Heterogeneous Asymmetric Hydrogenation of Prochiral Alkenoic Acid: Origin of Rate and Enantioselectivity Enhancement by Amine Addition

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S *Supporting Information*

ABSTRACT: The origin of rate and enantioselectivity enhancement by achiral amine addition in the asymmetric hydrogenation of alkenoic acid on chirally modified Pd has been a long-debated subject. We show by means of in situ attenuated total reflection infrared spectroscopy combined with modulation excitation spectroscopy that the rate enhancement in the presence of an amine originates from restructuring of surface acid—base type adducts dynamically involving the substrate, product, chiral modifier, and amine. Phase-sensitive detection provides insight into the surface dynamics at the solid—liquid chiral interface: the addition of the achiral amine changes the adsorption configuration of the chiral modifier on the Pd surface, leading to a better stereochemically controlled surface.

KEYWORDS: asymmetric hydrogenation, chiral modifier, heterogeneous catalysis, in situ IR spectroscopy, modulation excitation spectroscopy
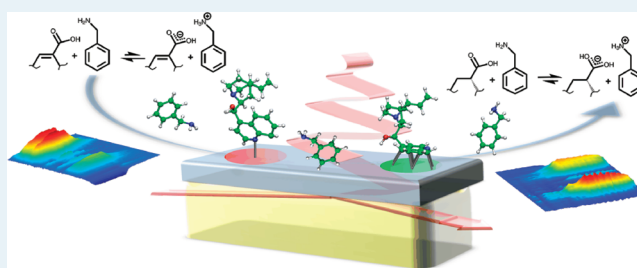
Chirality is of fundamental importance in natural science, and the efficient production of optically pure compounds is an important challenge in the chemical and pharmaceutical industries.[1,2] Among the various methods[2] applied to produce pure enantiomers of a chiral compound, catalysis is unique in the sense that with a small amount of optically active catalyst, a large quantity of the desired product enantiomer can be produced. Although homogeneous asymmetric catalysis with chiral transition metal complexes has shown remarkable efficiency and versatility, the application of heterogeneous asymmetric catalysis has been rather limited because of its relatively narrow application range, which is mainly confined to some specific asymmetric hydrogenations.[3−8] Nevertheless, the development of heterogeneous asymmetric catalysis could be rewarding due to its intrinsic advantages concerning handling, separation, and regeneration of the catalyst. Furthermore, heterogeneous catalytic reactions can more easily be operated in a continuous mode,[9,10] whereas homogeneous catalysis is dominated by batch processes.

One of the most efficient and elegant strategies of heterogeneous asymmetric hydrogenation is to create a chiral environment at the active metal surface by adsorption of a suitable chiral auxiliary (modifier).[3−8] Since its discovery by Orito et al.[11] in the late 1970s, the cinchona-modified platinum system has been the subject of intense research,[3−7] leading to considerable insight into the functioning of this fascinating catalytic system and to a significant broadening of the scope of substrates that can be transformed with high optical purity (up to 98%). In contrast, hydrogenation of functionalized olefins on

chirally modified Pd has not gained similar attention. A major drawback of the Pd-catalyzed C=C bond reduction is the significant deterioration of the intrinsic reaction rate and stereocontrol,[12] except for some substituted diphenylpropenoic acids with high enantiomeric excess (>90 ee %).[13−15]

A method to suppress this deterioration was suggested by Nitta et al., who showed that by simple addition of a base (e.g. benzylamine (BA)), the reaction rate and enantioselectivity are greatly enhanced.[16] This beneficial base addition could be extended to various substrates and bases.[12,17,18] Nitta and colleagues proposed that the rate enhancement might originate from facilitating desorption of product acids via an acid—base interaction. A decade later, enhancement of enantioselectivity was rationalized by Bartók and colleagues, who proposed the involvement of BA in the enantiodifferentiating step forming a tertiary complex with cinchonidine (CD) and a prochiral substrate.[19] However, the lack of experimental evidence did not allow drawing an unambiguous conclusion.

Sophisticated exploitation of the base effect requires a profound understanding of the underlying mechanisms. In this study, we shed light on the critical role of BA by means of in situ attenuated total reflection infrared (ATR-IR) spectroscopy in combination with modulation excitation spectroscopy (MES) and provide new insight into the origin of rate and

enantioselectivity enhancement in the asymmetric hydrogenation of unsaturated carboxylic acid. For this purpose, we selected a well-established catalytic system: the hydrogenation of phenylcinnamic acid (PCA) to 2,3-diphenylpropionic acid (DPPA) on a 5 wt % Pd/TiO_2 catalyst modified with cinchonidine (CD).

The key advantages of combining MES and ATR-IR spectroscopy are the enhanced signal-to-noise (S/N) ratio as well as the discrimination between active surface species and spectators.[20,21] Figure 1 shows IR spectra of PCA (a) and DPPA (e)
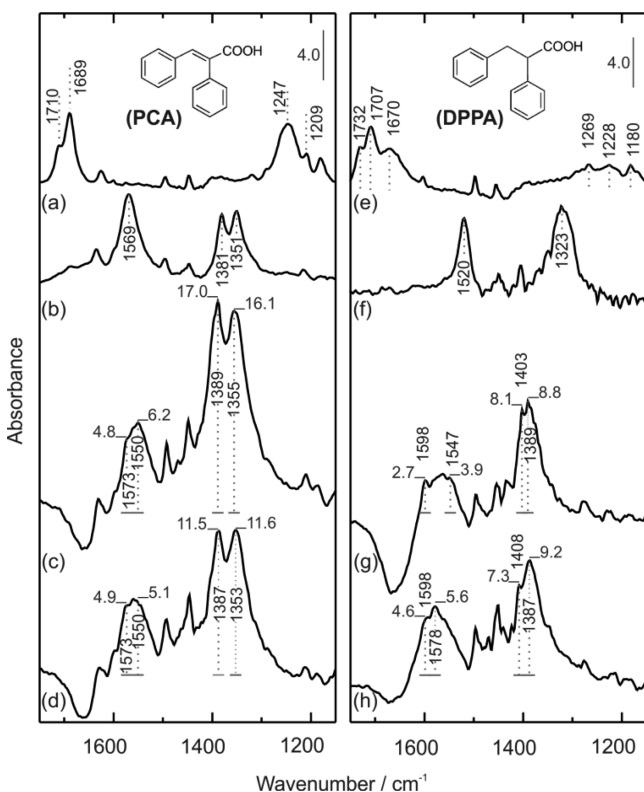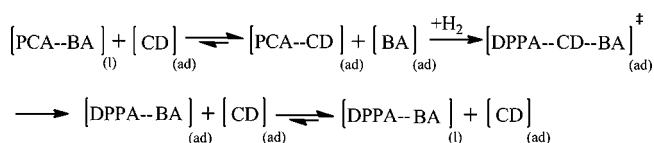

Figure 1. ATR-IR spectra of PCA (left) and DPPA (right) at 298 K; (a, e) 12.5 mM solution in MeOH, (b, f) 12.5 mM PCA or DPPA + 12.5 mM BA in MeOH, (c, g) 1 mM PCA or DPPA on CD-modified Pd/TiO_2, and (d, h) 1 mM PCA or DPPA + 1 mM BA on CD-modified Pd/TiO_2. All the solutions were saturated with pure H_2. The unit of absorbance is 10^{-3}.

in the liquid phase. Splitting absorption bands at 1710 and 1689 cm^{-1} for PCA, which are assignable to the C=O stretching vibration of carboxylic acids, indicate the presence of monomer and dimer species interacting via H-bonding.[22] DPPA even formed trimers, as indicated by the band at 1670 cm^{-1}. By adding BA to the liquid phase, new absorption bands emerged at around 1550 and 1350 cm^{-1}, which are assigned to asymmetric and symmetric stretching vibrations of carboxylates (COO^-), respectively (spectra 1b and f). This characteristic spectral change was reported to arise from an acid–base interaction, that is, PCA–BA and DPPA–BA (the ion charges are omitted here and hereafter).[23] Interestingly, as seen in Figure 1c and g, the IR spectra of the CD-modified Pd surface show the same features for both PCA and DPPA. This phenomenon clearly demonstrates an acid–base interaction between the coadsorbed species forming an adduct via the basic quinuclidine N atom of CD and the carboxyl group of PCA and DPPA: PCA–CD and DPPA–CD, respectively.

A striking difference was observed when BA was present on the surface (spectra 1d and h). For PCA, addition of base did not trigger any significant spectral changes for the diastereomeric PCA–CD surface complex, contradicting the proposed formation of a tertiary complex with BA and the involvement in the enantiodifferentiating step.[19] For DPPA, on the other hand, bands of the DPPA–CD surface complex decreased (especially highlighted for the band at 1547 cm^{-1}), and new bands appeared at 1408 and 1578 cm^{-1}. As evident from the distinction in the spectra, the prochiral alkenoic acid does not interact with BA, whereas after hydrogenation, the chiral acid weakens or even breaks interactions linked to the chiral modifier and favors a different type of acid–base complex: DPPA–BA.

Taking these findings into account, the actual effect of BA addition is most likely to restructure surface acid–base complexes from DPPA–CD to DPPA–BA and therefore to make the chirally active site (CD_{ad}, Scheme 1) accessible to another

Scheme 1. Proposed Catalytic Cycle in Presence of BA[a]

$$[PCA\text{-}BA]_{(l)} + [CD]_{(ad)} \rightleftharpoons [PCA\text{-}CD]_{(ad)} + [BA]_{(ad)} \xrightarrow{+H_2} [DPPA\text{-}CD\text{-}BA]_{(ad)}^{\ddagger}$$

$$\longrightarrow [DPPA\text{-}BA]_{(ad)} + [CD]_{(ad)} \rightleftharpoons [DPPA\text{-}BA]_{(l)} + [CD]_{(ad)}$$

[a]Indices l and ad represent liquid-phase and adsorbed species, respectively.

prochiral substrate, leading to an efficient catalytic cycle. The effect of BA addition on the global reaction system can be better highlighted in the time-resolved 2D surface plots (Figure 2)
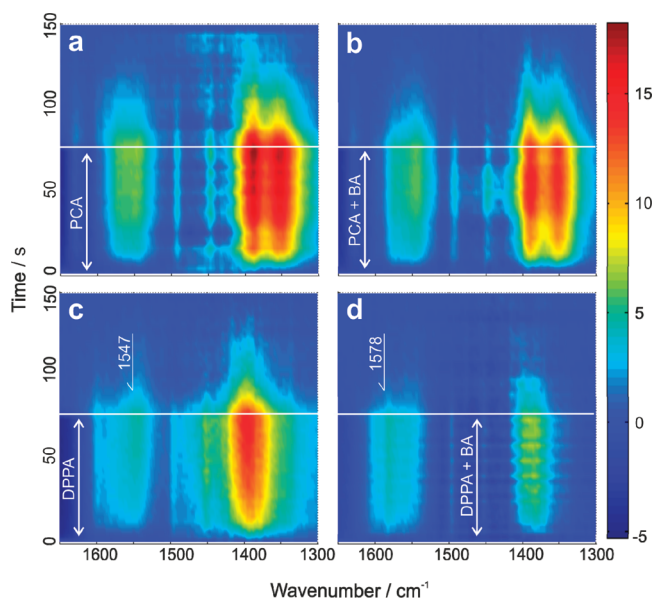

Figure 2. Time-resolved 2D surface plot of ATR-IR spectra during adsorption and desorption of (a, b) PCA and (c, d) DPPA over CD-modified Pd at 323 K in the (a, c) absence and (b, d) presence of BA. The unit of absorbance (color bar) is 10^{-3}.

obtained from MES experiments at 323 K. Two different solutions were periodically changed over the CD-modified Pd/TiO_2: (1) 1 mM PCA or DPPA in MeOH with or without BA and (2) MeOH. The background was taken with the latter solution.

As clearly seen in Figure 2, BA has almost no influence on the amount of PCA interacting with CD-modified Pd. On the contrary, the absorption bands originating from DPPA−BA decreased considerably. This finding reveals that BA does affect the DPPA−CD interaction and thereby facilitates desorption of the adsorbed DPPA. Note that the blue shift of the asymmetric stretching vibration of COO^- ($1547 \rightarrow 1578$ cm^{-1}) evidences that restructuring of the surface acid−base interaction from DPPA−CD to DPPA−BA also occurred rapidly at 323 K. The above findings explain the origin of the rate enhancement induced by BA as follows (Scheme 1): First, adsorbed CD picks up PCA from the liquid phase by breaking the PCA−BA acid−base interaction and leaves BA to cover unmodified Pd surface sites. As soon as PCA is hydrogenated to DPPA, it interacts with surface BA, providing better access to the chirally active sites. Finally, DPPA is released to the liquid phase with BA.

Although an increased intrinsic rate on chiral sites and selective blocking of unmodified achiral sites by the amine explain a higher ee, we have further extended our in situ spectroscopic study by combining it with phase-sensitive detection (PSD) to gain insight into the origin of enantioselectivity enhancement by BA.[21] This additional mathematical treatment of MES data allows extracting kinetic information according to the following equation :

$$A_k \cos\left(\varphi_k + \varphi_k^{\text{delay}}\right) = \frac{2}{T} \int_0^T A(t) \sin(k\omega t + \varphi_k) \, \mathrm{d}t$$

(1)

where T is the length of a cycle, ω is the demodulation frequency, φ_k is the demodulation phase angle, k is the demodulation index ($k = 1$ in this study), and $A(t)$ and A_k are the active species responses in time- and phase-domain, respectively. The phase-delay (0 to $-180°$), φ_k^{delay}, gives information on the sequence of actions occurring at the solid−liquid interface; a surface process at or closest to $\varphi^{\text{delay}} = 0°$ takes place first.

Figure 3 shows phase-domain ATR-IR spectra obtained by periodically changing two solutions over Pd at 323 K: 1 mM CD or 1 mM CD + 1 mM BA in MeOH for 75 s and pure MeOH for 75 s. As seen in Figure 3a, two different adsorption geometries of CD were detected on Pd: π-bonded CD at 1576 cm^{-1} and N-lone pair bonded CD at 1576 and 1589 cm^{-1}. The spectral features differ only slightly, but they can be distinguished in the infrared spectra due to changes in the dynamic dipole moment of quinoline rings,[24] which was also supported by ab initio calculations.[25] Without BA, these species showed similar dynamic behavior, that is, $\varphi^{\text{delay}} = -10°$, whereas the BA addition drastically changed it (see Figure 3b). First, BA detected at 1454 cm^{-1} adsorbed on the surface at $\varphi^{\text{delay}} = -30°$, then, N-lone-pair-bonded CD was formed ($\varphi^{\text{delay}} = -50°$), followed by a gradual formation of π-bonded CD ($\varphi^{\text{delay}} = -90°$). Finally π-bonded CD is most abundant on the surface ($\varphi^{\text{delay}} = -140°$). This sequential process indicates that the coexistence of CD and BA on the surface leads to a gradual transformation to π-bonded CD (Scheme 2). The critical role of π-bonded CD in the enantiodifferentiation is generally accepted.[3,7] Therefore, the enantioselectivity enhancement by BA is considered to originate from a better stereochemically defined surface due to the stabilization of π-bonded CD.

In conclusion, in situ ATR-IR spectroscopy combined with MES and PSD sheds light on the longstanding debate about the reason for the beneficial effect of achiral amine addition in the
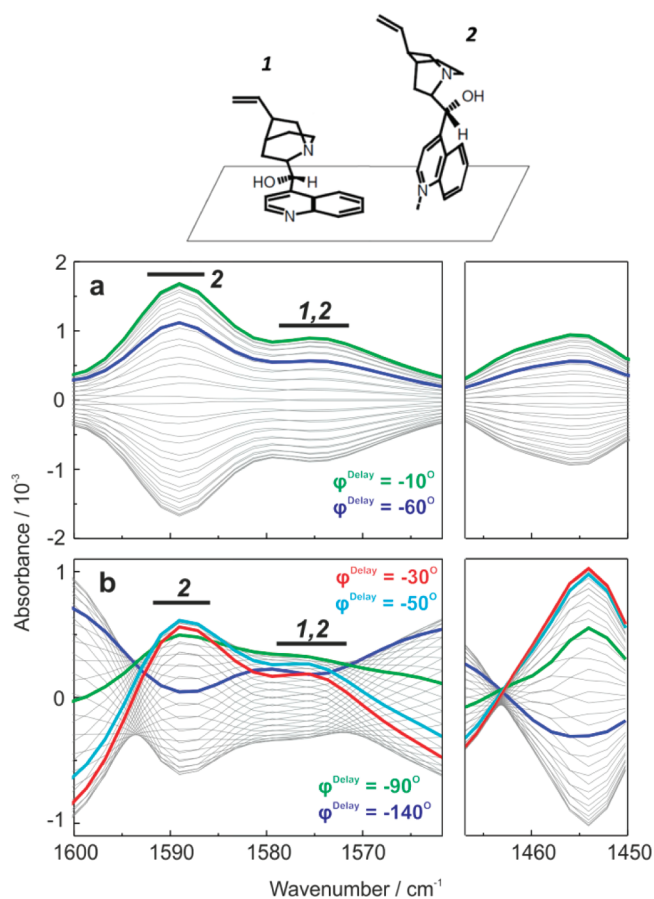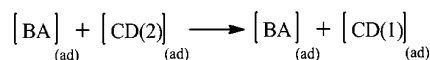

Figure 3. Phase-domain ATR-IR spectra during (a) CD and (b) CD + BA adsorption−desorption over Pd/TiO$_2$ at 323 K. The numbers **1** and **2** correspond to CD structures.

Scheme 2. Modification of CD Structure on Pd Surface by Adsorbed BA[a]

$$[\text{BA}]_{\text{(ad)}} + [\text{CD(2)}]_{\text{(ad)}} \longrightarrow [\text{BA}]_{\text{(ad)}} + [\text{CD(1)}]_{\text{(ad)}}$$

[a]Index ad represents adsorbed species. Proposed structures of adsorbed CD(1) and CD(2) are shown in Figure 3 (top).

heterogeneous asymmetric hydrogenation of unsaturated carboxylic acids. The enhanced rate is explained by restructuring of the surface acid−base complex from [prochiral substrate]−[chiral modifier] to [product acid]−[amine], facilitating catalytic cycles. In addition, time-resolved IR spectroscopic study confirmed the enhanced desorption of the product acid in the presence of the amine additive. The amine also contributes to a dynamic change in the adsorption configuration of the chiral modifier (N-lone-pair-bonded → π-bonded) on the Pd surface and leads to a better stereochemically defined surface.

■ EXPERIMENTAL SECTION

A film of Pd/TiO$_2$ catalyst (Engelhard) was deposited on a ZnSe internal reflection element (bevel of 45°, 52 mm × 20 mm × 2 mm, Crystran Ltd.), and placed in a home-built flow-through cell. ATR-IR spectra were recorded on a Bruker IFS-66/S spectrometer equipped with a liquid-nitrogen-cooled MCT detector at 4 cm^{-1} resolution. Modulation−excitation experiments were carried out by periodically (75s) changing between

two different flowing solutions. The cycles were repeated eight times to obtain stable responses of active species, and the last five cycles were integrated into one cycle to average the spectra and to enhance the S/N ratio. Details of the experimental procedure are available in the Supporting Information.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details (the catalyst layer preparation, ATR-IR spectroscopy, MES experiments) and IR spectra of CD and BA on Pd/TiO$_2$. 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.

■ ACKNOWLEDGMENTS

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