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Selective Formation of Imines by Aerobic Photocatalytic Oxidation of Amines on TiO_2**

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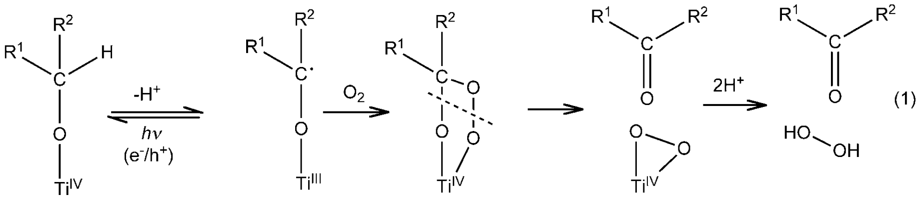
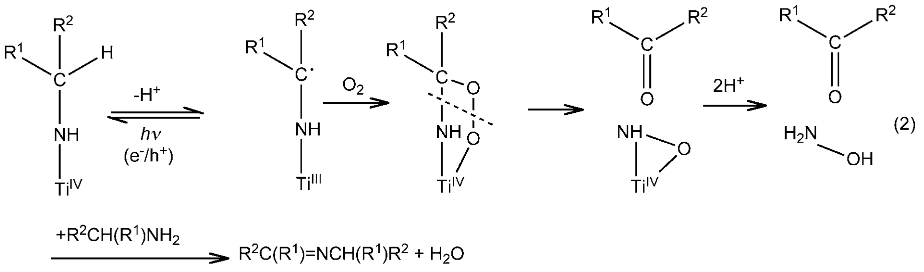


Imine derivatives are important building blocks for the synthesis of fine chemicals and pharmaceuticals.[1] Generally, their synthesis involves condensation of an amine and a carbonyl compound. To circumvent the problem caused by the excessively active nature of ketones or aldehydes, an alternative strategy for the direct oxidation of amines has attracted much interest.[2] Dioxygen, or more preferably dioxygen in the air, embodies the quintessential oxidant for chemical synthesis. Unfortunately, the reactivity of dioxygen is difficult to control; it typically reacts under harsh conditions with poor selectivity. Recently, much attention has been paid to organic synthesis photocatalyzed by TiO_2.[3] In H_2O, the selectivity of TiO_2 photocatalysis is especially poor, so that, it is efficient in the degradation of organic pollutants.[4] Even when the reactions are performed in inert organic solvent to prevent generation of OH radicals, the selectivity is usually very low owing to the unselective autooxidation of the photogenerated radicals. However, it has been shown that high selectivity can be realized in the TiO_2 photocatalytic system when both generation of the OH radical and unselective autooxidation are avoided.[5]

By using ^{18}O-labeling experiments, our research group has discovered that an oxygen-atom transfer dominates the photocatalytic transformation of alcohols into the corresponding carbonyl compounds on TiO_2 in benzotrifluoride. This transformation has a different mechanism than that of noble-metal/transition-metal complex catalysis. All the experimental results support a mechanism as shown in Equation (1).[6] Such a mechanism avoids the unselective autooxidation processes, which commonly occur in TiO_2 photocatalysis in the presence of dioxygen, and hence should lead to high selectivity in the photocatalytic oxidation of alcohols. This mechanistic insight can direct us to envision new reactions. Herein, we report our findings on a series of benzylic amines that were selectively transformed into the corresponding imines using 1 atm of air as the oxidant by TiO_2 photocatalysis in acetonitrile. The formation of imines involves a two-step process: a selective oxygenation step to generate the aldehydes and a subsequent condensation step to afford the imines. The high selectivity for the formation of imines is attributed to both the highly selective formation of aldehydes from amines [Eq. (2)] via a similar mechanism to that which governs the aerobic oxidation of alcohols [Eq. (1)], and the easy nucleophilic attack of such nascent aldehydes by the unreacted amines to yield the corresponding imines.



Control experiments (see Table S1 in the Supporting Information) revealed that TiO_2, dioxygen, and UV irradiation are all necessary for these reactions. It was found that the selectively oxidative coupling proceeds smoothly using 1 atm of air as the terminal oxidant. The pressure of O_2 (Table S1, entry 4) did not influence the reaction significantly, thus suggesting that the participation of O_2 is not involved in the rate-determining steps. The cutoff light below 350 nm instead of 300 nm did not improve the selectivity (Table 1, entry 2) and therefore excludes the involvement of a background photochemical reaction. Acetonitrile was found to be the best solvent among those examined (Table S2). Table 1 summaries the results of the photocatalytic oxidation of various amine derivatives. The transformation of all the benzylic amines examined showed high selectivity and gave

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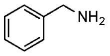
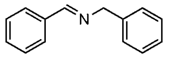
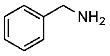
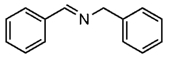
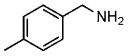
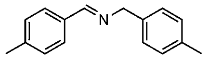
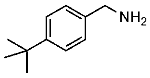
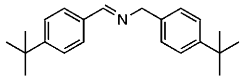
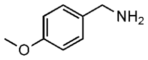
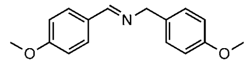
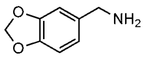
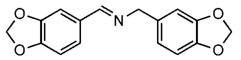
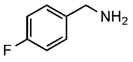
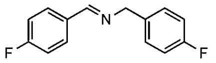
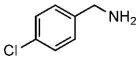
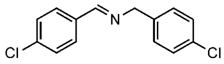
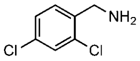
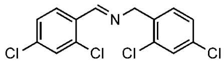
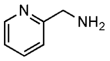
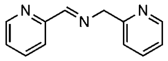
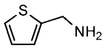
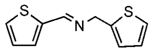
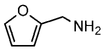
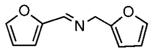
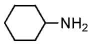
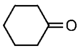
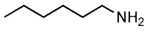
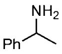
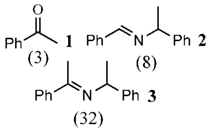
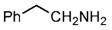
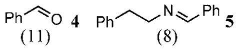
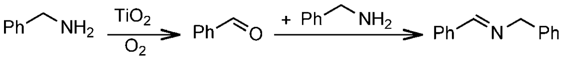
Table 1: Oxidation of amines photocatalyzed by TiO_2.[a]

Entry	Substrate	Product	*t* [h]	Conv. [mol %][b]	Select. [mol %][b]
1			9	99	85
2[c]			5	93	87
3			5	99	91
4			6	99	92
5			8	99	88
6			15	77	71
7			6	99	90
8			10	99	86
9			10	99	90
10			5	99	84
11			6	78	77
12			6	81	33
13[d]			5	80	6
14[d]		–	5	quant.	–
15[d]			8	65	–
16[d]			5	73	–

[a] Reaction conditions: 0.1 mmol of amine, 10 mg of TiO_2 (Degussa P25), 100 W Hg lamp cutoff below 300 nm, 5 mL of acetonitrile, 1 atm of air. [b] Determined by GC analysis using bromobenzene as the internal standard. [c] 500 W Xe lamp cutoff below 350 nm. [d] Data in the parentheses is the selectivity based on the initial amine.

the imine products (Table 1, entries 1–9). In addition, substituents on the benzylic amines did not affect the selectivity significantly, but slightly changed the conversion rates. It should be mentioned that this approach was also applicable to heteroatom-containing substrates (Table 1, entries 10–12), whose products are usually inaccessible by transition-metal complex catalysis owing to deactivation of the catalysts caused by the strong coordination of these amines to the metal center. The relatively low selectivity for furfurylamine (Table 1, entry 12) might result from the instability of the afforded imine. When nonbenzylic amines such as cyclohexylamine and *n*-hexylamine were chosen as the substrates (Table 1, entries 13 and 14), no imines were formed and only fragmentation products were detected. This finding is in line with poor selectivity for the oxidation of these substrates with dioxygen resulting from the unselective autooxidation caused by the activation of multiple reactive sites. This notion is further verified by the oxidation of 2-phenylethylamine and 1-phenylethylamine (Table 1, entries 15 and 16) in which some of the products (**2**, **4**, and **5**) result from unselective autooxidation at multiple reactive sites.

There may be doubts that the *N*-benzylidenebenzylamine might be generated via an oxidative dehydrogenation of the amines [Eq. (4)]. This pathway is usually proposed for the oxidation of amines.[7] Low selectivity is associated with these systems under homogenous photochemical conditions. However, the single issue of the high selectivity for *N*-benzylidenebenzylamine could not unequivocally confirm that the oxygenation pathway [Eq. (3)] is the main pathway to contribute the formation of the final imines in the present system. We could not completely exclude the possibility that there might be some unknown factors that would lead to a high selectivity via a dehydrogenation pathway in TiO_2 photocatalysis. In that case, benzylimine is susceptible to H_2O (the concomitant product of oxidation) to generate benzaldehyde. Therefore, this renders it impossible to distinguish these two pathways [Eqs. (3) and (4)] for those substrates such as benzylamine and its derivatives in Table 1. As a result, additional proof was needed to confirm that the mechanism is via an oxygenation process to generate the aldehyde [Eq. (3)]. We chose dibenzylamine rather than benzylamine as the substrate to synthesize *N*-benzylidenebenzylamine. Thus, product analysis can be an important method to distinguish these two mechanisms [Eqs. (3) and (5)] vs. [Eqs. (4) and (6)]. If the reaction proceeds via a dehydrogenation pathway, which ensures a high selectivity for benzylamine as the substrate [Eq. (4)], an equal or even better selectivity should be realized for dibenzylamine because it is a



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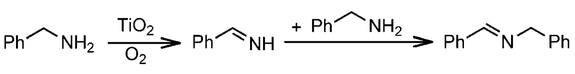
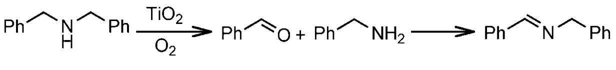
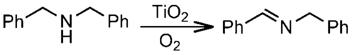


(4)



(5)



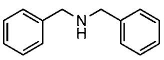
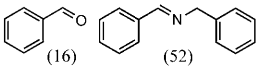
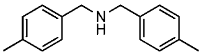
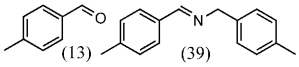
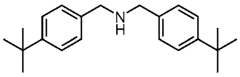
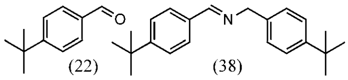
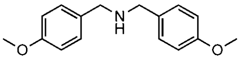
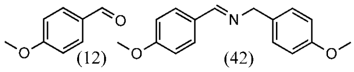
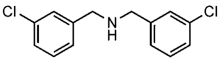
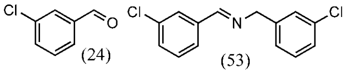
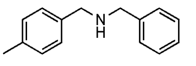
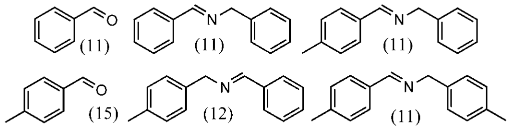
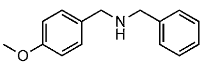
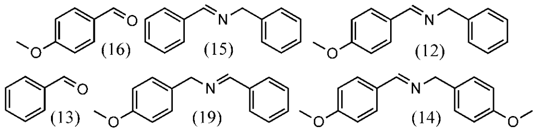
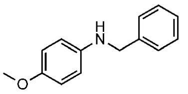
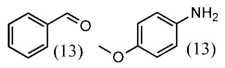
(6)

one-step pathway [Eq. (6)] for the formation of *N*-benzylidenebenzylamine. In the case of the oxygenation pathway, a detour for the aldehyde and benzylamine will occur [Eq. (5)].[8] The benzylamine generated in situ could also self-couple to give *N*-benzylidenebenzylamine under the present conditions [Eq. (3)]. Thus, some accumulated aldehyde will be detected as the final product in addition to imines. The results for the oxidation of dibenzylamine and its derivatives are summarized in Table 2, entries 1–5. The selectivity for the afforded imines (38–53 %) dropped significantly compared with the results shown in Table 1 (85–92 %), therefore indicating that an oxygenation pathway [Eqs. (3) and (5)] is preferred rather than the dehydrogenation pathway [Eqs. (4) and (6)]. The detection of significant amounts of aldehydes for all these substrates (Table 2, entries 1–5) is a clear indication that the reaction proceeded via an oxygenation pathway [Eqs. (3) and (5)].

To further confirm the oxygenation pathway in the formation of imines, we selected asymmetric dibenzylamine derivatives as the probe substrates. There are almost equal opportunities for the activation of C_α–H bonds on both sides adjacent to the nitrogen atom (see discussion below) and equal reaction rates for the condensation between different aldehydes and amines. There should be only two imines produced (Scheme S1) via a dehydrogenation pathway [Eq. (6)]. However, if the reaction proceeds via the oxygenation pathway [Eq. (5)], there should be four different imines produced and two accumulated aldehydes as the final products. The molar ratios for the four imines should be close to 1:1:1:1 (Scheme S2). As shown in Table 2, entries 6 and 7, we did observe four different imines with molar ratio close to 1:1:1:1 and two accumulated aldehydes. The notion was further supported by the oxidation of *N*-benzyl-4-methoxyaniline (Table 2, entry 8) in which only benzaldehyde and 4-methoxyaniline were detected as the products. The difficulty of the condensation between benzaldehyde and 4-methoxyaniline prevents the formation of the imine.

In an attempt to determine the parameters related to the reaction rate, a series of kinetic experiments were conducted for the photocatalytic oxidation of amines. Preliminary kinetics measurements indicate that the reaction exhibits pseudo-first-order kinetics (Figure S1). The oxidation of benzylamine and its derivatives with both electron-donating and -withdrawing substituents at the *para*-position were examined to obtain a Hammett plot (Figure 1). The slope of the linear plot gave a ρ value close to zero. This ρ value indicates that the reaction is not sensitive to substituents and electronic perturbation does not occur in the C_α–H activation step.[9]

Table 2: Oxidation of secondary benzylic amines on TiO_2.[a]

Entry	Substrate	Conv. [mol %][b]	Product (select. [mol %])[b]
1		91	 (16) (52)
2[c]		90	 (13) (39)
3		95	 (22) (38)
4		72	 (12) (42)
5		70	 (24) (53)
6[d]		86	 (11) (11) (11) (15) (12) (11)
7[d]		90	 (16) (15) (12) (13) (19) (14)
8		38	 (13) (13)

[a] Reaction conditions: 0.05 mmol of amine, 2.5 mL of acetonitrile, 10 mg of TiO_2 (Degussa P25), 100 W Hg lamp cutoff below 300 nm, 1 atm of air, 8 h. [b] Determined by GC analysis using bromobenzene as the internal standard. [c] 5 h reaction time. [d] 4 h reaction time.

Kinetic isotope effect experiments between $C_6H_5CH_2NH_2$ and $C_6H_5CD_2NH_2$ showed a k_H/k_D value of 1.3 ± 0.1, which indicates that cleavage of the C_α–H bond is not involved in the rate-determining step. These kinetic data resemble those in the oxidation of alcohols on TiO_2, and is important information for the future design of photocatalyst in order to improve the efficiency of the photocatalytic system for the oxidation of amines.[6]

In summary, we have achieved highly selective photocatalytic oxidation of amines on TiO_2 using 1 atm of air as the oxidant. The oxidation of amines involves a highly selective formation of aldehydes whose further condensation with the unreacted or in-situ generated amines affords the corresponding imines. These findings further demonstrate the generality of the reaction by the involvement of a selective oxygenation pathway in TiO_2 photocatalysis with dioxygen as the oxidant. Such fundamental insights could help us to envision new reactions for the oxidation of organic substrates

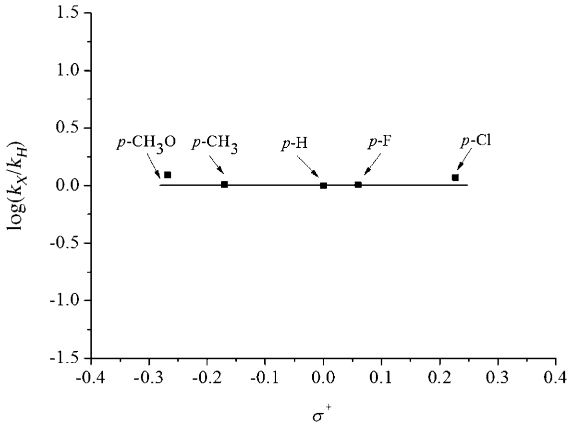


Figure 1. Hammet plot for the oxidation of substituted benzylamines photocatalyzed by TiO_2 with 1 atm of air; the reaction conditions are given in Table 1.

and pave the way to new synthetic method for synthesizing nitrogen-containing products via oxidation using dioxygen as the oxidant and TiO_2 as the photocatalyst.

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[8] According to Equation (2), benzaldehyde and *N*-benzylhydroxylamine should be the direct products. However, the disproportionation of *N*-benzylhydroxylamine will produce benzylamine and dioxygen. This step is omitted in Equation (5) for clarity.

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