Review

TiO₂ Photocatalyzed C–H Bond Transformation for C–C Coupling Reactions

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Abstract: Fulfilling the direct inert C–H bond functionalization of raw materials that are earth-abundant and commercially available for the synthesis of diverse targeted organic compounds is very desirable and its implementation would mean a great reduction of the synthetic steps required for substrate prefunctionalization such as halogenation, borylation, and metalation. Successful C–H bond functionalization mainly resorts to homogeneous transition-metal catalysis, albeit sometimes suffering from poor catalyst reusability, nontrivial separation, and severe biotoxicity. TiO₂ photocatalysis displays multifaceted advantages, such as strong oxidizing ability, high chemical stability and photostability, excellent reusability, and low biotoxicity. The chemical reactions started and delivered by TiO₂ photocatalysts are well known to be widely used in photocatalytic water-splitting, organic pollutant degradation, and dye-sensitized solar cells. Recently, TiO₂ photocatalysis has been demonstrated to possess the unanticipated ability to trigger the transformation of inert C–H bonds for C–C, C–N, C–O, and C–X bond formation under ultraviolet light, sunlight, and even visible-light irradiation at room temperature. A few important organic products, traditionally synthesized in harsh reaction conditions and with specially functionalized group substrates, are continuously reported to be realized by TiO₂ photocatalysis with simple starting materials under very mild conditions. This prominent advantage—the capability of utilizing cheap and readily available compounds for highly selective synthesis without prefunctionalized reactants such as organic halides, boronates, silanes, etc.—is attributed to the overwhelmingly powerful photo-induced hole reactivity of TiO₂ photocatalysis, which does not require an elevated reaction temperature as in conventional transition-metal catalysis. Such a reaction mechanism, under typically mild conditions, is apparently different from traditional transition-metal catalysis and beyond our insights into the driving forces that transform the C–H bond for C–C bond coupling reactions. This review gives a summary of the recent progress of TiO₂ photocatalytic C–H bond activation for C–C coupling reactions and discusses some model examples, especially under visible-light irradiation.

Keywords: TiO₂ photocatalysis; C–H bond functionalization; C–C bond coupling; free-radical addition; photo-induced electron transfer (PET)

1. Introduction

In the last decade, we have witnessed a surge of catalytic methodologies for direct functionalization of the inactive C–H bonds of organic molecules to serve different purposes [1–11].

Compared with traditional transition-metal catalyzed cross-coupling reactions commonly start with substrates with indispensable leaving groups such as Cl, Br, I, alkylsilyl, organometallic, and carboxylates [12–14], this approach provides multiple advantages for synthetic chemistry. The biggest advantage is that direct C–H bond functionalization can bypass the nontrivial prefunctionalization of substrates such as the preparation of toxic halogenated and hazardous organometallic compounds, greatly simplifying the workup procedure and expanding the range of available substrates. However, because of the well-known large bond dissociation energy and poor selectivity, currently most C–H bond direct functionalization strategies mainly rely on homogeneous transition-metal catalysis with the assistance of complex ligands or auxiliaries, and these strategies are often conducted in the presence of a stoichiometric amount of oxidants such as benzoquinone and the Ag (I) and Cu (II) salts [2,4,11]. Despite this, homogeneous transition-metal catalysis has garnered considerable success in C–H functionalization, though the nontrivial catalyst separation and difficulty in recycling are still inherent drawbacks. Moreover, trace amounts of transition-metal residues in purified products pose a challenge to the wide application of said products in the pharmaceutical industry [15]. From this perspective, heterogeneous catalytic C–H bond transformation reactions are more desirable [16]. Among these reactions, TiO₂ photocatalysis, which has been thoroughly explored since the 1970s for its use in water-splitting, dye-sensitized solar cells (DSSCs), and air and water decontamination [17–21], was considered to be a promising choice for use in inert C–H bond functionalization. On the one hand, due to its extremely high stability to light, oxidants, reductants, and strong acidic and basic conditions, TiO₂ photocatalysts can be reused and recycled many times using only a simple centrifugation procedure without any apparent loss of catalytic activity [22]. On the other hand, and maybe more importantly, the photogenerated holes on TiO₂ nanoparticles show such remarkably high activity in reaction to organic molecules that they can nearly activate any inert C–H, C–C, and C–X bond in term of its oxidizing potential. Figure 1 shows, in principle, the activation of organic substrates by TiO₂ photocatalysis. Under ultraviolet (UV) (wavelength $\lambda < 387$ nm, or ultraviolet component of sunlight) irradiation (Figure 1a), charge separation occurs on the TiO₂ nanoparticles, generating holes in the valence band and electrons in the conduction band. The TiO₂ photo-induced valence band hole (h^+_{vb}) possesses strong oxidativity ($E_{1/2} = 2.7$ V vs. normal hydrogen electrode), which drives the interfacial oxidative cleavage of the inert C–H bonds of organic molecules through the single electron transfer (SET), proton transfer (PT), or proton-coupled electron transfer (PCET) pathway [23–27]. In this case, unlike the pattern of homogenous transition-metal catalysis (TMC), only the substrates that are readily adsorbed while on the surface of TiO₂ nanocrystal catalyst can be functionalized, since photo-induced holes cannot diffuse into bulk solutions.

On the other hand, TiO₂ photo-induced conductive-band electrons (e^-_{cb}) have moderate reductivity ($E_{1/2} = -0.5$ V vs. normal hydrogen electrode), which is just suitable enough to utilize molecular dioxygen as an electron acceptor, yielding superoxide radical anion, a hydroperoxide radical, hydrogen peroxide, and H₂O successively to fulfill the catalytic cycle [28–36]. In this case, some of these reactive oxygen species (ROS) can directly react with organic substrates or indirectly react with the intermediates of the catalytic cycle. Direct reactions of ROS with substrates are generally not selective and render organic substrates as partial or complete mineralization. Therefore, for the purpose of organic synthesis, these side reactions originating from ROS should be avoided by controlling the reaction conditions. For example, in order to eliminate any side reactions of ROS, the reaction must require anaerobic conditions. In this case, conduction band electrons could transfer to some other electron acceptor, such as a proton, benzoquinone, Ag⁺, or an organic sacrificial agent with concomitant formation of an H₂, hydroquinone, or Ag precipitation, to finish the catalytic cycle. In some cases, the C–H bond cleavages are assisted by the direct oxygen atom transfer that is driven synergistically by the TiO₂ photogenerated h^+_{vb} and e^-_{cb} , which yields a stable target product [31,33]. Due to the very high redox potential of TiO₂ photo-induced h^+_{vb} and ROS, it still remains a challenge to tame these reactive oxidants for highly selective organic transformations [37–58]. Regarding this purpose, visible light is used as an irradiation source

that significantly increases the selectivity of the desired reactions via a sensitization mechanism different from the case in which the TiO_2 catalyst itself is directly excited as UV light (see Figure 1b). In this process, the primary nonselective oxidations of the photo-induced h^+_{vb} are totally excluded, and instead, the adsorbed or self-formed sensitizers (common organic dyes) absorb the visible light and become excited, injecting the electron into the TiO_2 conduction band and generating a dye radical cation that is left behind. The radical cations perform the C–H bond functionalization task. Recently, by consistently fine-tuning the TiO_2 photocatalysts, especially for visible-light excitation and reaction parameter optimization, the following delicate examples of challenging organic synthesis photocatalyzed by TiO_2 have appeared: aerobic oxidation of alcohol to aldehydes [31,35,37,51,59–69], aerobic oxidative condensation of benzylamines to imines [30,36,49,70], olefin epoxidation [71,72], C–H arylation with aryl diazonium compounds [73,74], desilylative Michael addition between benzyltrimethylsilane and electron-poor olefins [75–78], pyridine anti-Markovnikoff addition to diphenylethylene [38], 4-aryltetralone synthesis by styrene [2 + 2 + 2] cyclo-addition [79,80], and amine alkylation with alcohol as an alkylating reagent [81–85]. These reports successfully fulfilled the organic transformations with high yield, excellent selectivity, mild conditions, and wide substrate scope. Corresponding to this new field, a number of excellent reviews have focused on TiO_2 photocatalysis in organic synthesis [39,40,42,43,47,50,52,56,57,63,86–88]. However, the incredible potential of C–H bond functionalization by TiO_2 photocatalysis for C–C coupling reactions has not been fully tapped yet. In this review, we concentrate on discussing and analyzing the state-of-the-art examples of TiO_2 photocatalysis with a focus on C–H bond functionalization for highly selective C–C bond formations.

Figure 1. Activation of organic compound C–H bonds through TiO_2 photocatalysis under (a) ultraviolet (UV) and (b) visible-light irradiation. (a) C–H functionalization reactions of generic hydrocarbons started by TiO_2 photocatalyst under UV light excitation; (b) C–H functionalization reactions of generic hydrocarbons started by TiO_2 /dye-sensitization mechanism under visible-light irradiation. Adapted with permission from [47]. Copyright 2014, ACS.

2. C–H Activation Available to Convert Simple Molecules into Desired Complex C–C Coupling Products

The ultimate aim of organic synthetic chemistry has always been to develop appropriate methods with the least synthetic steps, mildest conditions, most easily available substrates, and excellent yields. A promising strategy to realize this aim is to selectively functionalize, aiming C–H bonds in the substrate chain moiety or cyclic skeleton and placing a desired functional group or branch chain in it. For this purpose, many famous catalytic reactions were developed, such as Friedel–Crafts [89–91] and Heck [92,93] reactions. In the conventional Friedel–Crafts reaction, AlCl_3 Lewis acid catalyst was applied to catalyze electrophilic C–H alkylation or acylation between alkyl halides, acyl halides, and arenes. This transformation realized the aromatic ring sp^2 C–H activation and further set the required alkyl or acyl functional group on the desired position [94–97]. In the Heck reaction, aryl halides or pseudo-halides and alkenes are efficiently coupled by Pd (0) catalysts. Pd (0) catalyst was suitable for oxidative addition of aryl halides and coordination with alkenyl C=C bonds. The pivotal carbopalladation step realized C–H transformation, while the final reductive elimination released the C–C coupling product and regenerated the Pd (0) catalyst [98] (see Figure 2). The key to this successful transformation was that the ligands around the Pd center accurately tuned its electronic and steric environment during the catalytic cycle. The electron-rich and sterically congested phosphine or *N*-heterocyclic carbene (NHC) ligands facilitated both the oxidative addition and reductive elimination steps. These transition-metal catalyzed C–H functionalization reactions greatly enlarged the scope of organic synthesis, simplifying the redundant prefunctionalization procedures. However, these important catalytic reactions based on AlCl_3 and noble-metal catalysts are either environmentally unfriendly or economically costly. Therefore, to develop more green and sustainable methods, non-noble metal catalyzed C–H functionalization has always been a meaningful subject in the advanced organic synthesis field.

Figure 2. Scheme of Pd-catalyzed Heck reaction and its catalytic cycle. Adapted with permission from [98]. Copyright 2000, ACS.

TiO₂ photocatalysis is receiving attention in the field of C–H bond functionalization not only because of its intrinsic robust redox catalytic activity, but also its unconventional C–H transformation modes. Although some unsystematized and discrete examples could not demonstrate similarly wide substrate scope with Friedel–Crafts and Heck reactions, as they lacked the general strategy and approach for chiral asymmetric C–H functionalization, two points deserve to be highlighted: (i) the cross-dehydrogenative coupling (CDC) reaction could be realized between two parent C–H bonds without any halogenated one, and (ii) some inert C–H bonds that were difficult to be activated in noble-metal catalysis could be efficiently functionalized. These two points demonstrate that TiO₂ photocatalytic C–H functionalization does not proceed via a similar pathway as traditional homogeneous noble-metal catalysis or zeolite solid catalysis in high temperature and pressure with acid-base catalysis sites. From the view of TiO₂ photocatalysis, the reaction pathways of organic molecules are not limited to the well-known localized valence band h^+_{vb} oxidation and conduction band e^-_{cb} reduction pathways [36]. In some examples it must couple multiple intermediates generated in the TiO₂ interface to realize very inert C–H bond functionalization. Obviously, homogeneous noble-metal catalysis sometimes does not possess this property. Instead, noble-metal catalysis generally has to resort to strong acids, bases, oxidative or reductive co-catalysts, and additives to realize such inert C–H bond activation and functionalization [99,100]. In comparison with AlCl₃-based Friedel–Crafts alkylation or acylation, TiO₂ photocatalysis has more promise in arene C–H functionalization, since AlCl₃ is a too-strong Lewis acid that has narrower functional group tolerability toward acid-sensitive group on aromatic ring than TiO₂ photocatalysis. Moreover, since the much stronger coordinating ability and the higher electrophilic property of AlCl₃, in AlCl₃-catalyzed Friedel–Crafts alkylation, it is very difficult to control the regioselectivity over multisite alkylation. Because of this uniqueness, TiO₂ photocatalysis has received considerable attention in initiating C–H transformation for constructing C–C bonds in different target organic compounds. It can be anticipated that TiO₂ photocatalysis will realize more challenging C–H activation for C–C bond or other C–X bond formation reactions if its generality is established. With deeper insight into the functionalization mechanisms, one can design and optimize TiO₂ photocatalysts to initiate reactions in the most economic and suitable fashion only by irradiating to activate them, unlike conventional transition-metal catalysis with heating of the solvent, substrates, and products.

This review centers on the theme of C–H functionalization and comments on the current accomplishment of TiO₂ photocatalytic C–C bond coupling examples. Although there is currently no unified agreement about the reaction mechanism of every example, the facts of every model example are still very concrete and the corresponding mechanism is still very important. Thus, our review is different from most published critical and tutorial reviews in this field. First, we introduce the reaction and its main unique properties. Then the mechanism provided by the original authors is presented. More importantly, we comment on the intrinsic property of the TiO₂ photocatalyzed reaction based on the original text's evidence. The mechanisms and reaction pathways are emphasized and discussed in comparison with traditional homogenous catalysis as much as possible. These discussions and comparisons may contribute to the success of other C–H bond functionalization for new C–C target compound synthesis via mild TiO₂ photocatalysis even directly using visible light or sunlight.

2.1. Activating C–H Bond to React with C=C or C–X Bond for C–C Coupling Reactions

The most common pathways of C–H bond functionalization for C–C coupling reactions are through photo-induced h^+_{vb} oxidizing the adsorbed organic substrates R–H along the single-electron transfer (SET) scheme, yielding intermediate high-energy R–H^{•+} radical cation in an energetically uphill pathway. The unstable R–H^{•+} experiences a spontaneous deprotonation event, generating carbon-centered radical R[•]. The reactive radical attacks the C=C bond of another substrate in either an electrophilic or nucleophilic manner, bringing out a new adduct radical species, R–C–C[•]. Then this new radical accepts conduction band e^-_{cb} , yielding carbanion species R–C–C[−], and the proton transfer generates the final functionalized C–C coupling R–C–CH compound (see Figure 3).

Gaining satisfactory selectivity from this kind of reaction initiated through h^+_{vb} oxidation is very challenging, especially in aqueous solution in which $OH^\bullet$ free radical formation from solvent H_2O oxidation often results in nonselective attacking of substrate [101]. In fact, the organic pollutant decomposition reactions in water usually proceed through this mechanism to deep mineralization [102]. To obtain synthetically useful C–H functionalization, the designed TiO_2 photocatalytic process must avoid this kind of aqueous decomposition pathway.

Figure 3. TiO_2 photocatalytic activation of C–H bond for addition reaction with C=C olefinic bond.

Rueping et al. reported that heterogeneous TiO_2 photocatalyzed C–H arylation of heteroarenes with aryldiazonium salts [73]. In their investigations, they discovered that this transformation could be successfully accomplished even under visible-light irradiation. By further mechanistic study with UV-Vis spectra, they illustrated that the red shift of the TiO_2 catalyst absorption spectrum to the visible-light region was mainly due to the formation of TiO_2 -diazoether surface species. This surface species was proposed to absorb visible light and initiate the C–H bond transformation for subsequent C–C bond coupling with heteroarene substrates (see Figure 4). The use of visible-light irradiation was crucial to ensure high selectivity and yield, which avoided h^+_{vb} random oxidation. This method demonstrated a wide substrate scope in 19 successful examples (as shown in Table 1). Furthermore, an important muscle relaxant drug, dantrolene, was synthesized using this method in two steps with very good yield. This is a very important TiO_2 photocatalytic C–H bond activation following the C–C coupling example. The significance is that along normal photochemical reactions under UV irradiation, heteroarenes such as furans and thiophenes are commonly inclined to [2 + 2] cycloaddition or [4 + 2] Diels–Alder reaction products when aromatic diazo compounds are present [103,104]. Although the mechanism the authors provided was not soundly supported by experiment evidence, the proposed first step of formation and transformation of aryldiazoether to aryl radical was possible (see Figure 4). However, the event that photogenerated h^+_{vb} and e^-_{cb} was attributed to direct excitation of the TiO_2 semiconductor was not likely. Herein, >420 nm irradiation did not excite normal TiO_2 nanocrystal catalyst, because the energy of incident light was below the gap energy (<387 nm). Thus, the most probable reaction pathway was that the surface complex formed between the diazoether and TiO_2 nanoparticle surface hydroxyl would be activated by visible light, and the excited surface complex may sensitize ethanol oxidation to provide electrons injecting into the conduction band. Subsequently, diazo compounds accept the electron with the extrusion of N_2 , yielding aryl radical. Heteroarene substrates trapped in situ form aryl radical, forming the radical intermediate. Since the h^+_{vb} was not formed, the TiO_2 -diazoether complex continued to accept the electron from the radical intermediate, yielding a carbocation intermediate, which upon spontaneous deprotonation rearomatized to the final product. The net reaction should be ethanol oxidation to acetaldehyde, while diazo was reduced to N_2 and proton left behind was combined with BF_4^- to form HBF_4 . This example of TiO_2 photocatalyzed C–H arylation indicates a direction for designing a feasible protocol of C–H functionalization for C–C coupling reaction by a SET pathway, even mediated by

visible light or sunlight. The key to this successful C–H functionalization is based on the use of easily fragmenting aryldiazonium salts, which facilitated aryl radical generation upon TiO_2 conduction band e^-_{cb} SET reduction.

Table 1. Substrate scope of heteroarene C–H arylation with aryldiazonium salts. Adapted with permission from [73]. Copyright 2015, ACS.

 Yield 94%	 Yield 79%	 Yield 90%	 Yield 90%
 Yield 83%	 Yield 77%	 Yield 80%	 Yield 64%
 Yield 80%	 Yield 96%	 Yield 88%	 Yield 72%
 Yield 67%	 Yield 55%	 Yield 53%	 Yield 54%
 Yield 79%	 Yield 53%		

Reaction conditions: 0.1 mmol aryldiazonium salt, 0.1–1 equiv P25 TiO_2 , 1 mL EtOH, 1 mL heteroarene, irradiation with 11 W compact fluorescent lamp (CFL) from 3 cm distance, yield after chromatographic purification.

Figure 4. Proposed mechanism of TiO₂ photocatalytic heteroarene C–H arylation by aryl diazonium salts. Adapted with permission from [73]. Copyright 2015, ACS.

Sometime later, the same group reported the continuous-flow reactor version of this photocatalytic C–H bond arylation [74]. They innovated a falling-film membrane reactor (FFMR) (shown in Figure 5) to adapt to the heterogeneous photocatalyst TiO₂ nanocrystal film. By elaborate synergy of this FFMR with TiO₂ nanoparticles, TiO₂ photocatalyst was calcined and bound to the stainless layer of reactor by a polyvinyl alcohol binder. XRD (X-ray diffraction), TEM (Transmission electron microscope), SEM (Scanning Electron Microscope), and EDX characterization displayed unchanged crystallinity, morphology, and size after calcination and immobilization. A comparison of the photocatalytic C–H bond arylation results demonstrated that the FFMR continuous-flow design provided approximately 60,000-fold enhancement of specific reactor compared with conventional batch reactor, along with excellent yields up to 99%. Moreover, this immobilized photocatalyst bed also generated enhanced stability and reusability against TiO₂ photocatalysis in batch reactor.

Figure 5. Falling-film membrane reactor (FFMR) lab plant with an HPLC pump, thermostat, nitrogen gas supply, and power supply with light-emitting diode (LED) array. Reprinted from [74]. Copyright 2018, RSC.

Wang et al. developed a simpler and more user-friendly version of this heterogeneous photocatalytic transformation by a PANI-g-C₃N₄-TiO₂ composite catalyst [105]. They expedited the protocol by in situ generation of aryldiazonium salts through the reaction of aniline with MeSO₃H and tBuONO. Sequentially, the diazonium salts participated in the following aryl radical generation by electron reduction, radical addition with heteroarene furan, thiophene and pyridines, and the deprotonation step furnishing the final C–C coupled products (see Figure 6). Apart from the initiation step of evolution of aryldiazonium salts, this ternary composite photocatalyst system proceeded along a similar reaction route as the previous example by Rueping [73]. However, this example differed considerably from Rueping's work on the composition of photocatalyst. In Rueping's system, a commercial photocatalyst, P25 TiO₂, was applied, whereas in Wang's system, a hybrid PANI-g-C₃N₄-TiO₂ photocatalyst was utilized. The difference in photocatalyst composition determined the intrinsic difference in the origin of visible-light response. For Rueping's system, the surface complex of diazoether–TiO₂ accounted for the absorption of incident visible-light photons, while in Wang's system, despite the uncertainty of confirming the catalytic sites, the visible-light absorption was mainly attributed to the narrow-gap semiconductor PANI. Thus, PANI-g-C₃N₄-TiO₂ composite catalyst could respond to visible-light irradiation, thereby initiating a variety of photocatalytic organic transformations, including C–H transformation and C–C formation, only by absorbing visible-light irradiation. TiO₂ alone could initiate a few photocatalytic C–H transformations for C–C and C–hetero bond formation under visible-light irradiation, but only to the extent that the substrates themselves must coordinate or complex onto the TiO₂ surface to form colored surface complexes for adsorption of visible-light driving ET-reaction. Apparently, available substrates are very limited; only a few polar aromatic compounds containing heteroatoms such as oxygen, nitrogen, or sulfur substituent function groups may be applicable. On the contrary, PANI-g-C₃N₄-TiO₂ absorbs visible light by PANI itself and does not require the specific substrate's heteroatom. Therefore, this hybrid photocatalysis system has wider substrate scope and reaction types for visible light-mediated transformations than TiO₂ alone. In combination with PANI charge separation initiated by incident visible-light photons and consecutive surface reaction of in situ generated aryldiazonium salt with photo-induced h^+_{vb}/e^-_{cb} pair in an acetone/water or pure aqueous environment, this catalytic reaction yielded the final arylated products with good to excellent yield. Apart from heteroarenes, other kinds of substrates, such as enol ether and benzoquinone, were also easily arylated predominantly in their α -position. Good functional group tolerability and high chemo- and regioselectivity were achieved apart from the excellent yields in the present photocatalysis. The same group also showcased another protocol for easy synthesis of 2,5-diaryl 1,3,4-oxadiazoles by the same synergistic ternary composite photocatalyst (PANI-g-C₃N₄-TiO₂) under visible-light illumination [106]. A broad scope of benzohydrazides and phenylglyoxylic acids were explored, and moderate to good isolated yields were obtained. No reaction occurred when 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) was added or nitrogen was used instead of an air atmosphere. Based on these mechanistic studies and control experiments, the authors proposed a plausible reaction mechanism. Initially, benzohydrazide and phenylglyoxylic acid were condensed in the presence of K₂CO₃, providing a 2-(2-benzoylhydrazono)-2-phenylacetate intermediate. This intermediate was then converted to its corresponding radical by h^+_{vb} SET oxidation. After decarboxylation and intramolecular radical addition to carbonyl oxygen, the new 2,5-diaryl-1,3,4-oxadiazole radical was formed. The final electron transfer from superoxide radical anion closed the total catalytic cycle. The photocatalyst displayed very good recyclability and reusability. After simple centrifugation and washing with ethyl acetate and water, the photocatalyst could be reused for six consecutive runs without apparent loss of catalytic reactivity. This example indicates that under visible-light illumination, modified TiO₂ photocatalyst can photocatalyze the formation of five-membered heterocyclic compounds in an environmentally friendly and user-friendly manner.

Figure 6. Proposed mechanism for C–H arylation reactions through aniline activation catalyzed by PANI-g-C₃N₄-TiO₂. Adapted and reprinted from [105]. Copyright 2018, RSC.

Apart from the C–H bond arylation reaction, TiO₂ photocatalyst was also applied in the C–H bond alkylation transformations. Koenig et al. reported that upon visible-light irradiation, organic dye-anchored TiO₂ photocatalyst could be combined with chiral secondary amine organocatalyst for highly chemoselective and stereoselective aldehyde α -C–H alkylation with electron-deficient alkyl bromide (see Figure 7) [107]. After loading with Texas Red derivative dye, TiO₂ nanoparticles could even photosensitize this α -C–H alkylation reaction under 530 nm green-light irradiation and provide good *ee* value when a chiral secondary amine organocatalyst was added to the suspending solution. However, when chiral organocatalyst was covalently bound to TiO₂ photocatalyst, no product formation was observed and the catalytic system was totally ineffective. This was mainly due to the oxidative decomposition of the organocatalyst on the TiO₂ surface upon illumination. Much more efficient electron transfer occurred between the anchored chiral organocatalyst and the TiO₂ oxidizing surface compared with the free chiral organocatalyst in solution. High chemo- and stereoselectivity achieved in the TiO₂-photosensitized C–H alkylation reactions originated from the strong activation capacity of dye-modified TiO₂ catalyst even under very low temperature ($\sim -20^\circ\text{C}$), since photo-induced ET thermodynamic behavior is generally less influenced by reaction temperature than homogeneous chiral organocatalysts and existing transition-metal catalyst. For the latter, the reaction never took place under low temperature, or lost chemo- and stereoselectivity while the temperature was raised. The findings on surface modification and immobilization for efficient asymmetric C–H functionalization by TiO₂ photocatalysis under visible-light irradiation provided many tips and insights into the design of TiO₂ photocatalytic organic transformations with more chemo-, regio-, and stereoselectivity. Many asymmetric reactions in which substrates are difficult to activate by the prevailing chiral catalysts under obligatory low temperature for high *ee* values may go smoothly with the modified TiO₂ photocatalysts under low temperature.

Figure 7. TiO₂ photocatalytic enantioselective alkylations using MacMillan's chiral secondary amine organocatalyst.

Yoshida et al. reported that TiO₂ photocatalyzed perfluoroalkylation via indirect C–H bond activation of electron-rich arenes and styrene derivatives [108,109]. Upon UV light irradiation, the TiO₂

conduction band e^-_{cb} could reduce perfluoroalkyl iodide to generate perfluoroalkyl radical and iodide anion through the SET process (see Figure 8). The sp^2 C–H bond functionalization of arene or styrene was indirectly performed by perfluoroalkyl radical attack to the arene or styrene π system and yielded the radical adduct. Then the radical adduct experienced SET oxidation by TiO_2 h^+_{vb} on the catalyst surface, yielding carbocation species. The final energetically downhill deprotonation step finished the whole catalytic cycle. In this process, methanol co-solvent and $NaBF_4$ additive acted as hole and electron modulator to accelerate this reaction. Using this method, several arenes and α -methyl styrene could be successfully perfluorohexylated and perfluorobutylated in moderate yields, providing formal C–H functionalized products. This discovery demonstrated the potential of TiO_2 photocatalysis to set a perfluoroalkyl group on certain C–H bonds. The selectivity of this transformation was moderate, since the iodide anion, which was generated from photo-induced conduction band e^-_{cb} reduction of perfluoroiodide, would possibly combine in the last step with arene cation, generating perfluoroaryl iodide byproducts.

Figure 8. TiO_2 photocatalyzed perfluoroalkylation of arenes.

Not only organic dye efficiently sensitized wide band-gap semiconductor TiO_2 ; transition-metal oxides were also decorated on the P25 TiO_2 surface, serving as an effective sensitizer for some important organic synthesis. Shen et al. reported that NiO/TiO_2 nanocomposite could photocatalyze the functionalization of *N,N*-dimethylaniline's *N*-methyl C–H bond to generate the C–C coupling cyclization product tetrahydroquinoline by a further addition reaction with electron-poor maleic imides (see Figure 9) [110]. By a simple chemisorption-calcination procedure from $Ni(acac)_2 \cdot 2H_2O$ precursor and P25 TiO_2 , modified NiO/TiO_2 nanocomposite was formed. The NiO modification extended the TiO_2 absorption edge to the visible-light region by elevating the TiO_2 valence band position. This modification greatly decreased the TiO_2 band gap and enough oxidation ability remained for *N*-methyl C–H functionalization. After screening the optimum condition for this C–H transformation, the authors explored a wide variety of substrate scope (see Table 2). Moreover, the authors demonstrated that even with the TiO_2 photocatalyst loading only 1% mol, it still provided excellent yield of C–C coupling cyclized tetrahydroquinoline target product. In the proposed mechanism, two C–H bond transformation events were involved: one was a sp^3 C–H bond of *N*-methyl in *N,N*-dimethylaniline, and the other was the aromatic ring sp^2 C–H bond. Besides being a well-known deprotonation route for C–H bond transformation by the photo-induced hole along a SET process, ROS was proposed to play a key role in abstracting hydrogen from *N,N*-dimethylaniline [111,112], generating α -aminoalkyl radical species. The successful C–H bond transformation and subsequent ring-closing C–C coupling mostly rely on electron-poor Michael-acceptor maleic imides as substrates. This catalytic reaction displayed high selectivity. The origin of this high reactivity was mainly attributed to NiO 's ability to attenuate photo-induced h^+_{vb} oxidability. NiO loading levelled up the h^+_{vb} redox potential, thus reducing the possibility of other undesired transformations. This example demonstrates that very efficient transformation and high turn-over number (TON) and turn-over frequency (TOF) can be achieved by the transition-metal oxide sensitized TiO_2 photocatalysis system for useful C–H

functionalization events rivaling or even surpassing its counterparts such as Ru, Ir complexes and organic dye photocatalysts.

Almost in the same period of this report, Kappe et al. reported the same transformation by a monodispersed TiO₂ nanocrystal (see Figure 10) [113]. In a continuous-flow reactor setup, monodispersed TiO₂ nanocrystals in the shape of spheres or rods were synthesized by heating the mixture of titanium isopropoxide and capping reagent oleic acid in a CH₂Cl₂/toluene mixed solvent at high temperature for a certain period. The as-synthesized nanocrystal sample was characterized by HRTEM and XRD to indicate its monodispersed shape and size. The small nanocrystals displayed nanorod or spherical shape. The authors applied the monodispersed TiO₂ nanocrystals to the C–H functionalization of *N*-methylaniline and *N,N*-dimethylaniline *N*-methyl C–H bond. The C–H bond was selectively cleaved and linked with *N*-methyl maleic imide olefinic carbon by irradiating with a 365 nm UV LED torch. The monodispersed TiO₂ nanocrystals demonstrated parallel activity toward efficient C–H transformation compared with commercial P25 nanomaterials.

Table 2. Visible light-mediated cyclization of tertiary anilines and maleimides with P25/NiO as photocatalyst. Adapted and reproduced from [110]. Copyright 2015, ACS.

Entry	R1	R2	1	R3	2	3	Yield (%)
1	Me	H	1a	Ph	2a	3a	75
2	Me	H	1a	4-MeOPh	2b	3b	64
3	Me	H	1a	4-MePh	2c	3c	89
4	Me	H	1a	4-FPh	2d	3d	81
5	Me	H	1a	4-ClPh	2e	3e	62
6	Me	H	1a	Me	2f	3f	67
7	Me	H	1a	t-Bu	2g	3g	69
8	Me	H	1a	Bn	2h	3h	68
9	Me	4-Me	1b	Ph	2a	3i	85
10	Me	4-Me	1b	4-MeOPh	2b	3j	68
11	Me	4-Me	1b	4-MePh	2c	3k	93
12	Me	4-Me	1b	4-FPh	2d	3l	86
13	Me	4-Me	1b	4-ClPh	2e	3m	73
14	Me	4-Me	1b	Me	2f	3n	77
15	Me	4-Me	1b	Bn	2h	3o	77
16	Me	4-MeO	1c	Ph	2a	3p	69
17	Me	2-Me	1d	Ph	2a	3q	64
18	Me	4-F	1e	Ph	2a	3r	86
19	Me	4-Cl	1f	Ph	2a	3s	75
20	Me	4-Br	1g	Ph	2a	3t	61
21	Me	4-Br	1g	4-MePh	2c	3u	68
22	Me	4-Br	1g	4-ClPh	2e	3v	52
23	Me	4-Br	1g	Me	2f	3w	65
24	Me	4-Br	1g	Bn	2h	3x	45
25	Et	H	1h	Ph	2a	3y	71
26	Ph	H	1i	4-MePh	2c	3z	48

Reaction conditions: 1.25 mmol of 1a, 0.625 mmol of 2a, and 1 mol% P25/NiO in 25 mL of *N,N*-Dimethylformamide (DMF), irradiation with 3 W blue LED lamp for 12 h in Ar atmosphere. Yield after chromatographic purification.

Figure 9. Surface-modified NiO/TiO₂ photocatalyzed reaction mechanism of tertiary anilines with maleic imides. Adapted and reproduced from [110]. Copyright 2015, ACS.

Figure 10. (a) TiO₂ photocatalyzed tandem addition–cyclization reaction of *N*-methylmaleimide and *N,N*-dimethylaniline and (b) the continuous-flow photoreactor setup. Adapted and reproduced from [113]. Copyright 2013, Springer.

To widen the scope of TiO₂ photocatalysis for inert C–H functionalization, we reported that a more challenging pyridine ortho-C–H bond could be selectively cleaved and connected with an unactivated olefin 1,1-diphenylethylene along an anti-Markovnikoff mode (Figure 11) [38]. Although the heteroarene scope was limited to pyridine and picolines, the realization of pyridine C–H bond cleavage was not a trivial matter, since the dissociation energy of pyridine sp² C–H bond was very large. The SET redox potential of pyridine and picolines is high, and it is extremely difficult for the TiO₂ photo-induced valence band h⁺_{vb} to oxidize. However, we discovered that when an excessive amount of pyridine was applied, this transformation proceeded easily by a possible concerted two-electron transfer process. We demonstrated this reaction pathway by Fe(III)-ortho-1,10-phenanthroline titration

of photo-induced e^-_{cb} and electron-paramagnetic-resonance (EPR) characterization of conduction band e^-_{cb} experiments. From the experimental results, no conduction band electron accumulation was detected when 4-picoline was subjected to TiO_2 photocatalytic conditions under UV illumination, while other compounds with known SET reaction mechanism in TiO_2 photocatalytic conditions all demonstrated notable electron accumulation signals. This result indicated that TiO_2 photocatalytic functionalization of pyridine ortho-C–H bond into C–C bond with 1,1-diphenylethylene did not proceed along the same SET pathway as benzyltrimethylsilane, *N,N*-dimethylaniline, and *N*-methylpyrrolidine. We excluded the stepwise SET process and suggested that the most probable pathway was the concerted two-electron transfer process. This example demonstrates that by an unconventional concerted two-electron transfer process, TiO_2 photocatalysis likely was able to fulfill very challenging inert electron-poor heteroarene sp^2 C–H functionalization to construct useful C–C bonds. The good selectivity was mainly rooted in the highly specific concerted two-electron transfer rather than the common free-radical mechanism. Significantly differing from alternative transition-metal catalysis in a kind of anti-Markovnikoff reaction of pyridines with obligatory electron-rich olefins [114,115], the main advantage of the TiO_2 photocatalytic method is that between two reactants, olefin and pyridine, only pyridine molecules could be adsorbed on to the polar TiO_2 surface and activated into carbocation via this unconventional activation mode, which diffused into the solution phase to react with olefin. This protocol can maximally prevent preferentially activating olefin along the SET route into an undesired polymerization side reaction by the free-radical mechanism.

Figure 11. (a) TiO_2 photocatalytic anti-Markovnikoff addition reaction. (b) Accumulated electron evidenced by Fe(III)-*o*-phenanthroline titration and low-temperature electron-paramagnetic-resonance (EPR) experiments in TiO_2 photocatalytic reactions between 1,1-diphenylethylene and different substrates. Reproduced with permission from [38]. Copyright 2015, RSC.

In a very recent report, the C–H bond functionalization of tetrahydroisoquinolines was used to construct C–C bonds with the carbon-centered radical generated from decarboxylation of active esters (*N*-hydroxyphthalimide esters) by a dye-sensitized TiO_2 photocatalyst system (see Table 3) [116]. In this example, commonly used eosin-Y dye was replaced with a similar erythrosine-B dye, which showed

much higher reactivity and selectivity toward C–C coupling products. This method was applicable to a wide variety of both tetrahydroisoquinolines and active ester substrates. Electron-rich methyl and methoxy, electron-poor fluorophenyl and chlorophenyl, and fused-ring naphthalene substituents on tetrahydroisoquinoline did not greatly reduce the isolated yield. Moreover, a variety of alkyl radical precursor *N*-hydroxyphthalimide esters were chosen as the substrates to test the universality of this method. Primary, secondary, and tertiary alkyls were introduced into the target molecule, with moderate to good yield. Alkene, alkyne, thienyl, cyclobutyl, tetrahydropyran, cyclohexanone, and Boc-protected amino functional groups were well tolerated. Moreover, the most sterically congested tertiary alkyls, or even extremely sterically crowded bridge-head carbon, were all effectively coupled with tetrahydroisoquinoline. The cyclopropyl radical clock experiments were undertaken in the present system. The ring-opening olefinic product demonstrated that the photocatalytic C–H alkylation probably proceeded via a radical mechanism (see Figure 12).

Table 3. Substrate scope of dye-sensitized TiO₂ photocatalyzed C–H decarboxylative alkylation. Adapted and reproduced from [116]. Copyright 2018, ACS.

Reaction conditions: 0.5 mol% erythrosine B (1.8 mg), 160 mg P25, *N*-hydroxyphthalimide esters 0.80 mmol, *N*-aryltetrahydroisoquinoline 0.40 mmol, 2,2,2-trifluoroethanol (8.0 mL) in Ar atmosphere, 50 °C, irradiated with blue LED for 14 h.

Figure 12. Proposed mechanisms of dye-sensitized TiO_2 photocatalyzed C–H decarboxylative alkylation. Adapted and reproduced from [116]. Copyright 2018, ACS.

Although initial free-radical formation routes such as the extrusion of CO_2 from active esters generating stable *N*-hydroxyphthalimide anion and alkyl radical seemed reasonable, the possibility of a biradical coupling in bulk solution was too low for efficient transformation. Thus, it was more likely that surface binding of the tetrahydroisoquinoline radical extended its life and favored coupling with alkyl radical.

2.2. C–H Bond Functionalization for C–C Bond Coupling Reactions

In the above-mentioned bimolecular coupling transformations, C–X or C=C of one reagent couples with the C–H bond of another reagent, in which the C–H bond cleavage and C–C coupling reaction are usually discrete and passive. Generally, the initiation step is C–X cleavage and activation to generate the carbon-centered radical to involve in the sequential C–C coupling reaction (see Figure 3). Thus, the question has been posed whether TiO_2 photocatalysis could realize the cleavage of both C–H bonds in two different molecules to fulfill the most challenging cross-dehydrogenative coupling (CDC) reaction. Recently, Rueping et al. reported that aza-Henry, Mannich-type, and cyanation reactions could be facilitated by TiO_2 photocatalyst under visible-light irradiation (Figure 13) [22]. The authors showed that Aeroxide P25 or pure anatase TiO_2 particles could mediate the C–H bond functionalization of tetrahydroisoquinoline and initiate the C–C cross-coupling reaction with nitromethane, acetone, and cyanide. In this manner, useful products such as β -nitro amines, β -amino ketones, and α -amino nitriles could be constructed with excellent yields. This work paved the way for further application of TiO_2 photocatalysis in visible light-induced C–C (or C–P) bond formation via cleavage of two C–H bonds (or one C–H bond and one P–H bond). The authors did not provide the underlying mechanism of this C–H functionalization event, but this is a milestone discovery to independently realize the transformation and coupling of two C–H bonds in two substrate molecules, especially the functionalization of two saturated sp^3 C–H bonds. For the traditional transition-metal catalysts, such an activation of two inert sp^3 C–H bonds is almost impossible, unless one substrate is prefunctionalized or other auxiliary reagents are added to the system. The TiO_2 photocatalytic mechanism behind this successful transformation remains an interesting mystery for further exploration.

Figure 13. TiO_2 photocatalyzed oxidative Mannich, aza-Henry, and cyanation reactions.

In another example of activating two C–H bonds, *N*-heterocyclic arene C–H bond was also cleaved by sequential SET and radical attack event via TiO_2 photocatalysis (see Figure 14). Sunlight induced the functionalization of some heterocyclic bases in the presence of polycrystalline TiO_2 [43,117]. In this work, polycrystalline TiO_2 mediated two C–H bond cleavage events to facilitate C–C formation between sp^2 C–H bond in heterocyclic bases such as quinoline, quinaldine, lepidine, and quinoxaline and sp^3 C–H bond in formamide, dimethylformamide, and dimethylacetamide. The use of H_2O_2 greatly assisted the sp^3 C–H bond activation. TiO_2 photo-induced conduction band e^-_{cb} reduced H_2O_2 , yielding hydroxyl free radicals and hydroxide ions via the SET process. The hydroxyl free radical initiated a hydrogen-atom transfer (HAT) process to spontaneously abstract hydrogen from aldehyde-H or methyl-H. The as-formed nucleophilic carbon-centered radical attacked heteroarene via a Minisci-type mechanism, and the final deprotonation and electron transfer occurred spontaneously by the driving force of rearomatization and acid-base neutralization to form the final product.

Figure 14. TiO_2 photocatalyzed heterocyclic bases of C–H activation with amides.

The same group later reported that not only formamide aldehyde C–H and *N*-methyl C–H bonds could be cleaved under TiO_2 photocatalysis condition, but more inert ether α -methylene C–H was also functionalized and bridged with electron-poor *N*-heterocyclic bases such as quinoline, quinaldine, lepidine, quinoxaline, isoquinoline, and 4-cyanopyridine [118]. In the presence of TfOH and H_2O_2 , using H_2O or H_2O /acetonitrile mixed solvent, tetrahydrofuran, tetrahydropyran, dioxane, diethylether, and dioxolane ether α -methylene, C–H was linked to quinoline via a similar radical Minisci-type pathway. The yields were not satisfactory, ranging from 25% to 75% for four different ethers. The main reason for the moderate yields was the necessary use of protic solvent and an aqueous environment, which on the one hand was helpful in facilitating ET from the polar TiO_2 surface to the apolar or weak polar substrate, but on the other hand increased the undesired hydroxyl free-radical production. The more robust hydroxyl free radicals and other possible ROS led to more uncontrollable side reactions such as overoxidation, undesired HAT, and oxygen-atom transfer processes, thereby greatly decreasing the yield of desired main products. Moreover, the authors also explored the substrate scope of heterocyclic bases to couple quinoline, quinaldine, lepidine, quinoxaline, isoquinoline, and 4-cyanopyridine with trioxane. In these transformations, only very

moderate yields ranging from 7% to 40% were obtained. Neither anatase nor rutile TiO₂ nanoparticles could provide satisfactory yield. Although the yield was moderate in this reaction, the results proved that very challenging and inert C–H bond could be selectively cleaved and functionalized by TiO₂ photocatalysis in the SET process.

Apart from the ether α -C–H bond, a similar alcohol α -C–H bond was also utilized for C–C coupling reaction. Zhu et al. reported that when metallic platinum was loaded to TiO₂ nanoparticles, the composite photocatalyst could photocatalyze the α -C–H bond functionalization of ethanol, generating hydroxyethyl radicals [119]. The as-formed hydroxyethyl was further dehydrogenated via a “current doubling” effect on the TiO₂ surface under UV illumination. This process was detrimental for the desired C–C coupling reaction due to the formation of aldehyde byproducts. However, the selectivity of the C–C coupling main reaction could be significantly enhanced by tuning the TiO₂ surface hydroxyl group. The surface hydroxyl group reacted with H₂O, generating hydroxyl free radical. If hydroxyethyl radical remained on the TiO₂ surface, it suffered from reacting with hydroxyl free radical, yielding acetaldehyde byproducts. To avoid this side reaction, the authors engineered the TiO₂ surface by a fluorination modification. The fluorinated P25 TiO₂ provided the highest selectivity (64%) of 2,3-butanediol from ethanol compared with untreated anatase, rutile, brookite, and P25 TiO₂.

For the same C–C coupling reaction, Zhu et al. also reported that upon phase and pore engineering of TiO₂ photocatalyst, the ethanol α -C–H bond could also be efficiently transformed into C–C bond in 2,3-butanediol [120]. P25 TiO₂ crystalline phase composition was tuned by sintering at different temperatures. Polycrystalline TiO₂ with different anatase-to-rutile ratios was formed by this method. The higher the sintering temperature, the more rutile the phase profile. The authors discovered that the rutile phase was beneficial for the ethanol C–C coupling reaction rather than oxidation and overoxidation to aldehyde, acids, and CO₂. Such intrinsic selectivity was due to rutile TiO₂ possessing fewer surface hydroxyl groups. The surface hydroxyl group was detrimental for useful C–C coupling reaction as mentioned above. Moreover, the authors demonstrated that a more determining factor for the success of the useful C–H alkylation was the pore effect. They showed that the more developed the pore system, the greater the Brunauer-Emmett-Teller (BET) surface area and the less selectivity for C–H alkylation reaction. The reason was similar to the crystalline phase effect. Dense hydroxyl groups inside pores would interact with hydroxyethyl radical in the internal space of pores, generating many overoxidation byproducts. In order to prove the pore influence on C–H alkylation selectivity, the authors deliberately designed a paraffin-blocked porous rutile Pt–TiO₂ photocatalyst system (see Figure 15). The inner space was totally crammed with nonpolar paraffin. The paraffin molecule exhibited very weak polarity and very few hydroxyl groups. In this way, hydroxyethyl radical inside the pore did not effectively interact with catalyst. This facilitated its desorption for efficient coupling reaction in bulk solution, yielding useful C–H alkylation products.

In fact, successful C–H bond functionalization for the purpose of C–C bond coupling based on TiO₂ photocatalysis is very limited in both reaction type and substrate scope compared to conventional homogenous catalysis. However, these beneficial attempts provided a sound basis of theory and practice for future designs and modifications of TiO₂ photocatalysts as well as corresponding reaction conditions.

Figure 15. Schematic of the process of passivating the internal channels of rutile-TiO₂ nanotubes (rutile-TNTs) by filling paraffin into the tubes, and an illustration of the pore effect on selectivity control of ethanol oxidation. Reproduced with permission from [120]. Copyright 2011, RSC.

3. Conclusions

We have provided an overview of examples of TiO₂ photocatalytic C–H transformation for C–C coupling reaction. Although in its infancy compared with its application in water-splitting, DSSC, and water and air pollutant decomposition, TiO₂ photocatalysis has already demonstrated potential in C–H bond functionalization for organic synthesis purposes. Various C–H bonds, including amino and ether *N*- and *O*-ortho aliphatic α -C–H, inert arene sp^2 C–H such as benzene and pyridines, benzylic C–H, C–H adjacent to benzylic and the *N*-ortho position in tetrahydroisoquinoline, can be efficiently and selectively functionalized via either SET, HAT, or the two-electron transfer mechanism. By means of such a strategy, the inert C–H bonds in nonprefunctionalized organic substrates could be transformed to useful C–C bonds in diverse complex organic functional molecules. This has developed a somewhat robust method to prepare complex and challenging target organic compounds by using simple, ample, and commercially available raw materials. Nevertheless, compared with its homogeneous counterparts Ru, Ir complex and organic dye photocatalysts, current TiO₂ photocatalysis demonstrates very narrow substrate scope and limited reaction types and still has plenty of room for improvement. More challenging and unconventional C–H bond cleavage and functionalization transformations are waiting to be realized by more elaborate design of either the TiO₂ photocatalyst itself or skillful choice of co-catalyst, additive, and reaction parameters. If research focus is concentrated on TiO₂ photocatalytic C–H transformation for useful C–C coupling reactions, this research field will provide us with milder, greener, safer, more significantly sustainable and efficient strategies to supplement the disadvantages of other transition-metal catalysts and organocatalysts in the C–H activation task.

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