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Metal-Loaded Semiconductor-Photocatalysis of Alcohols for Selective Organic Synthesis: A Personal Account

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- 1 Introduction
- 2 Dehydroxylative hydrogenolysis of allylic alcohols
- 3 Acceptorless dehydrogenation of activated/unactivated alcohols
- 4 N-Alkylation of amines using alcohols as alkylating agents
- 5 Summary and outlook

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Metal-Loaded Semiconductor-Photocatalysis of Alcohols for Selective Organic Synthesis: A Personal Account

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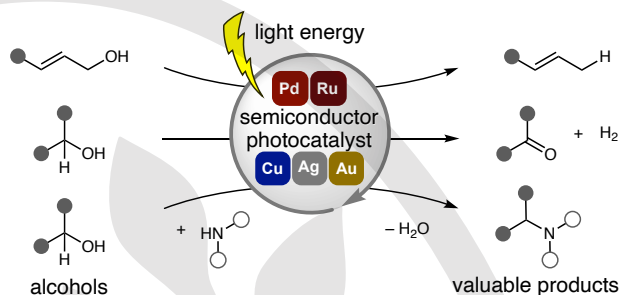
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Dedicated to Professor Hisashi Yamamoto on the occasion of his 80th birthday.



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Abstract In this account, we review our research over the last decade on metal-loaded semiconductor-photocatalyzed organic transformations using alcohols. Different from many reactions using alcohols as mere sacrificial electron donors, our study has demonstrated alcohols as useful organic building blocks incorporated into value-added products. Besides such recollections of previous results, we briefly introduce our ongoing project involving photocatalytic C–C bond-forming reactions via the C–C bond scission of tertiary alcohols.

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Keywords semiconductor, photocatalyst, alcohol, dehydroxylative hydrogenolysis, dehydrogenation, N-alkylation, N-methylation, β -scission

1. Introduction

Semiconductor photocatalysts (SPs) have drawn significant attention in a wide range of green science and sustainable technology.¹ This is because photo-irradiated SPs can simultaneously and continuously generate pairs of holes (h^+ s) and electrons (e^- s), that can promote attractive reactions via both oxidation and reduction processes under ambient conditions in one-pot operations. Since the properties of SPs, including the wavelength of absorbed light and the charge-carrier lifetime, can drastically be altered by loading metal-nanoparticle (NP) cocatalysts on the surfaces² or by doping impurity elements in the lattices,³ SPs have infinite potential for organic synthesis. In fact, a wide variety of SPs have been designed, prepared, and utilized for certain important environmental issues since the 1970s when the Honda-Fujishima effect was coined.⁴ Representative examples include water splitting (water oxidation coupled with proton reduction),^{5,6} CO₂-to-fuel conversion (water oxidation coupled with CO₂ reduction),^{7,8} or

organic pollutant degradation in which active oxygen species ($\cdot\text{OH}$, $\text{O}_2^{\cdot-}$) are supposed to be generated through water oxidation and/or O₂ reduction.^{9,10} Some developed green technologies seem close to being implemented in practice [CO₂ reduction with the solar-to-formate energy conversion efficiency of 7.2% (0.1 m² irradiation area)¹¹; water splitting with the solar-to-hydrogen energy conversion efficiency of 0.76% (9 m² irradiation area)¹²]. Although the application of the SPs in synthetic organic chemistry was falling behind before 2000, several research groups, including the groups of Saito,¹³ Yoshida,¹⁴ Pieber,¹⁵ König,¹⁶ Walton,¹⁷ Scaiano,¹⁸ and other researchers,^{19–21} reported their remarkable works on organic transformations using SPs during the past decade.

We have used SPs mainly for the useful and practical organic transformations of alcohols since they are widely available and many of them are inexpensive and safe.^{22,23} Looking back to the 1980s, Kagiya and Ohtani reported a series of germinal studies on SPs-induced organic transformations of alcohols. Representative examples were the alkylation of heteroatom nucleophiles by metal-loaded TiO₂ (M/TiO₂) photocatalyst, where alcohols were used as alkylating agents (in other words, alcohols were incorporated into product structures).^{24,25} Although their studies promised further potential of SPs for useful organic transformations of alcohols, the synthetic scope of organic substrates in light of both reactivity and selectivity has yet to be demonstrated. In most of the relevant contributions, alcohols have merely been used as sacrificial electron donors to promote desired reductive transformations, such as hydrogenation of unsaturated bonds, and dehalogenation or reductive coupling of organic halides.^{26,27} To open up the new potential of alcohols as carbon resources in photocatalysis, we have been focused on the synthetically useful transformations of alcohols by SPs beyond the mere use of alcohols as sacrificial agents.

In this account, we overview our research on “metal-loaded semiconductor-photocatalysis of alcohols for useful and practical organic synthesis” (Figure 1). Our related publications can be

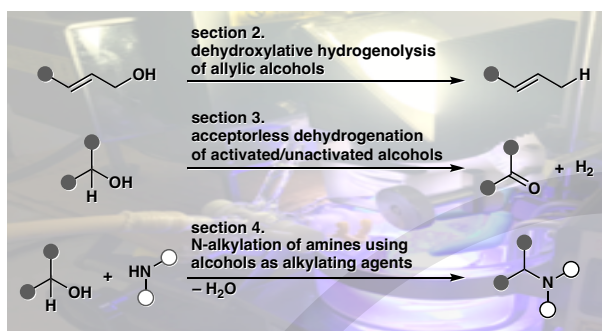


Figure 1 Overview of our contributions on SPs-induced alcohol transformations.

categorized into different reaction types; dehydroxylative hydrogenolysis of allylic alcohols (section 2), acceptorless dehydrogenation of activated/unactivated alcohols (section 3), N-alkylation of amines using alcohols as alkylating agents (section 4). Lastly, we summarize our past achievements and also briefly introduce the next direction of our research: SPs-induced C-C bond formation reactions through β -scission of tertiary (3°) alcohols (section 5). We hope that this account helps the readers understand the gist of the concept behind the semiconductor photocatalysis, use our synthetic methods for practical applications, and also spur further innovation in semiconductor photocatalysis for selective organic synthesis.

2. Dehydroxylative hydrogenolysis of allylic alcohols

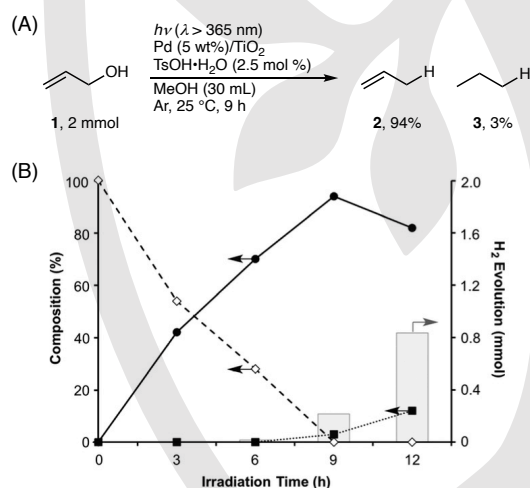


Figure 2 (A) Pd/TiO₂-Photocatalyzed dehydroxylative hydrogenolysis of allyl alcohol (**1**) giving propylene (**2**) along with a tiny amount of propane (**3**) under near-UV-visible light irradiation. (B) Composition-time profile of **1** (◇), **2** (●), and **3** (■), and amounts of observed H₂ (grey bar) versus varied irradiation times. Reproduced from ref 28. Copyright 2014 The Royal Society of Chemistry.

In the early 2010s, we started studying the reductive transformation of allylic alcohols to alkenes, so-called dehydroxylative hydrogenolysis, using Pd/TiO₂ under near-UV-visible light irradiation (Xe lamp, $\lambda > 365$ nm) with a catalytic amount of an acid additive.^{28–30} In general, alcohols are likely to be oxidized by the $h\nu$ s of TiO₂.^{26,27} Allylic alcohols were seemingly

reduced by the e^- s of TiO₂ when methanol was used as a solvent, which would function as a dominant sacrificial electron and hydrogen atom donor.

Initially, we reported the Pd/TiO₂-photocatalyzed dehydroxylative hydrogenolysis of the simplest and biomass-derived allylic alcohol, allyl alcohol (**1**) to propylene (**2**), which is a useful industrial carbon resource for the production of plastics (polypropylene) and other high-value-added chemicals (Figure 2A).²⁸ One of the most attractive features of this system is the high selectivity to retain olefinic groups (Figure 2B). The desirable dehydroxylative hydrogenolysis of **1** to **2** proceeded exclusively against hydrogenation of the C=C double bond of **2** to give propane (**3**) and H₂ evolution while **1** remained in the reaction mixture within 9 h. The side reactions started to be observed after the complete consumption of **1** in 12 h. Since the hydrogenation of the $\pi_{C=C}$ bond should be thermodynamically and kinetically more favorable than the hydrogenolysis of the σ_{C-O} bond, the unexpected selectivity to give **2** seemed to be originated from a spatial separation between the $\pi_{C=C}$ bond and the Pd/TiO₂ surface, which is explained later in detail (Figure 3C).

In a similar photocatalytic system using Pd/TiO₂, a variety of allylic alcohols underwent dehydroxylative hydrogenolysis over olefin reduction.^{29,30} Cinnamyl alcohol (*E*-**4**) selectively gave *trans*- β -methyl styrene (*E*-**5**). *cis*- β -Methyl styrene (*Z*-**5**), 3-phenyl-1-propene (**6**) and propylbenzene (**7**), which could be formed via isomerization or over-reduction, were hardly observed as side products (Figure 3A). The dehydroxylative hydrogenolysis of other allylic alcohols proceeded efficiently and selectively, in which a C=C double bond incorporated separately from the allylic position in carbon chains remained unreacted (Figure 3B). The regioselectivity of the reduced carbon was controlled and thus predictable, where a sterically less congested carbon is preferred for accepting a hydrogen atom. A β -substituted allylic alcohol **8** gave an internal alkene product **9** selectively against a terminal alkene (**10**). Geraniol (**11**) with an *E*-configuration and nerol (**14**) with a *Z*-configuration were converted stereospecifically into internal alkenes *E*-**12** and *Z*-**12**, respectively. When γ -substituted allylic alcohols were used as starting materials, hydrogen atoms were preferentially introduced to the less hindered α -position of the allylic alcohols **11** and **14**, and the γ -carbon of **15**. Ultimately, from **11**, **14**, and **15**, internal alkenes *E*-**12** and *Z*-**12** were obtained selectively against the terminal alkene (**13**). The C=C double bonds of the allylic alcohols and those distal from the reduced carbon are essentially not reduced and tolerated the Pd/TiO₂-photocatalytic conditions (**11**, **14**, and **15**). Additionally, the synthetic shortcut to a natural product, (*S*)-(+)-lavandulol (**17**) from a non-symmetrical diol (**16**) was enabled through the selective dehydroxylative hydrogenolysis at the carbon of the allylic alcohol against the homoallylic alcohol moiety. A 2 mmol of allylic alcohols underwent the photocatalytic hydrogenolysis smoothly, and the Pd/TiO₂ photocatalyst could be reused for five runs without significant loss of the catalytic activity. These results indicate that the Pd/TiO₂ photocatalyst is robust and the present method has a great potential for larger scale reactions.

We proposed one of the possible mechanisms (Figure 3C): TiO₂ generates $2e^-$ and $2h^+$ upon its photoexcitation. Methanol

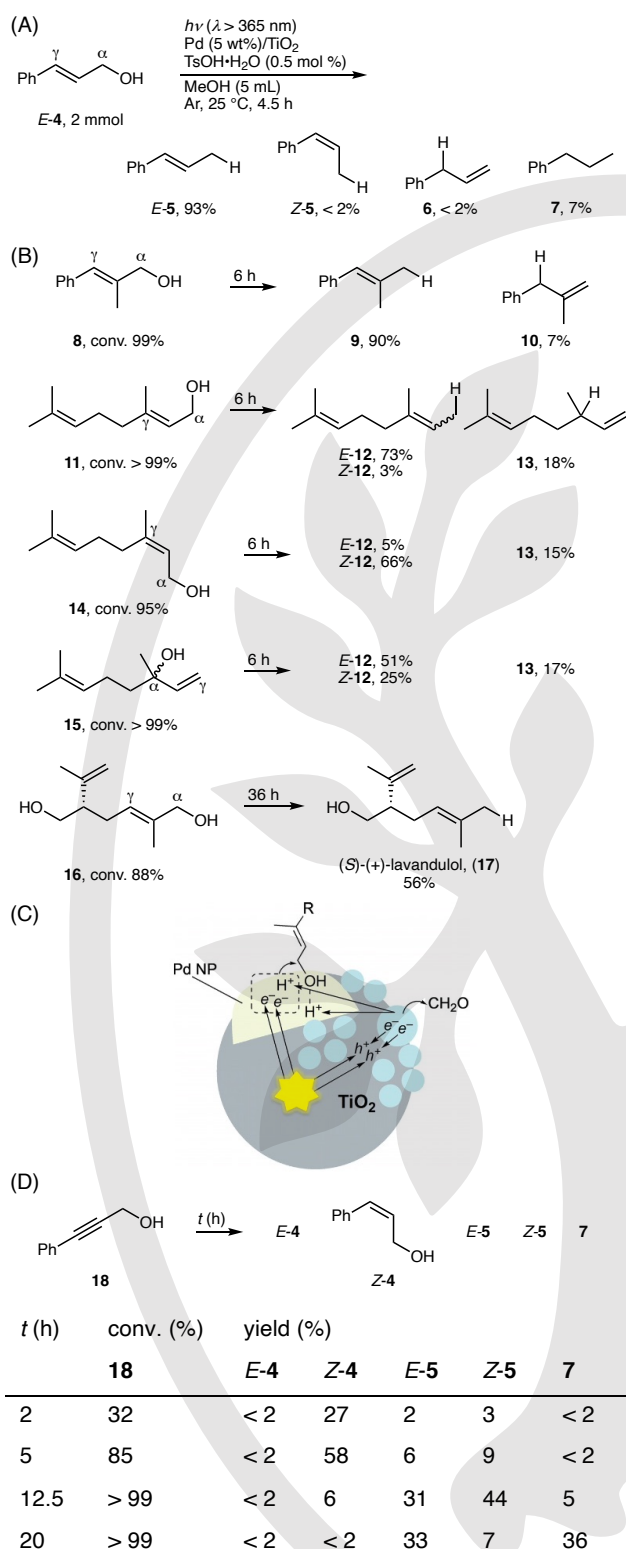


Figure 3 Pd/TiO₂-Photocatalyzed dehydroxylation of (A) cinnamic alcohol (**E-4**) and (B) other allylic alcohols under near-UV-visible light irradiation. (C) Proposed mechanism. A large circle in gray, a half circle in light green and small circles in light blue represent TiO₂, Pd NP and surface-adsorbed methanol, respectively. The acid additive would activate the OH groups of the allylic alcohols. (D) Time course of a reaction using a propargyl alcohol (**18**). Reproduced from ref 29. Copyright 2017 John Wiley & Sons, Inc.

undergoes two-electron oxidation by the $2h^+$ delivered from TiO₂, generating two protons and CH₂=O. One of the protons activates the OH group of the allylic alcohol by protonation. The other is reduced on a Pd nanoparticle (NP) by the $2e^-$ also delivered from TiO₂ to a formally-written hydride ($H^- = H^+ + 2e^-$) species. Nucleophilic substitution at the α - or γ -carbons of the activated allylic alcohol by the H^- species gives the corresponding alkene and H₂O. Allylic alcohols and methanol are likely to make a self-assembled alignment on the catalyst surface upon interacting with their OH groups, where the alkenyl carbon chains adopt upright structures over the solid surface so that the C=C double bonds could remain unreacted by their spatial separation from the catalytic surface.

To further probe the applicability of this system, 3-phenylprop-2-yn-1-ol (**18**) containing a C≡C triple bond was tested (Figure 3D). At the early stage of the reaction within 5 h, the C≡C triple bond was selectively hydrogenated to an allylic alcohol containing a C=C double bond with a Z-configuration (**Z-4**). In 12.5 h, the dehydroxylation hydrogenolysis of **Z-4** took place, giving alkenes (**Z-5** and **E-5**) predominantly against hydrogenation of the C=C double bonds. After the complete consumption of the unsaturated alcohols **18** and **Z-4**, **Z-5** and **E-5** were further reduced to **7** (20 h). In other words, the Pd/TiO₂-photocatalyzed hydrogenation of the C≡C triple bond did occur but that of the C=C double bonds was inhibited in the presence of the propargylic and/or allylic alcohols, where these alcohols would negatively affect the inherent hydrogenation ability of Pd/TiO₂, as Pb(OAc)₂, CaCO₃, and quinoline poisoned similarly the catalytic surface of the Lindlar's heterogeneous Pd catalyst.

We developed the chemoselective dehydroxylation hydrogenolysis of allylic alcohols with promising scalability, which could provide industrially important compounds and naturally-occurring products. Other researchers reported similar systems using Pd/SPs for dehydroxylation hydrogenolysis of benzylic alcohols, where the transformation of allylic alcohols was not tested.^{31–33}

3. Acceptorless dehydrogenation of activated/unactivated alcohols

In interdisciplinary collaboration research between Kudo's inorganic/photo-chemistry (Tokyo University of Science) and our synthetic organic chemistry, we learned basic skills to prepare Kudo's rhodium-doped and ruthenium-loaded strontium titanate (Ru/SrTiO₃:Rh) originally designed for photocatalytic water splitting and tried to apply the method to useful organic synthesis. Finally, we enabled redox-selective conversion of primary (1°) and secondary (2°) alcohols to aldehydes and ketones, respectively, along with H₂ evolution in a stoichiometric molar ratio of 1:1. The acceptorless dehydrogenation was promoted by Kudo's Ru/SrTiO₃:Rh catalyst in a biphasic system of toluene and aqueous H₃PO₄ under visible light irradiation (Xe lamp, $\lambda > 420$ nm) (Figure 4A).^{34–36} The Ru/SrTiO₃:Rh powder was efficiently dispersed over the interface between the toluene–water biphasic layers (Figure 4A), where the hydrophilic hydroxy groups of the alcohols could approach the Ru/SrTiO₃:Rh surface while other hydrophobic functionalities could not. That might be why the over-oxidation of hydrophobic benzaldehydes to carboxylic acids was hardly

observed (**20a–20i**), and that reactive but hydrophobic bromo, acetyl, nitro, alkenyl, and alkynyl groups could survive in both photo-oxidative and photo-reductive conditions (**20c–20g**). Stereochemistry around a C=C double bond of an allylic substrate was preserved (**20i**). 2° Alcohols were converted into the corresponding ketones **20j** and **20k**.

In addition to the synthetic value mentioned above, energetically noticeable benefits should be stressed here. The transformation of 1° or 2° alcohols to aldehydes or ketones with H₂ evolution was found to be thermodynamically uphill (endergonic, Gibbs free energy changes: $\Delta G^\circ > 0$) according to our DFT calculations (Figure 4A). Moreover, the Ru/SrTiO₃:Rh-promoted alcohol dehydrogenation could be run under sunlight irradiation (Figure 4B). These results suggest that solar energy could be converted into chemical energy through organic transformation. This study provided us the inspiration for our ongoing project “artificial photosynthesis directing toward organic synthesis” using water as the key reagent.³⁷

While the success in Ru/SrTiO₃:Rh-photocatalysis convinced us of the versatility of SPs in organic synthesis, the dehydrogenation protocol still had several drawbacks: (i) A simple 1° aliphatic alcohol **19l** was transformed into the corresponding aldehyde in relatively low yield (**20l**, Figure 4C). This could partially be attributed to the over-oxidation of **20l** to the carboxylic acid **21l**. (ii) The apparent quantum efficiency at the wavelength of 420 nm was determined to be < 1%. (iii) UV light irradiation aiming at a further acceleration of the reaction resulted in over-oxidation to a carboxylic acid **21a** and other side

reactions that afforded **22a** and **23a** (Figure 4D). (iv) The scalability was unclear.

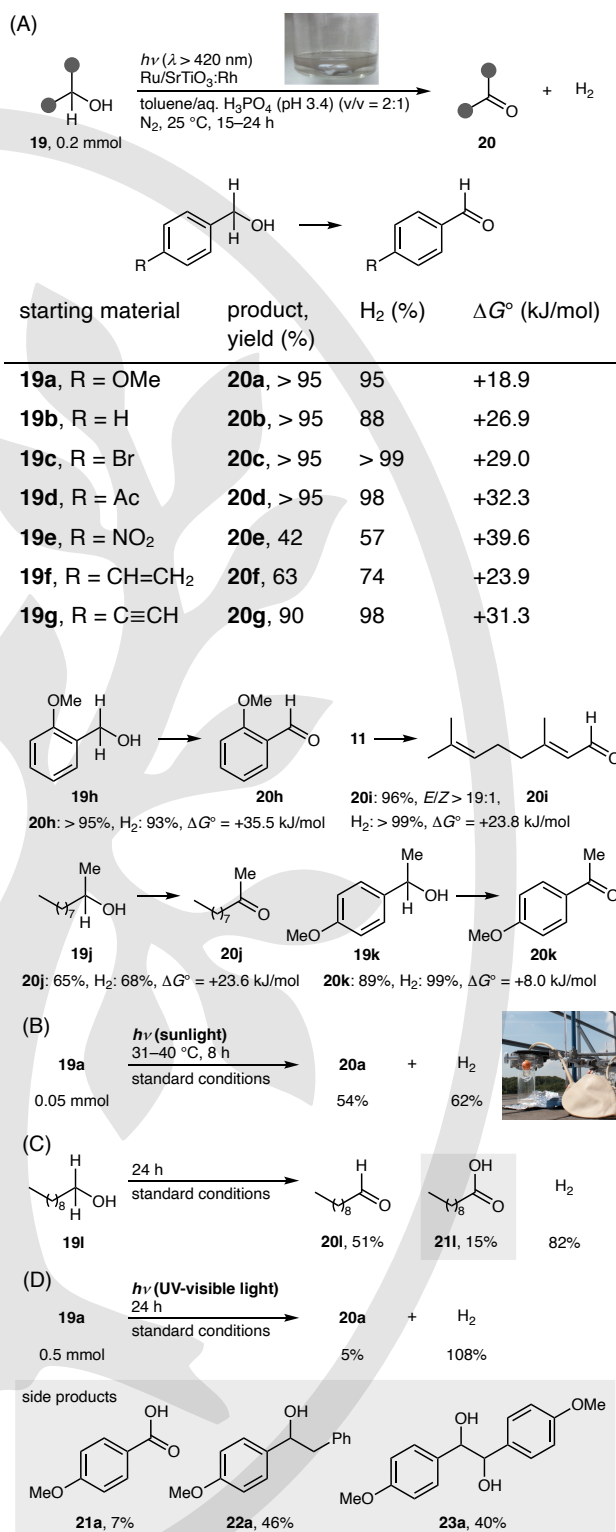


Figure 4 (A) Ru/SrTiO₃:Rh-Photocatalyzed acceptorless dehydrogenation of activated/unactivated alcohols under visible light irradiation, and a picture of the reaction system on the roof. Yields of H₂ were with respect to **19**. ΔG° values were calculated by DFT (M06-2X/6-311++G**) (B) A sunlight-induced reaction (C) A reaction using a 1° aliphatic alcohol (**19l**). (D) An unsuccessful reaction under UV-visible light irradiation. Reproduced from ref 36. Copyright 2013 John Wiley & Sons, Inc.

Figure 5 (A) M/TiO₂-Photocatalyzed dehydrogenation of a 1° aliphatic alcohol (**19m**) under UV-visible light irradiation. Yields of H₂ were with respect to **19m**. (B) Substrate scope of the Au/TiO₂-photocatalyzed dehydrogenation of 1° aliphatic alcohols.

Therefore, we next sought to establish an efficient and scalable method for the acceptorless dehydrogenation of 1° aliphatic alcohols. After screening different M/TiO₂ photocatalysts, we found that the abovementioned drawbacks of Ru/SrTiO₃:Rh could be overcome by using Au/TiO₂ in ethyl acetate under UV-visible light irradiation (Xe lamp, λ = 300–470 nm) at 45 °C (Figure 5A).³⁸ A 2 mmol of 1° aliphatic alcohol was smoothly and cleanly transformed into the aldehyde (Figure 5B). The apparent quantum yield was 20% at a wavelength of 365 nm. Potentially reactive and/or bulky functionalities tolerated the Au/TiO₂-photocatalytic conditions reasonably (**20n–20p**).

While there are several other reports on the SPs-promoted acceptorless dehydrogenation of alcohols, the generality of alcohols, the chemoselectivity, and the scalability have rarely been discussed.^{39–41}

4. N-Alkylation of amines using alcohols as alkylating agents

The success in the alcohol dehydrogenation using Au/TiO₂ spurred our research on the synthesis of more useful and complex organic compounds. Inspired by the borrowing hydrogen methodology successful for N-alkylation of amines using homogeneous transition-metal catalysts,^{42,43} we envisioned that the transformation could also be induced through sequential three steps by M/TiO₂ (Figure 6): (i) *h*⁺-promoted dehydrogenation of a 1° or 2° alcohol to an aldehyde or a ketone on the TiO₂ surface; (ii) condensation of an amine and the formed carbonyl compound giving an imine or iminium ion intermediate; and (iii) (H⁺ + *ne*[−])-promoted hydrogenation of the intermediate on the loaded metal-NP cocatalyst to give an alkylated amine.

Over the last decade, we have developed several M/TiO₂-photocatalytic methods for the efficient and scalable N-alkylation of amines using alcohols as alkylating agents, which provides useful and complex organic molecules including compounds of pharmaceutical importance. The attractive features of our methods include mild reaction conditions (ambient temperature) and high atom economy (H₂O as the sole byproduct).

We mainly focused on the N-methylation of amines using methanol as a methylating agent because of the following three reasons: (i) Among N-alkylation of amines, N-methylation using methanol is one of the most demanded reactions from biology and pharmaceutical chemistry.⁴⁴ (ii) The use of methanol is challenging in the thermally activated and transition metal-

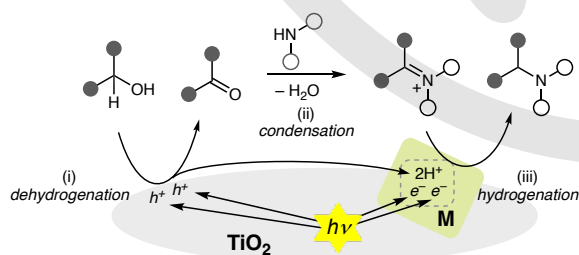


Figure 6 A schematic mechanism of M/TiO₂-photocatalyzed N-alkylation of amines using alcohols.

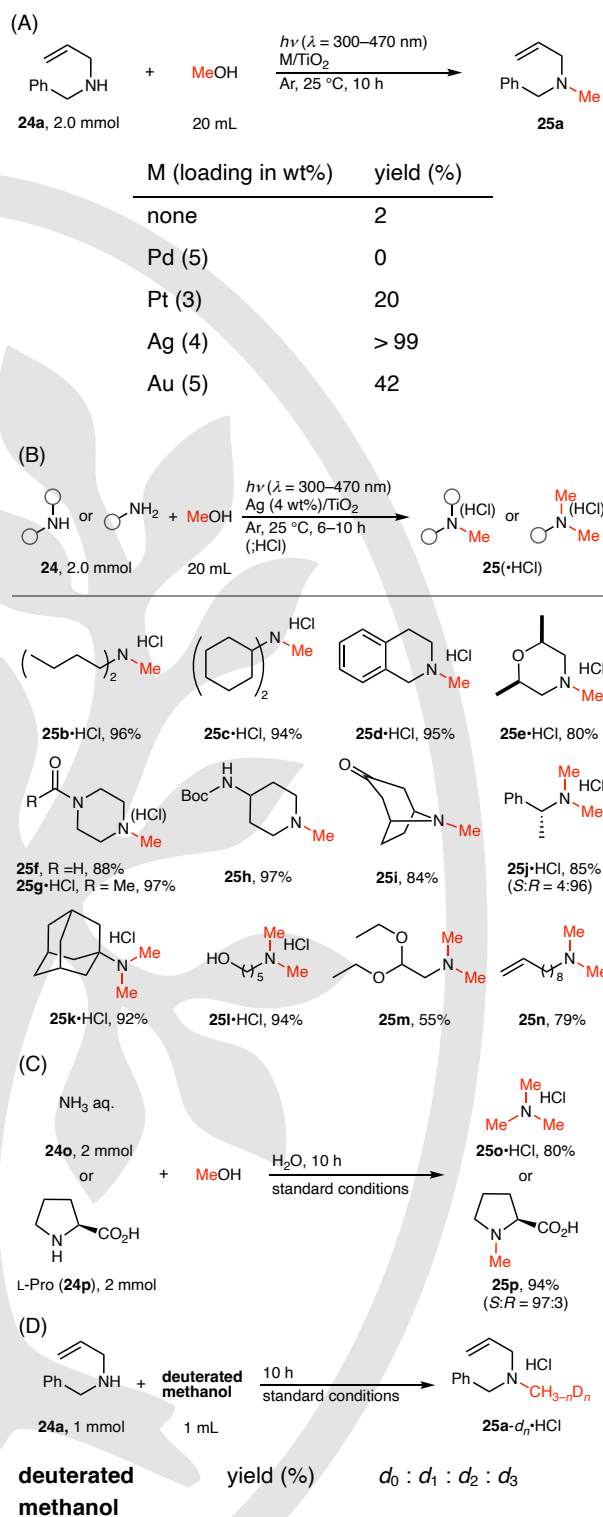


Figure 7 (A) M/TiO₂-Photocatalyzed N-methylation of *N*-allyl-*N*-benzyl amine (**24a**) using methanol under UV-visible light irradiation. (B) Substrate scope of the Ag/TiO₂-photocatalyzed N-methylation of amines. (C) N,N,N-Trimethylation of ammonia (**24o**) and N-monomethylation of L-Pro (**24p**) in a mixed solvent system of water and methanol (D) Controlled synthesis of deuterated *N*-methylamines. *n* = 1, 2, and 3.

catalyzed borrowing hydrogen methodology.^{42,43} (iii) We were aware that methanol would be reactive with the h^+ of TiO_2 according to our previous study using the Pd/TiO_2 -photocatalytic system^{28–30}.

After the screening of SPs including Au/TiO_2 and Pd/TiO_2 using *N*-allyl-*N*-benzyl amine (**24a**) as a model substrate, we unexpectedly found that Ag/TiO_2 allowed chemoselective, efficient, and scalable N-methylation of **24a** using methanol under UV-visible light irradiation (Xe lamp, $\lambda = 300\text{--}470\text{ nm}$) at room temperature (Figure 7A).⁴⁵ Gram-scale synthesis of **25a**•HCl was also successful (1.82 g, 92%). A series of 2° amines smoothly gave the corresponding 3° N-methylamines in good to excellent yields [**25b–25i**•HCl], Figure 7B]. This system was also effective for N,N-dimethylation of a variety of 1° amines [**25j–25n**•HCl]. Since the reactions proceeded cleanly, most of the formed 3° amines could be isolated as HCl salt precipitates after simple treatment with (an aqueous or an ether solution of) hydrochloric acid without column chromatography. A wide range of functional groups tolerated the photocatalytic conditions, such as allyl, benzyl, formyl, and *tert*-butoxycarbonyl (Boc) groups at nitrogen atoms, and also an alkenyl group and a ketone moiety. Note that selective N-methylation of amines containing these reactive functional groups is often difficult in transition-metal-catalysis under relatively harsh reaction conditions that frequently deteriorate them.^{42,43} Stereochemistry at a carbon α to a nitrogen atom was well preserved (**25j**•HCl). The Ag/TiO_2 -photocatalytic system could be extended to N-methylation of highly hydrophilic substrates such as aqueous ammonia and L-Pro in a water/methanol mixed solvent system, allowing the clean formation of trimethylamine (**25o**) and *N*-methyl-L-Pro (**25p**) (Figure 7C).

Reactions using CH_3OH , CH_3OD , CD_3OH , or CD_3OD selectively gave **25a-d**₀, **25a-d**₁, **25a-d**₂, or **25a-d**₃, respectively (Figures 7A and 7D). These results indicate that two hydrogen atoms of the methyl group of the product originate from the methyl group of methanol and that the rest of the hydrogen atom is from the protic hydroxy group of methanol.

Later on, we found that Pd/TiO_2 promoted N-methylation of furfuryl amine (**24q**) more smoothly in methanol than Ag/TiO_2 (Figure 8A).⁴⁶ Other N-methylated amines bearing heterocycle structural motifs (indole, imidazole, pyridine, pyrimidine, thiophene, *etc.*) could also be synthesized efficiently by the Pd/TiO_2 photocatalytic system (**25r–25y**, Figure 8B). The N-methylation using methanol, N-ethylation using ethanol, and N-deuterioalkylation using deuterated alcohols were also applied to the synthesis of pharmaceutical compounds such as loxapine (**25z**), (deuterio)venlafaxine [**25aa** (sub-gram scale) and **25aa-d**₆], (deuterio)butenafine (**25ab** and **25ab-d**₃), octacaine (**25ac**), and alverine-d₅ (**25ad-d**₅). It should be noted that adifenine could be synthesized through a cascade involving *in situ* Cbz-deprotection followed by the N,N-diethylation with ethanol (**25ae**). Furthermore, late-stage multiple N-methylation of colistin (a cationic lipopeptide antibiotic used for the treatment of gram-negative bacterial infection) was successful, as suggested by LC/ESI-MS analysis. The N-alkylation protocol using alcohols can be coupled with Pd/TiO_2 -photocatalyzed self-condensation of 1° amines to 2° amines. An *in-situ* generated 2° amine from 3-phenylpropane amine could be ethylated with ethanol over Pd/TiO_2 under light irradiation leading to **25ad**.⁴⁷

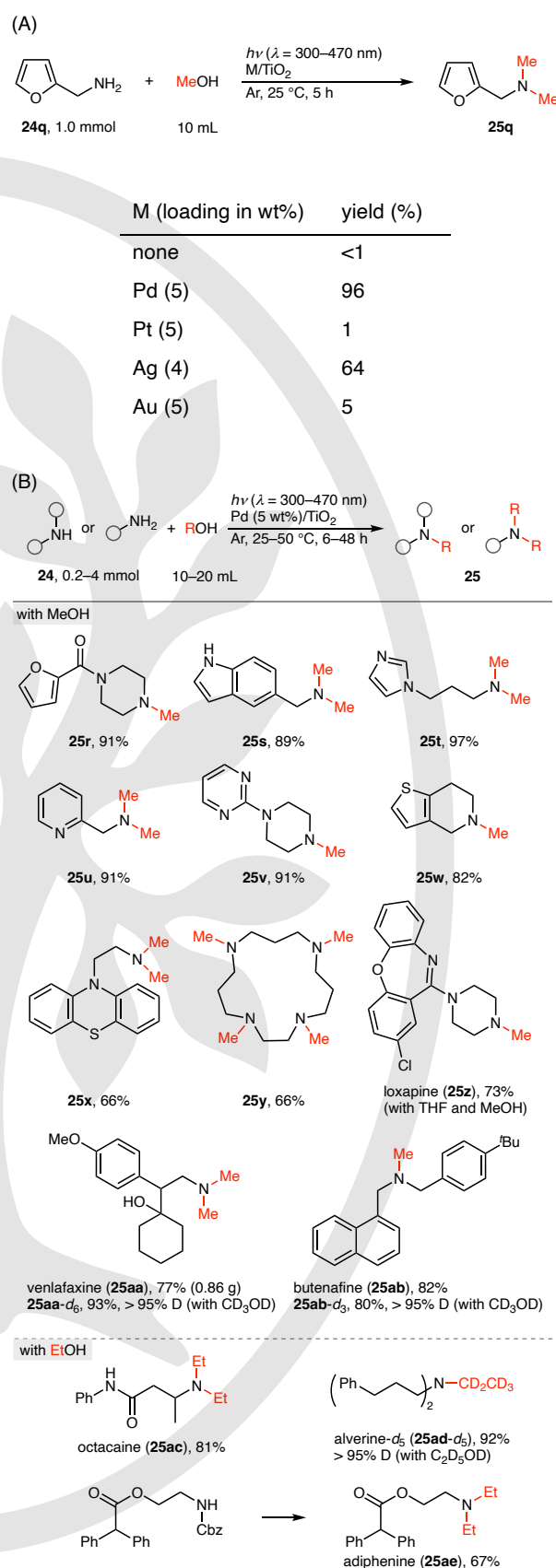


Figure 8 (A) M/TiO_2 -Photocatalyzed N-methylation of furfuryl amine (**24q**) using methanol under UV-visible light irradiation. (B) Substrate scope of the Pd/TiO_2 -photocatalyzed N-(deuterio)alkylation of heterocycle-containing amines and pharmaceutical intermediates.

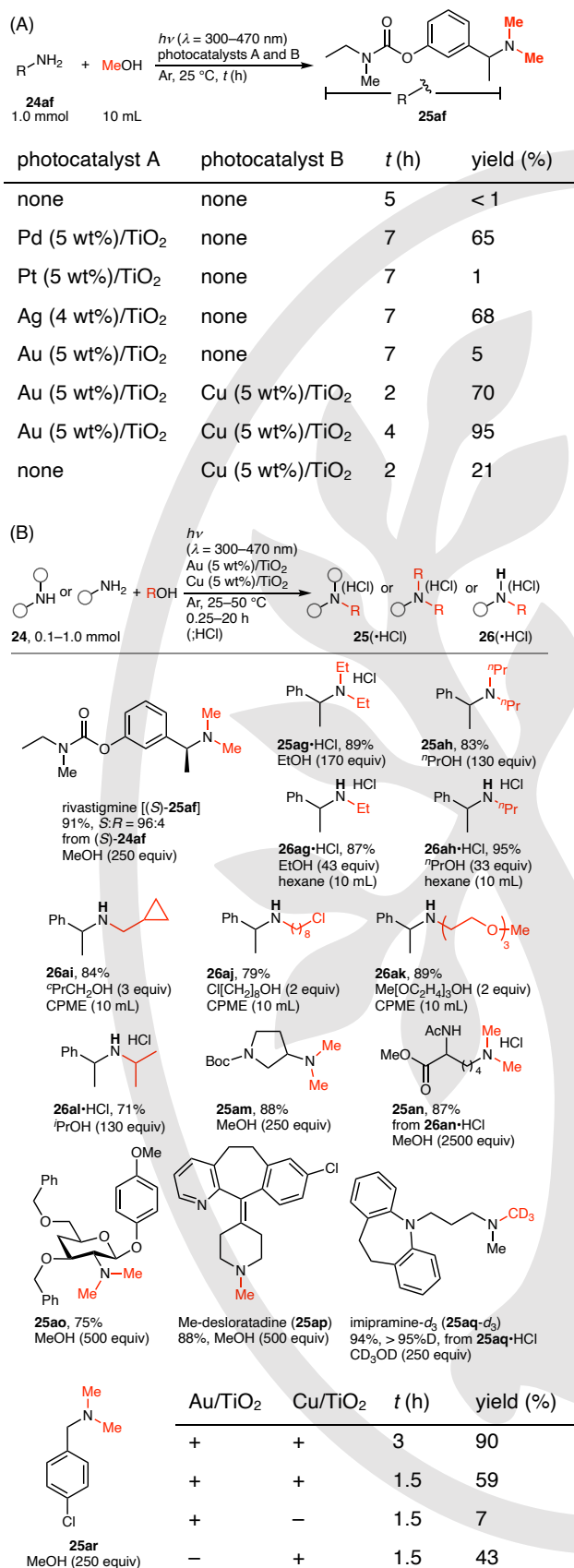


Figure 9 (A) M/TiO₂-Photocatalyzed N-methylation of **24af** using methanol under UV-visible light irradiation. (B) Substrate scope of the rapid N-(deuterio)alkylation of amines in a mixed photocatalytic system of Au/TiO₂ and Cu/TiO₂.

Although Au/TiO₂ showed the highest photocatalytic ability for dehydrogenation of 1° aliphatic alcohols among other M/TiO₂ tested (Figure 5),³⁸ Au/TiO₂ was not the first choice in the N-alkylation of several amines (Figures 7A, 8A, and 9A), since the hydrogenation of the imine or iminium ion intermediates, which is supposed to be the rate-determining step in the M/TiO₂ photocatalytic systems,^{33,48} would especially be slow with Au/TiO₂ (Figure 6). Therefore, we tested several combinations of Au/TiO₂ and other M/TiO₂ to accelerate overall orthogonal steps all the way to N-alkylation (Figure 9A). As a consequence, we established a rapid N-alkylation method using a combination of Au/TiO₂ and Cu/TiO₂, compared with individual performances of Ag/TiO₂, Pd/TiO₂, Au/TiO₂, and Cu/TiO₂.⁴⁹ A wide variety of N-alkylamines could be efficiently synthesized by the Au/TiO₂–Cu/TiO₂ mixed photocatalytic system (Figure 9B). The synergistic effect of the two photocatalysts was undoubtedly confirmed by control experiments using each photocatalyst separately used for the synthesis of different N,N-dimethylamines including **25ar**. N,N-diethylation and N,N-dipropylation of a 1° amine were also successful when ethanol and 1-propanol were used as solvents (**25ag** and **25ah**). Interestingly, monoalkylation was enabled when relatively small amounts of alcohols were used in organic solvents (**26ag–26al**). The monoalkylated products could subsequently undergo N-alkylation using different alcohols to give non-symmetrical 3° alkyl amines. The Au/TiO₂–Cu/TiO₂ mixed photocatalytic system accommodated the presence of pharmaceutically important functionalities (**25am–25ao**). Several pharmaceutical compounds could be synthesized by the methylation using methanol, including rivastigmine [(S)-**25af**] and Me-desloratadine (**25ap**). When CD₃OD was used, N-deuteriomethylation occurred smoothly, providing deuterated pharmaceutical molecules such as imipramine-*d*₃ (**25aq-*d*₃**) and **25af-*d*₆** (1.0 g, 91%). The heterogeneous SPs could easily be recovered after the reaction and reused for 10 cycles with a trivial decrease in reactivity. The scanning transmission electron microscope-energy dispersive spectroscopy (STEM-EDS) analysis of a recovered powder after a photocatalytic reaction indicated the formation of an alloy of heterobimetallic NPs of Cu and Au deployed on the TiO₂ surface.

As the culmination of our continuous study of this subject, we recently reported an M/TiO₂-photocatalyzed N-methylation protocol using methanol, which was further applied to twenty different α-amino acid motifs found in the protein in the human body. (M = Ag or Pd) (Figure 10).⁵⁰ Without protection, Gly, L-Ala, L-Val, L-Leu, L-Phe, L-Met, L-Ile, L-Arg, and GlyGly were smoothly N,N-dimethylated at the α-NH₂ group (**25as–25ay**, **25bb**, and **25bc**). A 1 mmol-scale reaction of L-Val was also successful (**25au**, 92%). N-monomethylation of L-Pro (**25p**) and N,N,N',N'-tetramethylation of L-Lys (**25ba**) proceeded well. In the case of L-His·HCl·H₂O, the imidazole moiety might be protonated, and the N,N-dimethylation at the α-NH₂ group proceeded efficiently and selectively (**25az·HCl**). When appropriately protected at reactive functionalities including OH and NH₂ groups of the side chains, L-Ser, L-Thr, L-Tyr, L-Asp·HCl, L-Glu·HCl, L-Asn, and L-Gln were converted into the corresponding α-N-methylated products in moderate to good yields (**25bd–25bf**, **25bh–25bk**). In accordance with our previous study,⁴⁶ O-Me-L-Trp containing a heterocycle structure underwent N,N-dimethylation at the α-NH₂ in the presence of Pd/TiO₂, which is more reactive for the

reduction of the intermediary imine and iminium ion than Ag/TiO₂ (**25bg**, see also Figure 6). In contrast, a reaction of *O*-Me-L-Trp•HCl using Ag/TiO₂ gave a six-membered ring product which would be formed by an intramolecular reaction of the

nucleophilic indole ring with protonated, electrophilic iminium ion intermediate (**25bg'**). L-Cys underwent a similar cyclization reaction through the intramolecular nucleophilic attack of the SH group (**25bl'**).

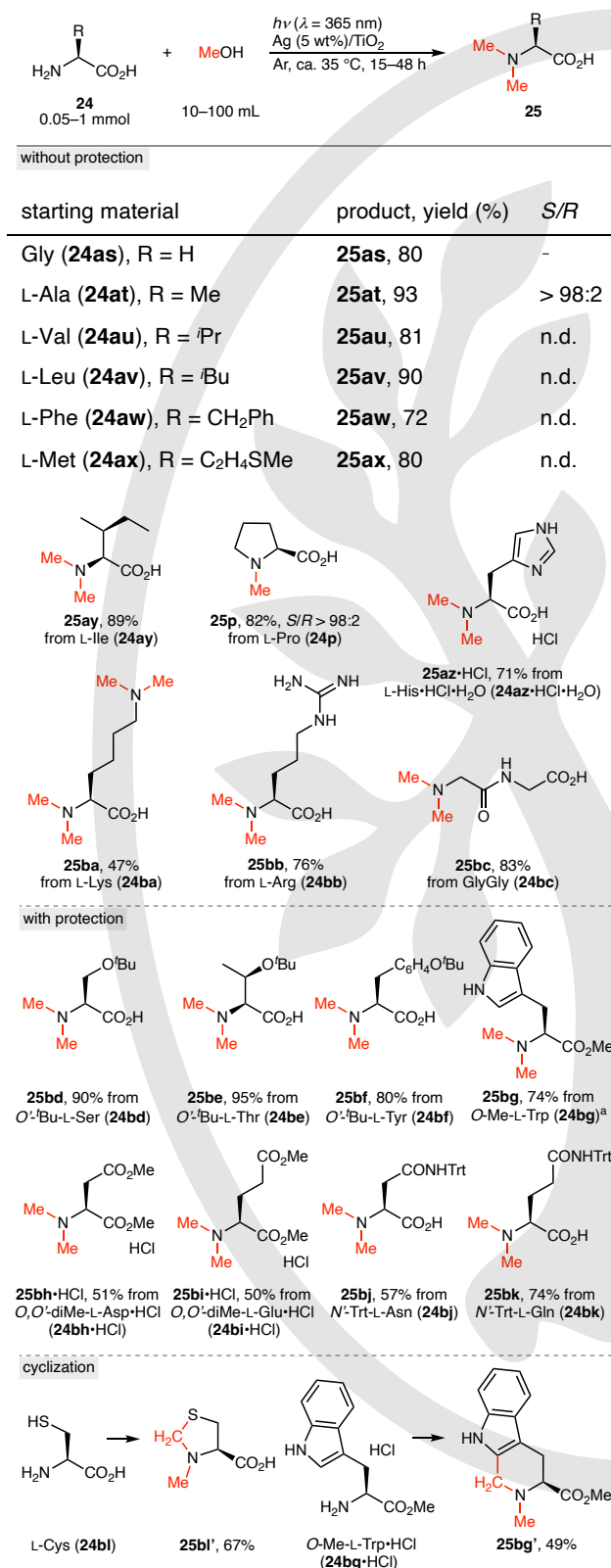


Figure 10 Ag/TiO₂-Photocatalyzed N-methylation of α-amino acid motifs using methanol under near-UV light irradiation. n.d. = not determined. ^aPd/TiO₂ was used instead of Ag/TiO₂

Most of the N-methylated α-amino acid products were isolated through simple filtration and concentration procedures without tedious purification processes such as an aqueous workup and column chromatography since the reactions cleanly proceeded, generating H₂O as the sole byproduct (few exceptions: **25bg**, **25bg'**, **25bj**, and **25bk**). The retention of the chirality was confirmed by polarimetric analysis, chiral gas chromatography-mass spectrometry analysis, and/or nuclear magnetic resonance spectroscopy.

The present protocol with the above-mentioned advantages would provide the future opportunity to synthesize biochemically important compounds. For instance, proteins containing N-methylated α-amino acid residues have great potential for biochemical application in proteomics⁵¹ and epigenetics.⁵² The structures of **25au**, **25av**, **25aw**, **25ay**, and **25bg** are found in naturally occurring compounds with potent bioactivity. **25bl'** has an *N*-methyl *N*,*S*-acetal structure available in the Kent ligation.⁵³

Throughout our continuous work on the M/TiO₂-photocatalyzed N-alkylation of amines using alcohols as alkylating agents, we have enabled a scalable synthesis of many complex molecules including pharmaceuticals by well-elaborated catalytic systems. Compared with other related works,^{33,54–57} we believe that our longstanding contribution to synthetic photocatalysis on the surfaces of SPs underpins the rethinking and a new horizon of selective organic synthesis and scalable production of fine- and platform chemicals.

5. Summary and outlook

For more than a decade, we have developed semiconductor photocatalysis utilizing methanol and 1°/2° alcohols for useful organic synthesis beyond the simple use of alcohols as sacrificial proton/electron donors (sections 2–4, Figures 11). In addition, Arisawa and some of the authors demonstrated that Pt/TiO₂ can promote the self-condensation of benzylic alcohols to give dibenzylic ethers under visible light irradiation.⁵⁸ Throughout our continuous study of this chemistry, we are now convinced that semiconductor photocatalysis should have a greater potential for making further innovations in several untapped organic transformations of alcohols.

To step forward, we are now interested in another reaction channel of alcohols on the TiO₂ photocatalytic surface: 3° alcohols undergo β-scission after being adsorbed on the TiO₂ surface, giving carbon-centered radicals and ketones, both of which would also be adsorbed and stabilized on the surface (Figures 11 and 12).⁵⁹ Although this adsorptive interaction was

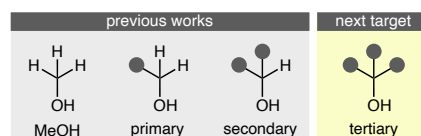
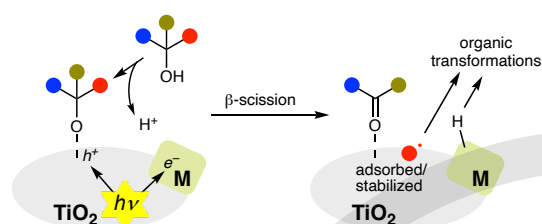


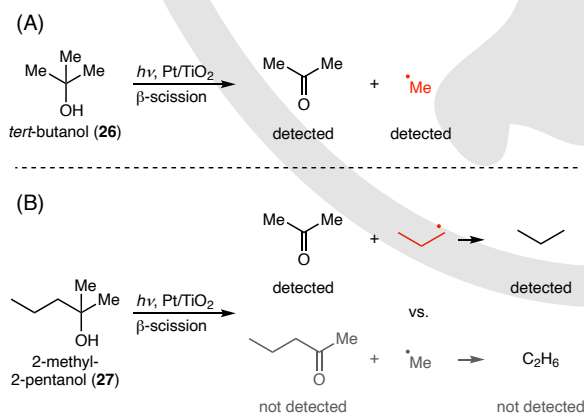
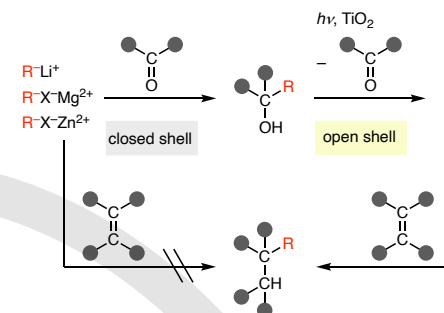
Figure 11 Summary and outlook.

Figure 12 M/TiO₂-Photocatalyzed β -scission of 3° alcohols.

experimentally confirmed by detecting a carbon-centered radical itself or products/intermediates derived from the carbon-centered radical, together with ketone detection by the mass-spectrometric analysis,^{59,60} it has not been extended to useful organic synthesis. We consider that this photoinduced β -scission is attractive from the following three aspects: (i) It would expand the synthetic utility of 3° alcohols as limiting reagents in organic synthesis; (ii) Judicious choice of symmetrical/non-symmetrical 3° alcohols would enable the selective formation of targeted carbon-centered radicals (Figure 13); and (iii) Organometallic reagents (R-Ms), which have been used as conventional two-electron nucleophiles, would be available as precursors of carbon-centered radicals (Figure 14).

(i) Considering that the photocatalytic β -scission of 3° alcohols on the TiO₂ surface is initiated by their adsorption, we could assume that the alcohols can be used as limiting reagents for C–C bond formation, as carboxylic acids undergo photocatalytic decarboxylative carbon-centered radical formation upon adsorption on the TiO₂ surface, followed by C–C bond formation.^{17,61}

(ii) The β -scission of 3° alcohols on the photo-irradiated TiO₂ surface can provide unstable carbon-centered radicals which are otherwise difficult to be generated. For instance, Heiz and co-workers revealed that methyl radical could be generated from symmetrical 3° alcohol, *tert*-butanol (**26**) using illuminated TiO₂ (Figure 13A).⁶⁰ The methyl radical is useful for the homologation of a carbon chain of synthetic importance.^{44,62} They also reported the exclusive formation of propyl radical against methyl radical from non-symmetrical 3° alcohol, 2-methyl-2-pentanol (**27**, Figure 13B).⁵⁹ The selectivity as to which alkyl radical (carbon-centered radical) would be favorably generated is affected by both thermodynamic and kinetic parameters: by the degree of

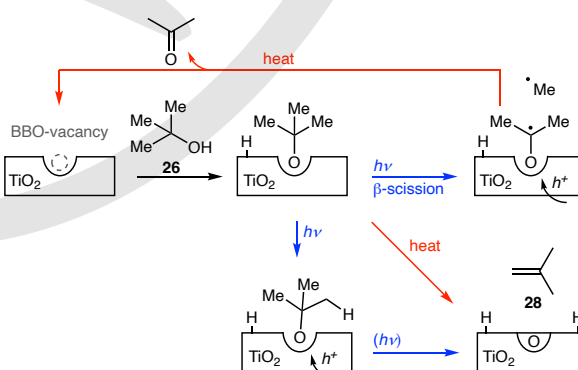
Figure 13 (A) Pt/TiO₂-photocatalyzed β -scission of *tert*-butanol (**26**), and (b) 2-methyl-2-pentanol (**27**).Figure 14 Switching from closed shell organometallic species to open shell carbon-centered radicals through the β -scission of the 3° alcohols on the TiO₂ photocatalytic surface. X = halogen

stabilization of the alkyl radical and the ketone by-product on the surface; and also by how small the activation energy of the transition state where the carbon chain to be released from the 3° alcohol pre-interacts with the surface.⁵⁹ Deep consideration of the thermodynamics and kinetics may enable the selective formation of the targeted carbon-centered radical.

(iii) Many R-Ms are unable to undergo addition reactions to C=C double bonds (Figure 14). In contrast, they can react smoothly with electrophilic C=O double bonds of ketones to give 3° alcohols. The β -scission of the 3° alcohols on the TiO₂ photocatalytic surface can release carbon-centered radicals (R•), which can undergo radical addition to the C=C double bonds. In other words, the TiO₂ photocatalytic surface would provide a platform for switching from closed-shell organometallic species (two-electron species) to open-shell carbon-centered radicals (one-electron species) through the formation of 3° alcohols.

Based on the wisdom obtained by our experiments and a plausible mechanism proposed by Heiz and co-workers (Figure 15),⁶⁰ we expect that critical parameters for applying the β -scission to useful organic synthesis may be (a) concentrations of bridge-bond oxygen (BBO)-vacancy on the TiO₂ surface, (b) reaction temperatures during photo-irradiation, (c) loaded metal-NP cocatalysts on the TiO₂ surface, and (d) coverage extents of H₂O molecules on the TiO₂ surface.

(a) BBO-vacancy is one of the most common defects of TiO₂, at which 3° alcohols undergo dissociative adsorption so that the 3° alkoxy groups and the hydrogen atom are separately deployed on TiO₂ (Figure 15). The concentration of BBO-vacancy of TiO₂ is relevant to the photocatalytic viability to promote the β -scission.⁶⁰ However, it is known that thermally and

Figure 15 Reactions of *tert*-butanol (**26**) on the TiO₂ surface.

photocatalytically induced dehydration of **26** giving isobutene (**28**) is also promoted at the BBO-vacancy.^{60,63} Therefore, a proper concentration of BBO-vacancy on the TiO₂ surface would be important for efficient and selective β -scission. Altering a way to calcinate TiO₂ is the most reliable method for controlling the concentration of BBO-vacancy.⁶⁴

(b) After the β -scission of 3° alcohols, residual ketones at the BBO-vacancy have a detrimental influence on the photocatalytic ability of TiO₂ (Figure 15).⁶⁰ Reaction temperatures are critical for the thermal desorption of the ketones from the BBO-vacancy. However, it is known that the dehydration of **26** is promoted at high reaction temperatures.⁶⁰ Therefore, an appropriate reaction temperature would enable efficient and selective β -scission.

(c) We have frequently observed the positive effects of loaded metal-NP cocatalysts on the photocatalytic ability in organic reactions (sections 2–4). According to the literature, loaded metal-NP cocatalysts can promote organic transformations by stabilizing organic radical species and/or by activating organic substrates.^{65,66} Therefore, metal-loading on TiO₂ is supposed to be a promising approach to promote selective β -scission.

(d) H₂O molecules affect the adsorption of alcohols and ketones on the TiO₂ surface.^{67,68} Sugimoto and co-workers recently reported that methyl radical would be stabilized on an SP surface, which would also be affected by H₂O molecules adsorbed on the surface, based on their theoretical calculation.⁶⁹ Thus water contents of the reaction mixture should be carefully optimized³⁷ for efficient and selective β -scission.

Studies of C–C bond formation reactions through the β -scission of 3° alcohols on the TiO₂-photocatalytic surface are now under scrutiny in our group by taking into account the abovementioned critical parameters. We envision unique transformations of 3° alcohols through the selective formation and transfer of a carbon-centered radical out of the three alternatives (three different substituents, such as alkyl, aryl, and alkynyl groups, bound to the carbon α to the hydroxy group of non-symmetrical 3° alcohols). The selectivity in the carbon group transfer in the heterogeneous TiO₂-photocatalytic system involving several radical species (Figure 15) should be different from that in the homogeneous catalytic aluminum system to transfer “two-electron” alkynyl groups of propargyl alcohols developed by Ooi and Maruoka.^{70,71} Additionally, this work would provide useful information on the stability and reactivity of the carbon-centered radicals on the photocatalytic surface for developing otherwise unexplored organic reactions under semiconductor photocatalysis.

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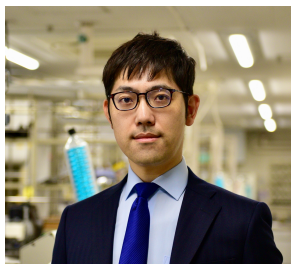
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Biosketches

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Hiroshi Naka is currently Associate Professor at Kyoto University. His research group specializes in sustainable catalysis and material design, with an emphasis on the development of deuteration reactions and their applications in organic chemistry. He obtained his B.S. (2003) and M.S. (2005) from the University of Tokyo. He received his Ph.D. (2008) from Nagoya University. His Ph.D. thesis focused on developing chemoselective aluminate bases under the supervision of Prof. Masanobu Uchiyama. As a Ph.D. candidate, he was also a JSPS research fellow at the University of Tokyo in 2005–2006. Hiroshi was a Research Associate in the laboratory of Prof. Yoshinori Kondo at Tohoku University (2006–2008). From 2008–2020 he was an Assistant Professor in the laboratory of Prof. Ryoji Noyori at Nagoya University, where he developed transition metal catalysis for selective hydration and heterogeneous photocatalysis for alcohol transformations in collaboration with Prof. Ryoji Noyori and Prof. Susumu Saito. Since 2020, he has been at the Graduate School of Pharmaceutical Science, Kyoto University. From 2023 he also serves as the director of the Deuterium Science Research Unit at Center for the Promotion of Interdisciplinary Education and Research, Kyoto University.



Susumu Saito, born in 1969 at Okayama, Japan, obtained his doctoral degree of Engineering (1998) from Nagoya University (NU). He attended Prof. E. Jacobsen's group at Harvard, USA, as Visiting Researcher (1994). His first academic position was Assistant Professor at Graduate School of Engineering, NU (1995), and he became Associate Professor of Institute for Advanced Research (IAR), NU (2002), and Full Professor and IAR Fellow, NU since 2015. He is an Asian Core Program Lecturer awarded from China (2009) and from Taiwan (2009), a recipient of Nagase Research Award (2018) and SSOCJ Tosoh Award for Environment and Energy (2019); PI of CREST project, JST since 2022. Saito's current interest is broad in organic chemistry/catalysis and one is focusing on the development of new concepts and catalytic methodology for organic synthesis using alcohols, carboxylic acid derivatives, CO₂, H₂, and H₂O as key ingredients under thermal, light, electric, and chemical energy. Pursuing catalyses include hydrogenation of inert carbonyl compounds such as carboxylic acids and unactivated amides; chemical upcycling of polymers; dehydrative C–C, C–N, C–O coupling, CO₂ transformation, artificial photosynthesis directing toward organic synthesis (APOS).