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Chiral α-hydroxy acid-coadsorbed TiO₂ photocatalysts for asymmetric induction in hydrogenation of aromatic ketones†

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Modification of titanium dioxide (TiO₂) photocatalysts with chiral reagents was evaluated by the hydrogenation of aromatic ketones. The strong adsorption of chiral mandelic acid (*R*)-MA on TiO₂ was confirmed by comparing the inhibition effect IR values. The enantio-selectivities were affected by not only the chiral reagents but also the TiO₂ crystalline samples, suggesting that the interaction between aromatic ketones and MA on TiO₂ should depend on the surface structure and morphology of TiO₂ particles.

Heterogeneous photocatalysis on semiconductors is a light-driven redox reaction at a solid/liquid or a solid/gas interface.¹⁻³ The photocatalysis, especially using TiO₂, has become an active area of research for storage of solar energy,^{4–6} environmental purification,⁷ sterilization,⁸ and so on. Despite such significant advances, little attention has been paid to the use to synthetic organic chemistry.9-15 Particularly, less is known about the use of semiconductor materials for asymmetric photocatalysis.¹⁶⁻²⁰ An enantioselective reaction was for the first time achieved in the reduction of 3-methyl-2-oxobutanoic acid using Pt-TiO₂ and a chiral Rh(I) complex by Sakata, Takaya and co-workers.¹⁶ In recent years, semiconductors were used in the enantioselective transformations involving the formation of chiral enamines or iminium ions from aldehydes and chiral amine catalysts.¹⁷⁻¹⁹ To date, the direct modification of TiO₂ with chiral molecules has not been investigated for asymmetric photocatalysis; thus, the development of chiral molecule-coadsorbed semiconductor materials still remains a challenging task.

In our previous studies, we demonstrated that TiO_2 -catalyzed hydrogenation of acetophenone (AP) and 2'-acetonaphthone (2-NP) occurs quantitatively to afford to the corresponding racemic

Scheme 1 Enantioselective photohydrogenation of aromatic ketones on TiO_2 . Carried out for a mixture of aromatic ketones, chiral reagents, and TiO_2 in deaerated ethanol suspension under UV light irradiation.

secondary alcohols 1-phenylethanol (APOH) and 1-(2-naphthyl)ethanol (2-NPOH), respectively.^{14,21-24} Our laboratory is newly interested in developing chiral TiO₂ photocatalysts, because it should be possible to evaluate these catalysts by our hydrogenation reaction. This communication for the first time reports the surface-selective and enantioselective photohydrogenation of aromatic ketones induced by chiral reagents coadsorbed on a TiO₂ surface (Scheme 1). In this study, the adsorption and function of chiral reagents on TiO₂ were evaluated by the inhibition ratio (IR) based on the reaction rates and the enantioselectivity, respectively. As shown below, it is worth noting that this hydrogenation was affected by not only the chiral reagents but also the crystalline phases, surface structures and morphology of TiO₂.

At first, the hydrogenation of AP and 2-NP was studied on UV-irradiated P25 TiO₂ (anatase/rutile = *ca.* 8/2) in the presence of chiral reagents such as mandelic acid (*R*)-MA (Table 1). The *S*-enantiomers of APOH and 2-NPOH were predominantly obtained by using (*R*)-MA. We preformed the blank test in the absence of TiO₂. The hydrogenation reactions did not occur under irradiation even in the presence of (*R*)-MA, thus the sequential double electron transfer by photo-irradiated TiO₂ is also essential for the present enantioselective hydrogenation as mentioned in our previous reports.²¹⁻²⁴

We next focus our attention to the reaction rates. The production of APOH and 2-NPOH occurred at the rates of



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Table 1 Reaction rates, inhibition ratios, and enantioselectivities of photohydrogenation of AP and 2-NP on P25 TiO2^a

		АРОН		2-NPOH			
Chiral reagents		Averaged reaction rate ^{b} (µmol L ⁻¹ h ⁻¹)	IR (%)	% ee ^c	Averaged reaction rate ^{b} (µmol L ⁻¹ h ⁻¹)	IR (%)	% ee ^c
	None	1.46×10^3	_	_	$2.14 imes 10^3$	_	_
	(<i>R</i>)-MA	22	99	37 (<i>S</i>)	26	99	37 (S)
н ₃ с-с-он он	(<i>R</i>)-LA	14	99	9 (<i>S</i>)	25	99	10 (S)
$\overset{H}{\swarrow}\overset{OH}{\underset{CH_3}\overset{OH}{\underset{O}\overset{OH}{\underset{CH_3}\overset{OH}{\underset{O}\overset{OH}{\underset{OH}}\overset{OH}{\underset{OH}}\overset{OH}{\underset{OH}\overset{OH}{\underset{OH}}\overset{OH}{\underset{OH}}\overset{OH}{\underset{OH}}\overset{OH}{\underset{OH}}\overset{OH}{\underset{OH}}}}}$	(<i>R</i>)-2PA	$0.74 imes 10^3$	49	2 (<i>S</i>)	1.03×10^3	52	1 (<i>S</i>)
$\bigwedge \overset{H}{\underset{{}_{\scriptstyle H^{\ast}}} \overset{OH}{\underset{{}_{\scriptstyle H^{\ast}}}}} $	(<i>R</i>)-1P1,2D	$1.00 imes 10^3$	31	Racemic	1.43×10^3	33	Racemic

^{*a*} Carried out for a mixture of aromatic ketones (0.13 mmol), chiral reagents (0.25 mmol) and TiO₂ (0.10 g) in deaerated ethanol solution (25 mL) under irradiation with UV light (>350 nm) at 305 K. ^{*b*} Average production rates for both enantiomers of secondary alcohols. ^{*c*} Defined by the following equation: % ee = 100 ([S] - [R])/([R] + [S]) at 5 h irradiation, where [R] and [S] are concentrations of enantiomers of the secondary alcohol.

1.46 and 2.14 mmol L⁻¹ h⁻¹ in the absence of chiral reagents on P25 TiO₂, respectively, while these became much slower to *ca.* 1/100 in the presence of (*R*)-MA (Table 1 and Fig. S1, ESI†). This outstanding MA-induced inhibition is attributable to the strong adsorption of (*R*)-MA at the surface Ti sites, which will also act as the reaction sites for photohydrogenation.^{21–24} A similar inhibition effect was observed when chiral lactic acid (*R*)-LA was used as an α -hydroxy acid (Table 1). Therefore, the interaction between α -hydroxy acids and Ti sites must be much stronger than that between aromatic ketones and Ti sites. Here we defined the inhibition ratio (IR) as below:

$$\mathrm{IR}\left(\%\right) = \left(1 - \frac{r}{r_0}\right) \times 100$$

where r and r_0 are the reaction rates in the presence and absence of chiral reagents, respectively.

Table 1 summarizes the averaged initial reaction rate, IR, and enantiomeric excess (ee) of the products at 5 h irradiation on P25 TiO₂. When (R)-MA was used as a chiral reagent in the hydrogenation of AP and 2-NP, relatively high enantioselectivities (37% ee of APOH and 2-NPOH) were attained with high IR values (99%). In contrast, the high enantiomeric excess and IR completely disappeared when replacing (R)-MA with ethyl (R)-mandelate (0% ee and IR = 0%). This means that the carboxylic acid on (R)-MA is essential for the adsorption of (R)-MA on TiO_2 . The enantioselectivities decreased when using the sterically less hindered (R)-LA (9–10% ee), although (R)-LA having a carboxyl group and a hydroxyl group exhibited a high inhibition effect (IR > 99%). In contrast, the use of chiral 2-phenylpropionic acid (R)-2PA, substituting a hydroxyl group of MA with a methyl group, led to decreases in IR (ca. 50%) and ee (1-2% ee). In the case of chiral 1-phenylethan-1,2-diol (R)-1P1,2D, the IR value was low (31-33%) and the ee value was almost zero. Therefore, both the hydroxyl and phenyl groups bonded at the chiral center carbon of (R)-MA play a crucial role on this asymmetric induction.

As the adsorption structure of LA on TiO₂, a bidentate ligand form chelated by hydroxyl and carboxylate functional groups was proposed.²⁵ The monodentate ligand forms of LA were also proposed by chelating the alkoxy or carboxylate group after H⁺ dissociation.²⁶ (*R*)-MA would bind at the surface Ti site in a similar manner. A proposed illustration for the bidentate and monodentate adsorption of (*R*)-MA and the interaction between the aromatic ketone and (*R*)-MA on the TiO₂ surface is depicted in Fig. 1. The substrates AP and 2-NP bind at the neighboring Ti sites, where the sequential electron transfer and protonation steps proceed.²³ The π - π interaction between the aryl group of substrates and the phenyl group of (*R*)-MA would be important for the stereoselective protonation.

We next examined the differences in reaction rates and enantioselectivities between anatase, rutile, and mixed phase TiO₂ crystalline samples. At first, the reaction rates (r_0) for the hydrogenation of AP and 2-NP in the absence of chiral reagents were compared by employing four kinds of TiO₂ samples (Table 2). P25 exhibited the fastest rates among these TiO₂ photocatalysts probably due to the efficient charge separation of excited electrons and holes in P25 TiO₂ as reported.^{27,28} Indeed, the hydrogenation using P25 was completed within 4 h of irradiation (Fig. S1, ESI[†]). On the other hand, the slowest TiO₂ photocatalyst was TIO-13 with a single anatase phase. There are several factors that determine heterogeneous photocatalytic reaction rates, e.g., surface areas, crystal structures, and crystallinity of photocatalysts.⁴ The faster reaction rate on TIO-7 than on TIO-13 may result from the larger specific surface area (Table 2). The similar trend was observed even in the reaction rates (r) for hydrogenation in the presence of (R)-MA.



Fig. 1 Proposed models for (A) bidentate and (B) monodentate adsorption of (R)-MA and interaction between aromatic ketone and MA on the TiO₂ surface.

Table 2 Enantioselective photohydrogenation of AP and 2-NP on each TiO₂ crystalline sample^a

TiO sample	Darticle	Specific surface	АРОН			2-NPOH		
(crystalline phase)	size ^e (nm)	area $(m^2 g^{-1})$	$r_0^{k} (\text{mmol}^{-1} \text{h}^{-1})$	$r^l (\mu \mathrm{mol}^{-1} \mathrm{h}^{-1})$) % $ee^{m}(R)$ -MA	$r_0^k (\mathrm{mmol}^{-1})$	h^{-1}) r^{l} (µmol ⁻¹	h^{-1}) % $ee^{m}(R)$ -MA
P25 $(A/R)^b$	$22^{f}/35^{g}$	$50^{h}, 61^{i}$	1.46	22	$37^{n}(S)$	2.14	26	$37^{n}(S)$
TIO-13 $(A)^c$	24	59 ^j	0.21	2.4	$43^{\circ}(S)$	0.41	2.6	43^p (S)
TIO-7 $(A)^{c}$	9	270^{j}	0.59	4.8	$2^{o}(S)$	0.82	5.3	$-7^{p}(R)$
Kanto Chem. $(R)^d$	126	—	0.44	3.1	Racemic ^o	0.69	2.5	Racemic ^p

^{*a*} Carried out for a mixture of aromatic ketones (0.13 mmol), chiral reagents (0.25 mmol) and TiO₂ (0.10 g) in deaerated ethanol solution (25 mL) under irradiation with UV light (>350 nm) at 305 K. ^{*b*} Mixture of anatase/rutile (*ca.* 8/2). ^{*c*} Single anatase phase. ^{*d*} Single rutile phase. ^{*e*} Estimated from XRD. ^{*f*} For anatase. ^{*g*} For rutile. ^{*h*} From ref. 28. ^{*i*} From ref. 29. ^{*j*} From ref. 30. ^{*k*} Reaction rates in the absence of MA. ^{*l*} Reaction rates in the presence of (*R*)-MA. ^{*m*} Defined by the following equation: % ee = 100([S] - [R])/([R] + [S]), where [*R*] and [*S*] are concentrations of enantiomers of the secondary alcohol. ^{*n*} At 5 h irradiation. ^{*p*} At 8 h irradiation.

Moreover, all cases exhibited high inhibition effect IR values (more than 99%). Thus, all TiO₂ samples led to the strong adsorption of (*R*)-MA. Interestingly, the enantioselectivities are not affected by the reaction rates. P25 and TIO-13 exhibited relatively high enantioselectivities, whereas TIO-7 (anatase) and Kanto Chem. (rutile) showed low and no % ee, respectively. It is important to note that the inversion of absolute stereochemistry (-7% ee) was observed in the hydrogenation of 2-NP on TIO-7; the *R*-enantiomer of 2-NPOH was obtained by using (*R*)-MA. To confirm the inversion of stereochemistry, this reaction was repeated by changing the chiral reagent from (*R*)-MA to (*S*)-MA (Fig. S2, ESI[†]). Indeed, the *S*-enantiomer of 2-NPOH was obtained in +7% ee when using (*S*)-MA.

To gain further insight into the effect of the nanostructure of TiO_2 particles on the reaction rates and enantioselectivities, we investigated X-ray diffraction (XRD) patterns and transmission



Fig. 2 XRD patterns and TEM images of (A) TIO-7 (blue line) and TIO-13 (red line), and (B) P25 crystalline samples. *R* denotes the rutile peaks.

electron microscopy (TEM) images for TIO-7, TIO-13 and P25 crystallites (Fig. 2). The XRD patterns for TIO-7 and TIO-13 indicate the same single anatase phase, though full widths at half maxima (FWHM) of the peaks are different (Fig. 2(A)). The average sizes of the anatase crystallites for P25, TIO-13, and TIO-7 are 22, 24, and 9 nm, respectively, estimated from FWHM of the diffraction peaks at $2\theta = 25.3$ and 48.1° using the Scherrer equation. These values are in agreement with the primary particle sizes reported for P25 (26 nm),²⁹ TIO-13 (30 nm)³⁰ and TIO-7 (8 nm).³⁰ It should be noted in the TEM images (insets in Fig. 2) that P25 and TIO-13 possess larger particle sizes with smooth and flat surfaces, whereas TIO-7 has a smaller size with a significant amount of edges and corners and a larger specific surface area. Consequently, a specific crystal facet on the anatase TiO₂ may be essential for the asymmetric induction. It has been reported that the main exposed surfaces of P25 are anatase (101) and (001), observed by high-resolution TEM and FT-IR.²⁹ In particular, the anatase (101) and (001) are favorable surfaces for the reductive and oxidative reactions in TiO₂ photocatalysis, respectively.^{31,32} Therefore, the reductive (101) surface could be a candidate for this enantioselective hydrogenation though the redox preference may depend on adsorbates.33,34

Fig. 3 shows the time dependence of enantiomeric excess for 2-NPOH production on P25 TiO_2 coadsorbed with (*R*)-MA. The value of ee exceeded over 60% within 1 h. Thus, high enantio-selectivity was attained at the initial time, but it decreased



Fig. 3 Time dependence of enantiomeric excess for 2-NPOH production on P25 TiO_2 in deaerated ethanol containing (*R*)-MA (0.25 mmol) under UV irradiation (> 350 nm).



Scheme 2 Photodecomposition of MA on TiO_2. The h^+ denotes photogenerated hole on TiO_2.

monotonically with irradiation time. Fig. S3 (ESI[†]) depicts the changes in HPLC chromatograms during the photoreaction. The formation of 1,2-diphenylethanone as a side product was observed at 4.4 min retention time. 1,2-Diphenylethanone is formed *via* the decarboxylation (photo-Kolbe reaction)³⁵ of (*R*)-MA induced by the photooxidation on TiO₂ followed by coupling of two hydroxybenzyl radicals and dehydration (Scheme 2). This side reaction may be suppressed by the use of highly uniform anatase TiO₂ nanocrystals with specific exposure of the reactive facets.³² On the anatase TiO₂ nanocrystals, the spatial separation of photoexcited charge carriers on different facets can depress the oxidative degradation of MA preferentially adsorbed on the reductive facet.

In summary, the adsorption and function of chiral mandelic acid (R)-MA on TiO₂ were evaluated by the inhibition ratios (IR) and enantioselectivities of the photohydrogenation of aromatic ketones, respectively. The enantioselectivity was strongly affected by the TiO₂ crystalline samples. Thus, this communication is the first report on the novel surface-selective and enantioselective photocatalysis occurred on TiO₂.

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Conflicts of interest

There are no conflicts to declare.

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