogen was used as a makeup gas (25 mL/min) and helium as a carrier gas (constant flow: 1.623 mL/min). The target analytes could be separated: TFAP (retention time 1.75 min, elution temperature 120.8 °C, (*S*)-1-phenyl-2,2,2-trifluoroethanol (10.7 min, 130.0 °C), and (*R*)-1-phenyl-2,2,2-trifluoroethanol (11.1 min, 130.1 °C). Products were identified using enantiopure (*R*)- and (*S*)-1-phenyl-2,2,2-trifluoroethanol.

The estimated standard deviation for the determination of the conversion (X) and enantiomeric excess (ee) was <1% and <2%, respectively, as determined by triplicate measurements of three samples taken at full conversion.

The possibility of an exchange of hydrogens versus deuteriums at positions in trifluorobenzylalcohol other than at the hydrogenated carbonyl group was checked by GC coupled to a high-resolution mass spectrometer (GC-HRMS). GC-HRMS analysis (GC: Hewlet Packard HRMS: Thermo Finnigan MAT95) was performed using the same GC conditions as for the GC-FID analysis. The HRMS was run with electron ionization in full scan mode (mass-to-charge ratio m/z: 50−200 atomic mass units (u)). No additional exchange at positions other than at the hydrogenated carbonyl group, that is, no positive ions in the mass spectrum above m/z 177 u could be detected. Therefore, we exclude the formation of compounds with molecular weights greater than 177 g/mol.

Time-Resolved ATR-IR Spectroscopy. TFAP conversion and (racemic) product alcohol formation in liquid-phase was additionally monitored by time-resolved attenuated total reflection infrared (ATR-IR) spectroscopy. ATR−IR spectra were recorded on a Mettler-Toledo ReactIR 45m spectrometer equipped with a liquid nitrogen cooled MCT detector at 4 cm^{-1} resolution. The commercially available multireflection diamond ATR DiComp probe (Mettler-Toledo), connected to the ReactIR through an optical conduit was fitted in the reactor bottom. A homemade PEEK-stirrer ensured very efficient axial-flow exchange, and no concentration gradient existed at the bottom-mounted probe window within the acquisition of one spectrum which was confirmed in preliminary experiments by stepwise addition of substrate and product. The spectral resolution of 64 scans per spectrum resulted in a time resolution of 30 s per sample spectrum. The limit of detection and sensitivity of the employed ATR-IR method for monitoring the concentrations of ketone substrate and alcohol product were equal to about 0.2 mmol/L and 0.083 au/(mol/L), respectively. The icontrol software from Mettler Toledo was used to process the time-resolved spectra, and the integrated peak areas were calculated to follow the reaction progress.

TFAP conversion was followed by the integrated area of the C═O carbonyl stretching vibration observed between 1710−1725 cm^{-1}, and PTFE formation was followed by its characteristic C−C stretch vibration observed between 1308−1223 cm^{-1} and C−O stretch vibration between 1071−1061 cm^{-1}. The OH (OD) band was also observed at 3621−3433 cm^{-1} (2690−2544 cm^{-1}) but because of their very strong ATR-IR absorption the two former described product vibrational modes were picked for a more accurate online analysis. In hydrogenations and deuterations, both peaks did not overlap with any other absorption band, and their normalized progress during ongoing reaction did not show any significant deviation within the measurable tolerance. From three repeated measurements, a standard deviation of ±3% was determined. In preliminary experiments, the linear correlation between concentration and the integrated area of the absorption peaks (Lambert−Beer) was confirmed at concentrations 0.05 M, 0.2 M, 0.5 M, and 1.2 M. After each experiment, conversion determined by GC was used to convert specific absorbance to concentration.

RESULTS

Influence of Modifier Concentration. As a starting point for our isotopic study, we reinvestigated the influence of the modifier concentration on the reaction rate and enantioselection at reaction conditions reported in the literature[12,23] (298 K, 5 bar H_2 pressure, low substrate concentration of 0.2 M and toluene as solvent). Addition of CD within a concentration range of 0.1−1.0 mM lead to the preferential formation of (*R*)-PTFE with an ee of around 30−35%. At these conditions, the effects of the modifier concentration on the rate and ee were moderate. In Figure 1, the initial rate ($r_{initial}$, from 0 to 10% conversion (X)) and the intermediate rate (r_{inter}, from 15−40% X) as well as the ee as a function of CD concentration are shown. The online and high time-resolved measurements of the liquid-phase allowed for an accurate determination of the reaction rate in different kinetic regimes. As expected, after an initial period the rate of reaction dropped for unmodified and all studied modified hydrogenations. Comparing the activity of the catalyst in the presence of CD, the highest rate enhancement (RE) was observed at 0.1 mM CD with a factor of 1.15 ($r_{initial}$) and 1.3 (r_{inter}). The phenomenon of an increase of the overall rate in presence of a strongly adsorbing modifier is known as “rate acceleration” or “rate enhancement” and has been observed for several other substrates.[2a,24] However, the activity gain observed with TFAP was only very modest

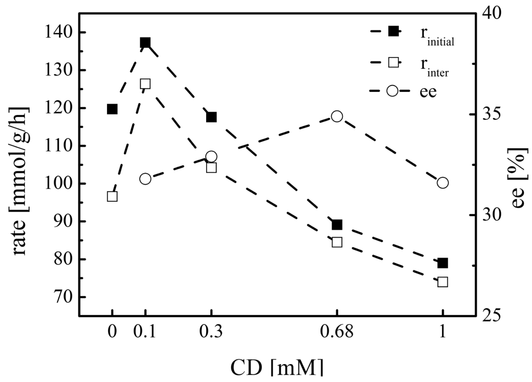


Figure 1. Reaction rate (squares) and ee (spheres) in the hydrogenation of TFAP at varying initial CD concentrations. The initial ($r_{initial}$) and intermediate (r_{inter}) rate refer to conversion regimes from 0−10% and from 15−40%, respectively. Conditions: 50 mg of catalyst, 0.2 M TFAP, 5 bar, 298 K, 10 mL of toluene.

compared with the highest RE reported for methyl pyruvate with a 25 to 100-fold increase.[25] Further increase of the modifier concentration even had a detrimental effect on the catalyst activity, probably because of unbalanced coverage of reactant and modifier on the Pt surface. In terms of enantioselectivity, the optimum was found around an initial concentration of 0.68 mM CD which is equivalent to a ratio of dissolved CD molecules to Pt surface metal atoms ($n(\mathrm{CD})_{\mathrm{dissolved}}/n(\mathrm{Pt}_{\mathrm{surface}})$) of 2.4. For the further kinetic study, we chose 0.3 mM CD ($n(\mathrm{CD})_{\mathrm{dissolved}}/n(\mathrm{Pt}_{\mathrm{surface}}) = 1.1$) as modifier concentration providing the best compromise between rate and ee (Figure 1).

Influence of Pressure. Next, we studied the influence of the hydrogen and deuterium pressure. Comparing the hydrogenations using H_2 and D_2, we observed a KIE, and the intermediate reaction rates (in between 15−40% X) were reduced by approximately 1/3 which was nearly constant in the studied pressure range. Interestingly, this kinetic effect did not significantly affect enantioselection (results are given in the Supporting Information). At low pressure (1.5 bar) the ee was improved to 42 ± 1% compared to 35 ± 2% at higher pressure (10 bar). More detailed kinetic information could be extracted from the time-resolved conversion data by the differential method. Since the gas pressure could be considered as constant in our reactor setup, we used the following simple power rate law to describe the kinetics of ketone conversion:

$$\mathrm{rate} = -\frac{\mathrm{d[TFAP]}}{\mathrm{d}t} = k[\mathrm{H_2}]^a \quad [\mathrm{TFAP}]^b = k_{\mathrm{app}}[\mathrm{TFAP}]^b \tag{1}$$

where b is the partial ketone reaction order and k_{app} includes the constant hydrogen or deuterium (also represented as $[\mathrm{H_2}]$ in eq (1)) concentration term which is to be corrected for higher solubility of D_2 in toluene (+2.5%). Linearization of the concentration gradient provided insight into the partial reaction order with respect to the reactant ketone, according to eq 2

$$\ln \mathrm{rate} = \ln\left(\frac{\mathrm{d[TFAP]}}{\mathrm{d}t}\right) = \ln(k_{\mathrm{app}}) + a\ \ln([\mathrm{TFAP}]) \tag{2}$$

In Figure 2, the linearized rates versus the substrate concentrations for the modified hydrogenation (A) and modified deuteration (B) are plotted for various pressures. Lower y-intercepts (k_{app}) reflect slower kinetics for the deuterations as well as for lower pressures.

However, with regard to the partial reaction order of TFAP interesting trends can be identified. The rate dependence of product alcohol formation on ketone concentration declined with decreasing pressure, for both hydrogenations (Figure 2A) and deuterations (Figure 2B). Moreover, even though reaction rates using the heavier isotope D_2 were lower because of the observed isotope effect, for all studied pressures nearly the same partial reaction order was found.

In addition, the linearized rates for two unmodified reactions are also plotted in Figure 2. Interestingly, at the given conditions nearly the same dependence of the rate on ketone concentration was observed for modified and unmodified reactions (exemplified in Figure 2A with 3 bar H_2 and in Figure 2b with 10 bar D_2). While the presence of modifier lead to enantioinduction and very little rate acceleration of the surface reaction, it did not seem to interfere significantly with the surface coverage of reactants.

Influence of Substrate Concentration. The strong dependence of enantioselection on ketone concentration is a peculiarity of TFAP hydrogenation[10,11] and has been experienced with several cinchona alkaloids used for chiral modification of Pt catalysts.[12] While the ee is known to increase with initial substrate concentration in the CD-modified

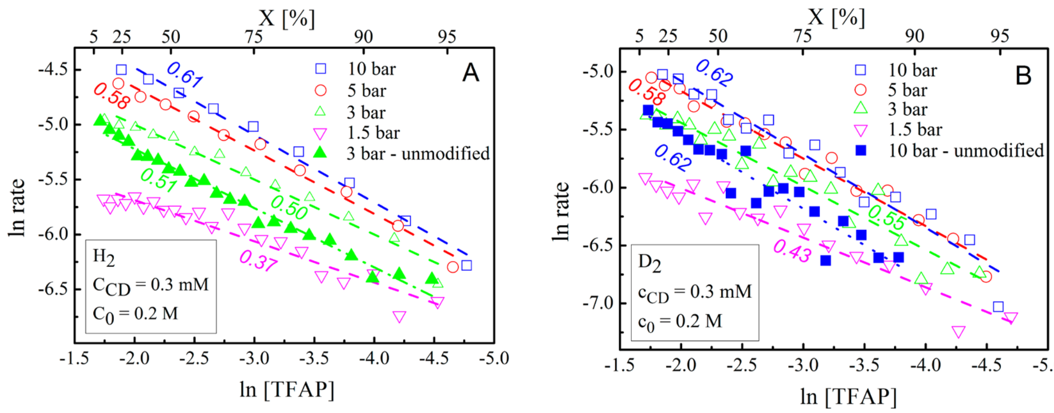


Figure 2. Partial reaction order with respect to TFAP for the hydrogenation (A) and deuteration (B) at varying pressures. Slopes for trend lines are given in the corresponding color, and all regression coefficients (R^2) were greater than 0.93. Conditions: 50 mg of catalyst, 0.2 M TFAP, 0.3 mM CD (or 0 mM CD for unmodified reactions), 298 K, and 10 mL of toluene.

reaction, to our knowledge the influence on the kinetics has not been subject of any study yet. Therefore, we investigated the effect of initial TFAP concentration at different modifier concentration, using H_2 and D_2.

In Figure 3, the reaction rate (A) and ee (B) in the hydrogenation (squares) and deuteration (spheres) of 1.0 M TFAP concentration at 5 bar pressure and at varying initial CD concentrations are presented. As a reference point, the experimental results obtained for hydrogenations at 0.2 M TFAP concentration (open diamonds) are also included. For the unmodified reaction (0 mM CD), higher initial substrate concentration slowed down the reaction rate. Interestingly, the presence of CD on the surface inverted the effect of higher initial ketone concentration on the reaction rate. At 1.0 M TFAP concentration, the modified reaction proceeded at a faster rate than at 0.2 M substrate concentration. As had been observed for lower TFAP concentration in Figure 1, the greatest RE was observed at 0.1 mM CD concentration. However, in this case the presence of the modifier enhanced the rate by a factor of 4.2 as opposed to 1.3.

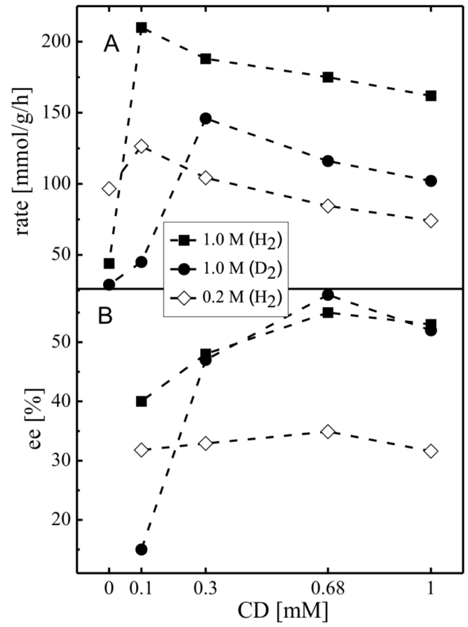


Figure 3. Reaction rate (A) and ee (B) using higher initial ketone concentration (c_0 = 1 M) in the hydrogenation (squares) and deuteration (spheres) at varying initial CD concentrations. The rate refers to the conversion regimes from 15−40% X. Conditions: 50 mg of catalyst, 1.0 M TFAP, 5 bar, 298 K, 10 mL of toluene.

The effect of substituting H_2 by D_2 revealed one major difference of the influence of the modifier concentration. In contrast to the fastest RE at very low modifier concentration using H_2, 0.1 mM CD seemed not to be sufficient to evolve the full potential of RE on the D_2-covered surface. Furthermore, such a low $n(\mathrm{CD})_{\mathrm{dissolved}}/n(\mathrm{Pt}_{\mathrm{surface}})/n(D_2)$ ratio of 1.0/2.8/1.5 (considering the solubility of deuterium at 5 bar pressure)[26] did not lead to an efficient chiral modification of the catalytic surface and enantioselection was significantly diminished compared to the hydrogenation. This unexpected difference, which was very well reproduced, highlights the influence of H_2-/D_2-coverage on the adsorption of CD. As the solubility of D_2 in toluene is only 2.5% higher than the one of H_2,[26,27] the deterioration cannot originate from deviating liquid phase concentrations but rather from differences in Pt−H and Pt−D bond strength,[28] and their resulting influence on modifier adsorption. For higher liquid CD concentrations, efficient enantioinduction was also achieved using deuterium, and the same trend as for hydrogenations with an optimum ee at around 0.68 mM was observed. With efficient chiral modification of the surface, the enantioselectivity was only marginally influenced by the isotope, as seen in Figure 3B. For modified hydrogenations and deuterations, higher TFAP concentration lead not only to higher catalytic activity but also brought about a major enhancement of the ee from around 35 to more than 50% (at 5 bar pressure). Note that the highest ee achieved in the enantioselective hydrogenation of TFAP under optimized conditions is 92%, but this ee is only achieved by addition of the acid additive trifluoroacetic acid (TFA).[9] In the present study we omitted the addition of TFA because of possible interference of the H/D isotope effect measurements by proton exchange reactions.

While the rate accelerating effect induced by CD in the hydrogenation of TFAP was also sensitive to the coverage of several surface species like modifier and H_2 or D_2, as shown in Figure 3A a major influence is connected to the ketone concentration. To better understand the origin of the accelerating effect, we investigated also the dependence of the rate on ketone concentration with the differential method at 1.0 M TFAP. In Figure 4, the linearized rates versus the ketone concentration are plotted for the unmodified and modified hydrogenation (A) and deuteration (B), respectively. The difference brought about by addition of the chiral modifier with

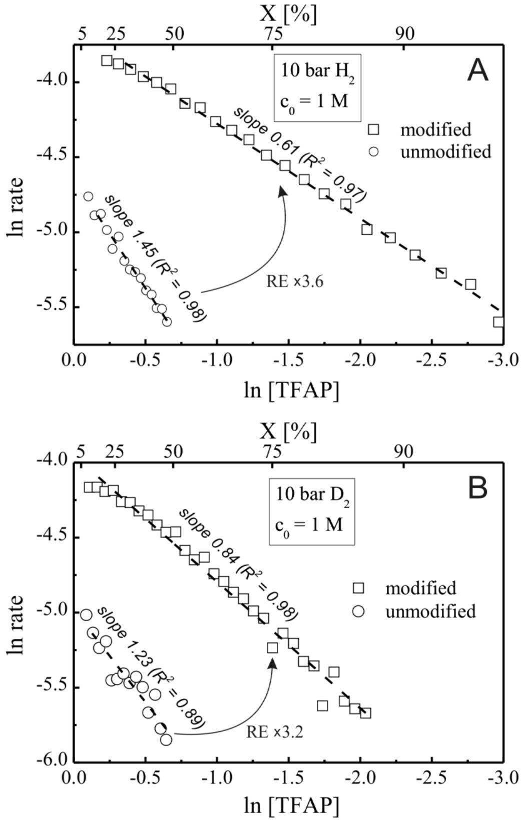


Figure 4. Partial reaction orders with respect to TFAP in the unmodified (spheres) and CD-modified (squares) hydrogenation (A) and deuteration (B). Conditions: 50 mg of catalyst, 1.0 M TFAP, 10 bar, 298 K, 10 mL of toluene.

respect to the partial ketone reaction order is striking. At 10 bar H_2-pressure and 1.0 M initial concentration, addition of 0.3 mM CD to the reaction mixture enhances the reaction rate by a factor of 3.6 compared to the reaction without addition of modifier. From the differential rate analysis a correlation between this significant RE and the decrease of the partial ketone reaction order from approximately 1.5 for the unmodified rate to 0.6 for the modified rate can be inferred. In the rate analysis at low ketone concentration in Figure 2 the partial ketone order was 0.5−0.6 even in the absence of CD, and no deviation could be observed in the presence of CD, but note that the RE was very small.

As shown in Figure 4B, the same trend was observed for the deuteration at high substrate concentration. While the deuteration with the heavier isotope D_2 was slower, the accompanied RE due to CD-modification of the Pt surface also lead to a decrease of the reactant ketone partial order for the observed overall rate. Again, at 0.2 M TFAP the deuteration rate on the modified Pt was barely enhanced, and the concentration dependence did not show any significant alteration upon surface modification (compare Figure 2).

Continuous Monitoring of the Liquid Phase. In the next part, we took a closer look at the role of trifluoro product alcohol formation in the catalytic reduction by studying the progress of the conversion depending on the initial modifier concentration and the nature of the gas. Because the acidic product is proposed to adversely affect the enantioselective surface reaction,[12] interference with the stereoselective surface process should be reflected in the kinetics of the reaction and ultimately be measurable in the liquid reaction solution.

In Figure 5, the time-resolved conversions during hydrogenation and deuteration at 5 bar pressure with different liquid modifier concentrations are depicted. For highlighting the effect of CD addition, the unmodified deuteration is also shown. In general, the initial reaction is fastest on the prereduced surface when the fully H_2/D_2-covered surface is exposed to ketone and modifier. After the high initial reaction rate, the kinetic behavior changed for all reactions. For the modified reactions though, a sudden bend of the conversion curve was observable which was even more pronounced at lower modifier concentration. Interestingly, depending on the used liquid concentrations of CD and the nature of the gas, the observed rate of reaction decelerated at a specific conversion, that is, when a certain PTFE concentration had been reached. The decrease of the rate is highlighted by the red tangents for CD-modified reactions. For instance, at 0.1 mM CD and using D_2, after an accelerated reaction up to approximately 20% conversion, product formation proceeded at a significantly lower turnover frequency (TOF) which was almost the same as that of the unmodified reaction, for example, the TOF dropped from 2980 to 780 h^{-1} (the unmodified rate in this conversion regime was 670 h^{-1}). When using 0.3 mM CD, the deceleration only occurred at much higher conversion, for example, at a product concentration of around 0.5−0.6 M the TOF decreased from 3000 (0−10% X, 2590 from 15−40% X) to 1210 h^{-1}. As mentioned above, enantioselection determined at full conversion was essentially favored at 0.3 mM CD concentration. For the hydrogenations, a similar dependence of the kinetics on product alcohol concentration was observed. In this case, the initially slower hydrogenation at 0.3 mM CD was higher than that at 0.1 mM CD at a conversion of approximately 60%. If the hydrogenation was carried out with 0.68 mM CD the reaction was slower but proceeded at a nearly constant rate until almost full conversion.

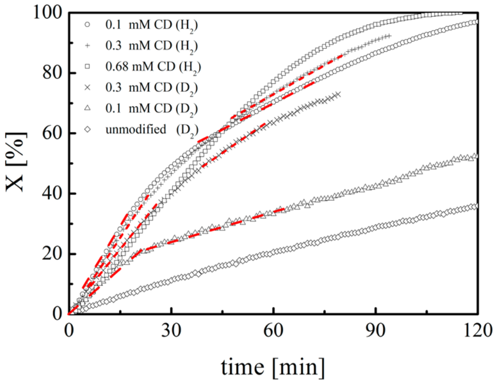


Figure 5. Effect of the nature of the gas (H_2/D_2) and CD concentration on the progress of reaction. The time resolution is 1 min/spectrum. Conditions: 50 mg of catalyst, 1.0 M TFAP, 5 bar, 298 K, 10 mL of toluene. Red lines indicate different kinetic regimes.

The observations in the liquid-phase indicate a competitive adsorption on the catalytic surface in which not only ketone and product alcohol but also modifier and hydrogen (or deuterium) are involved. Depending on their concentrations, ketone conversion can be significantly hampered at a specific product concentration. Comparing the unmodified deuteration with the 0.1 mM CD modified reaction it appears that the accelerated modified reaction was not maintained after a product concentration of around 20%. Apparently, at the higher modifier concentration of 0.3 mM, the modified surface could withstand product accumulation in liquid phase to a higher extent up to a conversion of around 50% which ultimately is also reflected in better enantioselection (compare Figure 3). The same behavior is observed for hydrogenations. However, comparing the modified hydrogenations and deuterations the bend of the conversion curve occurred at a higher product concentration on the hydrogen covered surface which is again an indication that also the hydrogen/deuterium coverage and their Pt−H/Pt-D bond strength are relevant for efficient surface modification. Furthermore, differences in the protonation of the quinuclidine moiety of CD by chemisorbed H or D could also be reflected for the modified reaction route.[29]

Kinetic Isotope Effect. The last part of the study was devoted to the investigation of the KIE which requires the determination of the rate constants of hydrogenation (k_H) and deuteration (k_D). Our approach for measuring the KIE is based on simple power rate law kinetics. The ratio of rate constants derived from power rate law kinetics carries mainly information about the kinetics of the elementary steps involving H_2, for example, the dissociation of hydrogen and the addition of the first and second hydrogen atom to the carbonyl bond. As our study and previously reported results show,[12] product alcohol strongly influences the surface reactions. To avoid hydrogenation and deuteration rates to be obscured by the influence of product, the experimental data was fitted in the intermediate conversion regime at relatively low conversion. For unmodified reactions, the rate constants were fitted between 10 and 20% conversion, while for modified reactions the rate constants were determined between 15 and 40% conversion. Furthermore, as determined by the differential method partial reaction orders of 0.5 and 1.0 with respect to the ketone liquid phase concentration were considered, and the power rate law described in eq 1 was applied. As the ee is dependent on the hydrogen pressure, kinetic rate constants and KIEs were determined for unmodified and modified reactions at three different pressures, 1.5, 5 and 10 bar.

To confirm the absence of any mass transfer limitations, we started our kinetic study by investigating the influence of the catalyst amount on the hydrogenation rate. As shown in Figure 6, at the highest hydrogen concentration applied in our study corresponding to 10 bar (fastest reaction) the measured rates for unmodified and modified hydrogenations increase linearly with the catalyst amount corroborating the kinetic control under the chosen conditions.[22] In the studied regime, enantioselection was best at higher $n(\mathrm{CD})_{\mathrm{dissolved}}/n(\mathrm{Pt}_{\mathrm{surface}})$ ratios with a maximum ee of 46% which is in line with the results regarding the influence of the modifier concentration.

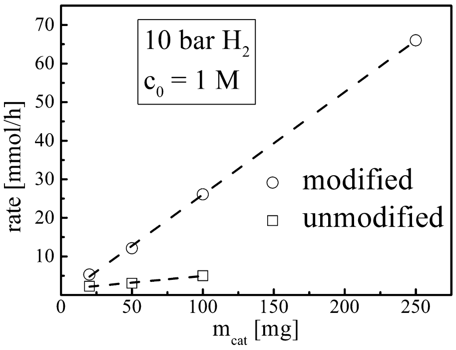


Figure 6. Dependence of the reaction rate on the amount of catalyst for the fastest studied unmodified (squares) and CD-modified (spheres) hydrogenation. Conditions: 1.0 M TFAP, 10 bar, 298 K, 10 mL of toluene. For standard reactions 50 mg of catalyst was used.

Surprisingly, decreasing the $n(\mathrm{CD})_{\mathrm{dissolved}}/n(\mathrm{Pt}_{\mathrm{surface}})$ ratio from 0.5 to 0.2 at the largest amount of catalyst leads to a slight improvement (ee from 35% to 40%). However, stereocontrol on the catalytic surface is also dependent on reactant and product concentrations and cannot be simply traced back to initial dissolved modifier-to-catalyst-ratios.

In Figure 7, the experimental data and the theoretical conversion curves for a partial ketone reaction order of 0.5 are plotted. For unmodified reactions (Figure 7, top) the power rate law describes the data points with good accuracy for all three H_2 and D_2 pressures, respectively.

For modified reactions (Figure 7, bottom), at 5 and 10 bar pressures the power rate law kinetics slightly overestimate product formation, but only at higher product concentration (X > 50%). These deviations for the asymmetric reactions are likely to occur because of the blocking of active (CD-modified) sites by increasing alcohol formation which is not taken into account in the power rate law. However, for the intermediate conversion range (15−40% X) the kinetics of CD-modified hydrogenations and deuterations are accurately described with eq 1. Generally, the kinetic fitting using a partial order of 0.5 was in better agreement than using a ketone concentration order of 1.0. In Table 1 and Table 2, the fitted rate constants and the resulting measured KIEs for the three different gas pressures are presented, respectively. We have also fitted the kinetic data applying a Langmuir−Hinshelwood−Hougen−Watson model where the global reaction rate (Scheme 1) is controlled by the addition of the first hydrogen atom. The corresponding results are shown in the Supporting Information.

The KIE for the unmodified hydrogenation of TFAP was on the order of 1.4 ± 0.1 for all studied pressures which confirms the involvement of hydrogen in the rate-determining step for TFAP solid−liquid−gas hydrogenations on Pt/Al_2O_3 at 298 K. For CD-modified hydrogenations, the measured isotope effects

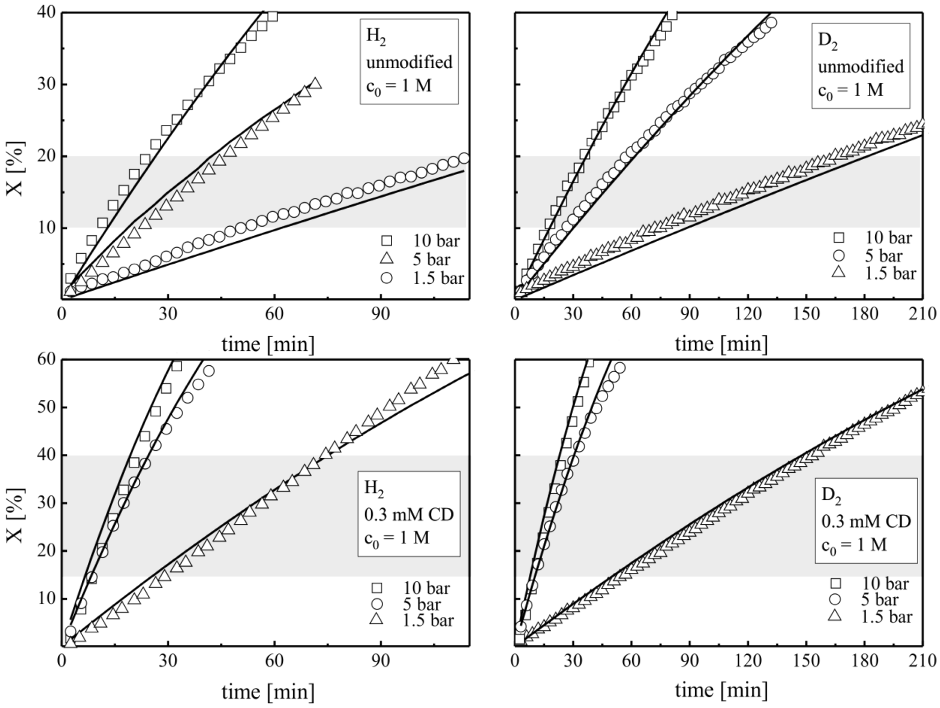


Figure 7. Comparison of experimental and fitted kinetic data obtained with a partial ketone reaction order of 0.5 for unmodified (top) and CD-modified (bottom) hydrogenation (left) and deuteration (right), respectively. The hydrogenation/deuteration is fitted for 1.5, 5, and 10 bar partial pressure.

Table 1. Rate Constant k_{app} [$\times 10^2 \times \mathrm{mol}^{0.5} \times \mathrm{L}^{-0.5} \times \mathrm{min}^{-1}$] for Hydrogenations and Deuterations at 1.5, 5, and 10 bar H_2/D_2-Pressures[a]

	unmodified		modified	
p [bar]	H_2	D_2	H_2	D_2
1.5	**8.3** ± 0.3	**6.0** ± 0.2	**32.9** ± 1.2	**19.0** ± 0.7
5	**22.9** ± 0.7	**17.1** ± 0.6	**92.8** ± 3.3	**71.7** ± 2.6
10	**39.9** ± 1.3	**28.9** ± 0.9	**118.3** ± 4.2	**85.7** ± 3.1

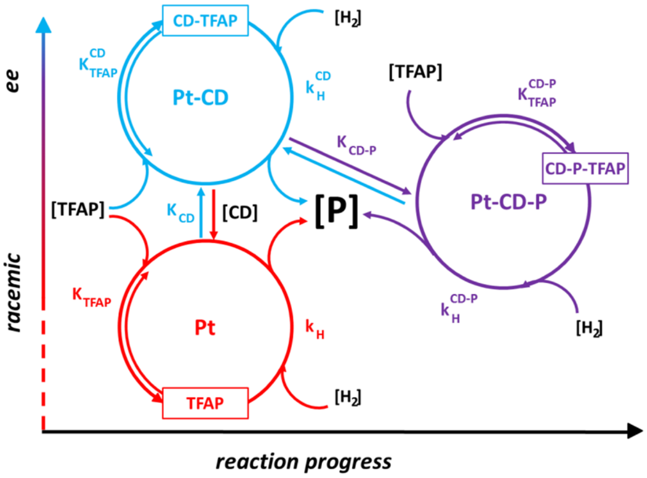
[a] Modified reactions were carried out at 0.3 mM CD. Standard errors originate from determined accuracies of the online liquid-phase measurements and the parameter estimation.

Table 2. KIE for Unmodified (0 mM CD) and Modified (0.3 mM CD) Reactions at 1.5, 5, and 10 bar H_2/D_2-Pressures

p [bar]	unmodified	modified
1.5	**1.4** ± 0.1	**1.7** ± 0.15
5	**1.3** ± 0.1	**1.3** ± 0.1
10	**1.4** ± 0.1	**1.4** ± 0.1

were on the same order of magnitude. Nevertheless, at 1.5 bar pressure a measurable deviation of the isotope effect was found. At low hydrogen pressure (coverage), when optimal enantioselection with an ee of 59% (56% for D_2) had been achieved, by addition of 0.3 mM CD an increase in the KIE from 1.4 to 1.7 was observed. An increase of the measured isotope effect must originate either from a decrease of a compensating, inverse isotope effect related to quasi-equilibrated reaction steps (thermodynamic equilibrium of surface intermediates) or from an enhanced rate of the hydrogen addition step(s) (KIE). To support this assumption, we also determined the isotope effect for increasing CD concentration at 5 bar pressure, for example, increasing enantiocontrol at isobaric conditions (see Supporting Information). Again, the measured isotope effect increased from 1.3 to 1.5 and 1.6 at 0.68 mM and 1.0 mM CD concentration, respectively.

Scheme 2. Schematic Representation of Three Parallel Reaction Cycles Occurring in the Hydrogenation of TFAP in H_2-Saturated Toluene on Unmodified Pt Sites (Red), CD-Modified Pt Sites (Blue) and CD-Modified Pt Sites Interfering with the Product Alcohol PTFE (Violet) Highlighting Their Dependence on Liquid-Phase Concentrations and Their Contribution to Enantioselection[a]



[a] Liquid-phase concentration of TFAP, product alcohol (P), CD, and H_2 are indicated in square brackets and adsorbed species by θ. Equilibrium adsorption constants are indicated by K and hydrogenation rate constants by k. For the sake of simplicity the addition of hydrogenation on the surface is presented as one step.

DISCUSSION

The study of kinetic hydrogen/deuterium effects in the heterogeneous asymmetric hydrogenation of TFAP on CD-modified Pt/Al_2O_3 reveals new information about this complex multiphase reaction and, in particular, sheds light on the role of hydrogen in the enantioselective surface reaction. The results gathered for the catalytic hydrogenation will be discussed in the context of the reaction network shown in Scheme 2 which is based on the two cycle mechanism commonly accepted for chirally modified metals[30] and its advancement as multiple cycle mechanism for α,α,α-trifluoromethyl ketones.[12] The proposed model focuses on the kinetics of the CD-modified hydrogenation of TFAP. It contains three different catalytic cycles and illustrates the interplay between the reaction participants H_2 (or D_2), TFAP, CD as well as product alcohol (P) in solution (square brackets) and adsorbed on the Pt surface (θ). The contribution of each cycle to the overall measured reaction rate and enantioselectivity differs and depends on the progress of reaction. The racemic hydrogenation cycle takes place at the unmodified Pt site (*Pt*), which can be transformed to an enantioselective site by addition of CD and its adsorption on the Pt surface (Pt-CD). While the ratio of modified to unmodified Pt sites cannot be determined from the time-resolved liquid phase measurements, variation of the CD concentration as well as the concentrations of ketone and hydrogen/deuterium reveals information about the differences of these two in parallel running catalytic cycles.

By applying the differential method to the time-resolved liquid reaction concentrations a decrease of the partial ketone reaction order was found at lower hydrogen/deuterium pressure (compare Figure 2). A reduced dependence of the reaction rate on liquid ketone concentration at lower hydrogen pressure could originate either from slower product formation requiring less CD-TFAP accumulation on the surface ($\theta_{\text{CD-TFAP}}$) or from a greater adsorption constant of the ketone ($K_{\text{TFAP}}^{\text{CD}}$) on the CD-modified site. However, the ketone liquid concentration dependence for hydrogenations and deuterations is nearly the same at equal pressures even though the reaction rate using D_2 is reduced by around 1/3 because of the primary isotope effect (simplified expressed: $k_{\text{H}}^{\text{CD}} > k_{\text{D}}^{\text{CD}}$, see below for discussion of the origin of the isotope effect) which indicates that the observed alteration of the partial reaction order brought about by varying the hydrogen/deuterium concentration cannot originate from a kinetic effect, that is, a slower elementary deuteration step ($k_{\text{D}}^{\text{CD}} \times \theta_{\text{CD-TFAP}} \times \theta_{\text{D}}$) does not lead to the reduction of the partial ketone order. More likely, adsorption of TFAP at the active site ($K_{\text{TFAP}}^{\text{CD}}[\text{TFAP}] = \theta_{\text{CD-TFAP}}$) is facilitated at lower H/D-coverage. For unmodified reactions, the same behavior of the partial ketone order was found and therefore, we propose a similar dependence of K_{TFAP} as for $K_{\text{TFAP}}^{\text{CD}}$ on hydrogen surface coverage θ_{H}. Competitive adsorption of reactants on the catalytic surface can explain the increase of the ketone adsorption constant ($K_{\text{TFAP}}^{\text{CD}}$ and K_{TFAP}) at lower gas pressure and ultimately the lower partial ketone order. Such a competition between trifluoro-activated ketones and dissociated hydrogen could also be linked to the peculiar effect on enantioselectivity, as hydrogen concentration (surface coverage) is a crucial factor for enantioselection and, contrary to the hydrogenation of α-ketoesters, higher hydrogen coverage diminishes the ee. Recently, hydrogen coverage dependent reconstruction of Pt nanoparticles supported on Al_2O_3 from biplanar to cuboctahedral morphology has been shown by the use of computational methods.[31] Reduced TFAP adsorption and low enantioselection at higher hydrogen pressure might also arise from crystallite effects and structure sensitivity of the catalyst due to hydrogen coverage could counteract the desired coadsorption of modifier and trifluoro ketone.[32]

Improved understanding regarding the kinetic phenomenon of an accelerated rate induced by adsorption of the chiral auxiliary to Pt sites was also derived. Depending on reaction conditions, addition of CD can induce strong RE in the hydrogenation of TFAP with a factor of around 4 ($r_{\mathrm{modified}}/r_{\mathrm{unmodifed}}$) which is accompanied by a change in the partial ketone order. In this context, the initial substrate concentration is a crucial factor for exploiting the maximum potential of RE. At low substrate concentration the CD-modified reaction is barely faster than the unmodified reaction (RE of about 1.3) and the ee is moderate. According to Scheme 2, it appears that at low [TFAP] the unmodified hydrogenation cycle (Pt) is kinetically only slightly disfavored, and the racemic reaction ($k_H \times \theta_{TFAP} \times \theta_H$) counteracts the enantioselective ($K_H^{CD} \times \theta_{CD\text{-}TFAP} \times \theta_H$) pathway. At high initial [TFAP] the racemic hydrogenation rate is significantly deteriorated, as shown for the unmodified reaction in Figure 3A. In accordance to the proposed competitive adsorption, high coverage of Pt by TFAP would retard formation of activated hydrogen resulting in lower activity. Another explanation considers the possibility of agglomeration of the activated ketone preventing the required adsorption on Pt[33] which would result in a lower K_{TFAP}. In contrast to the racemic reaction, in presence of modifier the macroscopically observed ketone conversion is strongly enhanced, and abundance of ketone results in a faster overall rate on the chirally modified surface. Examination of the reaction progress data reveals a major decrease of the liquid TFAP concentration dependence on the hydrogenation rate as the partial order is decreased from around 1.5 to 0.6 which is the same partial order determined at low ketone concentration. The same effect is observed for the accelerated deuteration on the modified Pt. Therefore, we assume a correlation between the lower partial ketone order and the higher activity. It appears that coadsorbed CD optimizes the surface coverage of the two competing reactants, $\theta_{CD\text{-}TFAP}$ and θ_H/θ_D, and RE is linked to an optimized adsorption of TFAP at the active site (K_{TFAP}^{CD}). While excess TFAP limits the kinetics of the unmodified hydrogenation, this activation barrier seems to be compensated by the presence of adsorbed CD, and the modified hydrogenation cycle is now kinetically favored over the racemic cycle leading to improved ee.

Regarding the competitive adsorption involving the acidic trifluoro-activated product alcohol the third reaction cycle (Pt-CD-P) in Scheme 2 becomes important. This hydrogenation cycle is a result of a disadvantageous transformation of Pt-CD by additional interaction with the acidic product alcohol [P] leading to reduced enantioselection and catalytic activity. In our previous study[12] it has been shown that the minor product enantiomer ((*S*)-1-phenyl-2,2,2-trifluoroethanol) forms an adduct with the alkaloid, and this complex controls the enantioselection of the Pt-CD-P cycle. Obviously, with ongoing reaction progress providing higher [P] the equilibrium will be driven more toward this transformation, and the Pt-CD-P cycle dominates the catalytic system leading to a decrease of the overall rate. The time-resolved ATR-IR measurement of the liquid reaction solution in Figure 5 reflects such changes in the overall reaction rate which, in turn, is assumed to originate from an alteration influencing the catalytic cycle or even from changing of the dominant catalytic cycle. Decomposition reactions, partial hydrogenation of the chiral modifier,[34] product accumulation as well as decreasing concentration gradients of reactant all influence the catalytic cycle. Such effects will be most pronounced if different surface species share the same active adsorption sites, for example, H_2/D_2, ketone, modifier, but also product, and interesting observations could be made with respect to liquid modifier concentration [CD] and nature of the gas ($[H_2]/[D_2]$).

Exemplified by the low ee using D_2 at 0.1 mM CD concentration, the dependence of efficient chiral modification on θ_H/θ_D was shown (compare Figure 5). Since increasing [CD] could also bring up enantioselection in the deuteration we propose that only after a certain threshold concentration dissolved CD molecules can occupy most of the available Pt sites and take the desired adsorption configuration at the solid-liquid interface suitable for imparting stereocontrol.[35] Higher initial [CD] ($n(\mathrm{CD})_{\mathrm{dissolved}}/n(\mathrm{Pt}_{\mathrm{surface}}) \approx 2.4$) helps to maintain the asymmetric reaction cycle pursuing formation of $\theta_{CD\text{-}TFAP}$ and resisting ongoing product formation, but at the expense of catalytic activity though. It can be inferred that excess [CD] intervenes with an efficient reaction but is necessary to replenish deactivated modified sites. Deactivation of the modified site might originate from partial hydrogenation of adsorbed CD[34] and from transformation of catalytic cycle Pt-CD to Pt-CD-P due to the propensity of formed product alcohol to bind to adsorbed CD. The significant drop of the reaction rate depending on [CD] and $[H_2]/[D_2]$ at a specific alcohol concentration in Figure 5 indicates that a change in the dominant catalytic cycle occurred. The kinetic progress monitoring of the liquid reaction solution shows that liquid phase concentrations and therefore the operation mode of reaction have a strong influence on the reaction rate which appears also to be connected to enantioselection.

In addition, measurement of the KIE confirms the participation of hydrogen in the rate determining-step of the liquid phase hydrogenation on Pt/Al_2O_3 at 298 K in the pressure range from 1.5−10 bar. Addition of CD to the reaction mixture only shows a deviation at conditions of optimal enantioselection. For distinguishing between contributions from individual surface steps (dissociation of H_2, addition of first or second hydrogen) knowledge about the surface coverage of reactants, intermediates, and also product would be necessary which, however, is experimentally not yet feasible for hydrogenations on supported metal catalysts under liquid phase conditions.[36] Particularly for chirally modified hydrogenations, missing information about intrinsic kinetics at an unknown number of modified sites hampers a more detailed description of the underlying reaction network.

However, the effect of the isotopic substitution is most pronounced when optimizing the enantioselective surface process with respect to ketone concentration, modifier concentration, and hydrogen pressure indicating the kinetic influence of the adsorbed modifier on the surface process. In accordance to simultaneously occurring hydrogenations at unmodified and modified surface sites, a greater $k_{\mathrm{app,H}}/k_{\mathrm{app,D}}$ observed for lower pressure and higher CD concentration could be an indication that at greater kinetic control of the rate-determining step involving hydrogen the enantioselective surface reaction is favored.

■ CONCLUSIONS

Using the substitution of hydrogen by its heavier isotope deuterium and time-resolved kinetic progress monitoring by ATR-IR spectroscopy the catalytic cycles occurring in the asymmetric hydrogenation of 2,2,2-trifluoroacetophenone to (*R*)-1-phenyl-2,2,2-trifluoroethanol on CD-modified Pt have been investigated. On the basis of these investigations, we propose that three different catalytic cycles are relevant to explain the observed catalytic behavior: asymmetric hydrogenation on CD modified Pt-CD sites, asymmetric hydrogenation on Pt-CD sites interfering with the acidic alcohol product, and racemic hydrogenation on unmodified Pt sites. The contribution of the different sites to the overall reaction depends on the reaction progress. Both the hydrogenation on the chirally modified and on the unmodified platinum catalyst show a significant kinetic isotope effect which indicates that the hydrogen addition is the rate determining step of these catalytic cycles. As mechanistic similarities are expected within the same substrate class the observed characteristic features may also be relevant for the asymmetric hydrogenation of other *α*,*α*,*α*-trifluoro-activated ketones on CD-modified platinum. The extension of these studies to other substrates as well as fundamental studies on the interaction of the different surface species involved in the catalytic cycles will help to gain deeper insight into this complex enantiodifferentiating catalytic system.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The experimental data (reaction rates and ee) for 0.2 M TFAP deuterations, the kinetic fit using the power rate law with the partial ketone order of 0.5 and the corresponding experimental data for the 0.68 and 1 mM CD-modified hydrogenations and deuterations (1.0 M TFAP, 5 bar partial pressure, 50 mg of Pt/Al_2O_3, 10 mL of toluene) are enclosed. In addition, kinetic description with a Langmuir−Hinshelwood kinetic model has been included. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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