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Photocatalysis

Aerobic Oxidative Coupling of Amines by Carbon Nitride Photocatalysis with Visible Light**

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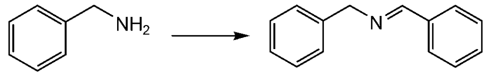
The use of sunlight as a driving force for chemical reactions shows great promise in synthetic chemistry.[1] As most organic molecules are transparent in the visible spectrum, light sensitizers are often employed to trigger organic transformations through electron transfer mediated by quenching reagents.[2] Metal–organic dyes have been used as such sensitizers because of the long lifetime of their excited states; however, there is a concern about the stability of dyes during long-term operations.[3] The inclusion of precious metals such as ruthenium in the dyes also restricts their practical applications.

Recently, our research group has introduced graphitic carbon nitride (g-C_3N_4) as a metal-free photocatalyst for hydrogen evolution using visible light.[4] Electrochemical and optical analyses have been therefore performed to reveal the top of the valance band and the bottom of the conduction band of g-C_3N_4. These bands were detected at 1.4 V and -1.3 V versus the normal hydrogen electrode, respectively.[5] Light-induced electrons with large reduction potential can easily activate molecular oxygen to mediate energy and electron transfer while the moderate oxidation potential of the holes prevents the synthesized organic compounds from being oxidized in an uncontrollable manner. This feature suggested that g-C_3N_4 can act as a gentle photocatalyst for promoting organic redox synthesis in a broader fashion. Indeed, when our work was extended to selective alcohol oxidation, it was found that light-excited g-C_3N_4 can activate O_2 for oxidation of alcohols to aldehydes/ketones with high selectivity.[6]

Herein, we advance carbon nitride photocatalysis mediated by carbon nitride species for the oxidation of amines into imines, which are regarded as important electrophilic intermediates in organic synthesis.[7] Although selective oxidation of secondary amines into imines can be achieved by employing stoichimetric amounts of reagents[8] with the noteworthy case of *o*-iodoxybenzoic acid,[9] effort has been devoted to developing catalytic systems using simple oxygen/air as the terminal oxidant. Recently, several transition-metal based catalysts[10] have been developed for this purpose, but they oxidize only a limited range of amines into imines at relatively high temperature (mostly $>110\,^{\circ}$C). We report the aerobic oxidation of amines into imines in excellent yields using a mesoporous graphite carbon nitride (mpg-C_3N_4) photocatalyst. We also integrate this oxidative coupling approach into a one-pot synthesis of benzoxazoles, benzimidazoles, and benzothiazoles, which are interesting and important compounds that occur widely as biologically active natural products, as well as marketed drugs or drug candidates.[11]

Results of control experiments and optimization of reaction conditions for the oxidation of benzylamine are listed in Table 1. No oxidation occurred in the absence of light or mpg-C_3N_4, even with high pressure O_2 (Table 1, entries 1 and 2). With mpg-C_3N_4, light, and O_2, the conversion reached

Table 1: Transformation of benzylamine catalyzed by mpg-C_3N_4.[a]



Entry	Solvent	T [°C]	Conv. [%]	Sel. [%]
1[b]	acetonitrile	60	–	–
2[c]	acetonitrile	60	–	–
3	acetonitrile	60	34	99
4[d]	acetonitrile	60	34	99
5[e]	acetonitrile	60	36	99
6	acetonitrile	80	60	99
7[f]	acetonitrile	80	61	98
8[g]	acetonitrile	80	16	99
9	acetonitrile	30	13	99
10	methanol	80	52	99
11	toluene	80	31	99
12	trifluorotoluene	80	35	99

[a] Reaction conditions: benzylamine (1 mmol), mpg-C_3N_4 catalyst (50 mg), solvent (10 mL), O_2 (0.5 MPa), $\lambda > 420$ nm, 2 h. [b] Without using the catalyst. [c] Without using light. [d] 0.2 MPa. [e] 0.8 MPa. [f] 5 mol% of radical scavenger 2,6-di-*tert*-butyl-4-methylphenol was added. [g] Under an atmosphere of Ar.

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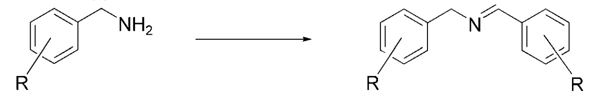
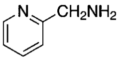
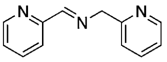
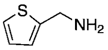
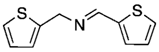
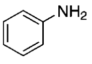
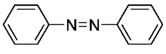
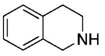
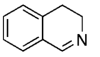
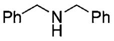
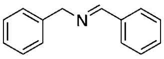
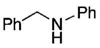
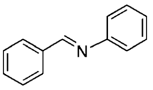
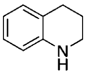
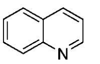
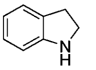
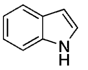
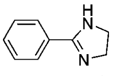
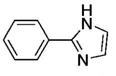
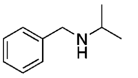
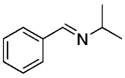
34 and 60 % at 60 and 80 °C, respectively, with high selectivity (99 %) to give *N*-benzylidene benzylamine (Table 1, entries 3–6). The yield remained unchanged (Table 1, entry 7) when a radical scavenger (2,6-di-*tert*-butyl-4-methylphenol) was added, thus excluding the possibility of an autooxidation process through a radical chain pathway. Acetonitrile was found to be the best medium among the solvents examined (Table 1, entries 8–12).

Thus, under optimized conditions (Table 1, entry 7), complete conversion of benzylamine into *N*-benzylidene benzylamine was obtained in 3.5 hours (Table 2, entries 1–4).The oxidation of various amines was therefore examined under these reaction conditions, and the results are also listed in Table 2. Benzylamines substituted with electron-donating groups (CH_3 and OCH_3) and electron-withdraw groups (Cl and CF_3) could also undergo oxidative coupling to the corresponding imines with high yields; however, the oxidation of the former (Table 2, entries 5 and 6) proceeded much more efficiently than those of the latter (Table 2 entries 7 and 8). Moreover, higher reaction rates for *para*-substituted benzylamines relative to the *meta* and *ortho* isomers reveal the presence of a steric effect (Table 2, entries 6, 9, and 10). Heterocyclic amines containing nitrogen and sulfur atoms, which usually poison most metal catalysts, could also be converted into the corresponding imines in excellent yields (Table 2, entries 11 and 12). Note that the oxidation of both pyridyl- and thiophene-methylamine appeared much more efficient than that of their phenyl counterparts. The oxidation of amines lacking a hydrogen atom at the α-carbon position, such as aniline, did not proceed under the chosen reaction conditions, and only a trace amount of azo compound was detected (Table 2, entry 13). Secondary amines also afforded the imines in moderate to excellent yields by oxidative dehydrogenation photocatalyzed by mpg-C_3N_4. But in the case of dibenzylamine, a comparably low selectivity (80 %) for the imine was observed (Table 2, entry 15), with the main by-product being benzaldehyde; the formation of which was ascribed to the oxidative cleavage of the C–N bond.[12] The same phenomenon also occurred in the case of *N*-benzylaniline (Table 2, entry 16), with by-products of benzaldehyde and aniline being formed. The oxidation of 1,2,3,4-tetrahydroisoquinoline proceeded quite smoothly with complete conversion and high selectivity in 2 hours (Table 2, entry 14). However, the reaction took place at a much lower rate for 1,2,3,4-tetrahydroquinoline, where a higher temperature and longer reaction time were necessary for the high conversion of the substrate (Table 2, entry 17). Regioselective oxidations were observed when unsymmetrical secondary amines were employed: the reaction proceeded to yield the conjugated *N*-benzylidene products in remarkably high selectivity rather than those generated from oxidation on the less activated site (Table 2, entries 14–18). Indole and an imidazole derivative were synthesized in high yields by the oxidation of the corresponding indoline and imidazoline (Table 2, entries 18 and 19). After the reaction, some products were isolated by distillation (Table 2, entries 1, 5–7, and 12).

Table 2: Oxidation of various amines using mpg-C_3N_4.[a] The general reaction is applicable to entries 1–10.



Entry	Substrate	Product	*t* [h]	Conv. [%]	Sel. [%]
1	R = H	R = H	3.5	99 90[b]	99
2	reuse 1		3.5	99	99
3	reuse 2		3.5	99	99
4	reuse 3		3.5	99	99
5	R = *p*-Me	R = *p*-Me	2.5	95 89[b]	98
6	R = *p*-OMe	R = *p*-OMe	2	95 91[b]	98
7	R = *p*-Cl	R = *p*-Cl	4	91 79[b]	90
8	R = *p*-CF_3	R = *p*-CF_3	5	95	96
9	R = *o*-OMe	R = *o*-OMe	2	69	99
10	R = *m*-OMe	R = *m*-OMe	2	72	99
11			1	95	96
12			2	99 82[b]	98
13			2	1	–
14			2	99	91
15			2	70	80
16			3	46	92
17[c]			4.5	90	91
18			5	46	98
19			4.5	88	97
20			3	82	87

[a] Reaction conditions: substrate (1 mmol), mpg-C_3N_4 catalyst (50 mg), CH_3CN (10 mL), 80 °C, O_2 (0.5 MPa). [b] Isolated by distillation. [c] 0.6 mmol of substrate, 100 °C.

The relationship between the activity and the wavelength of incident light was investigated. The results showed that the activity of mpg-C_3N_4 corresponded well with its optical absorption spectrum (Figure S1 in the Supporting Information). After the reaction, mpg-C_3N_4 could be easily separated and reused. There was no loss in terms of the catalytic activity during three consecutive runs (Table 2, entries 2–4). The recycled catalyst showed no significant differences with the fresh one in terms of local structure (as confirmed by X-ray diffraction analysis, see the Supporting Information).

To get more insight into the mechanism of the present catalytic reaction, the relative rates of oxidative coupling of *para*-substituted benzylamines (MeO, Me, H, Cl, and CF_3 groups) were examined. A reasonable linearity between the $\log(k_x/k_h)$ values and the Brown–Okamoto constant (σ^+) parameters for the oxidation of *para*-substituted benzylamines was obtained, thereby suggesting that the reaction proceeds via the intermediacy of a carbocationic species (Figure 1).[13] The kinetic isotopic effect (KIE) was inves-

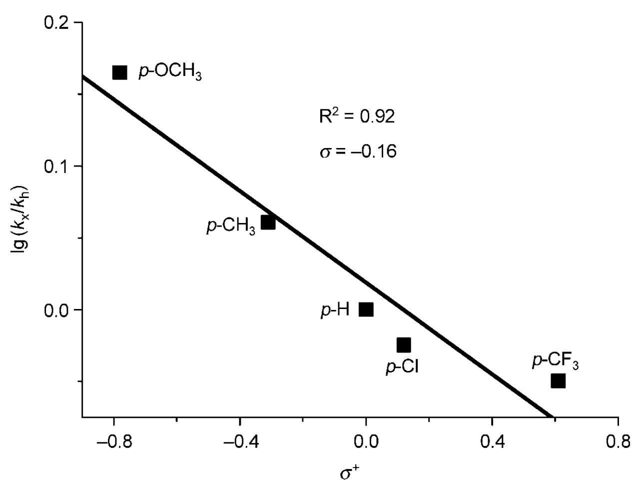
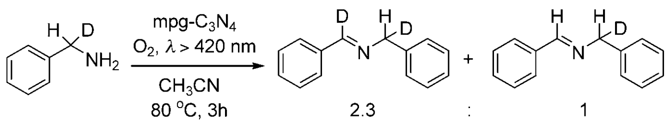


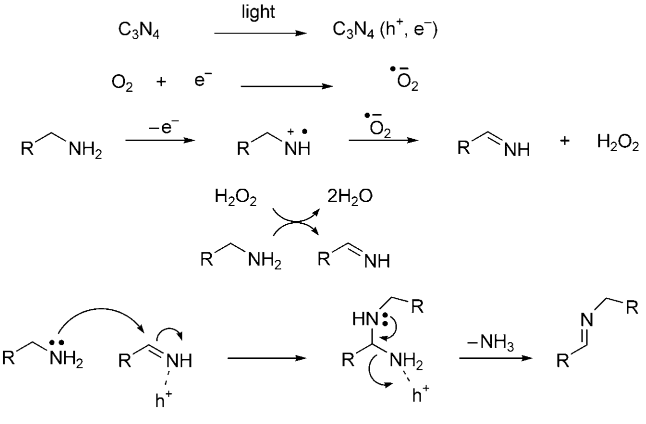
Figure 1. Hammett plots for the oxidation of substituted benzylamines with oxygen using mpg-C_3N_4 catalyst. Hammett plots were obtained from a ratio of conversion with reaction time of 30 min.

tigated by the oxidation of α-deutero benzylamine and a moderate k_H/k_D value of 2.3 was obtained (Scheme 1).



Scheme 1. Kinetic isotope effect on the oxidative coupling of α-deutero benzylamine.

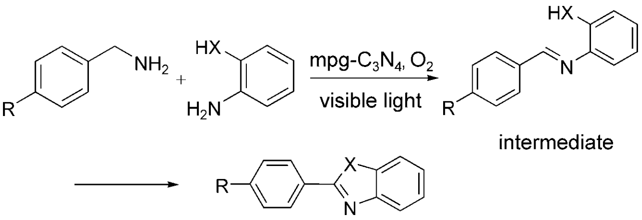
On the basis of the above results, the proposed reaction mechanism is presented in Scheme 2. Similar to inorganic photocatalysts that promote organic photosynthesis,[14] the reaction is initiated by electron (e^-) and hole (h^+) pairs photogenerated by the irradiation of mpg-C_3N_4. The photogenerated electron reduces molecular oxygen to produce $^{\bullet}O_2^-$, as already confirmed by electron spin resonance analysis in a previous report.[6] The oxidative coupling of amines then proceeds through several steps. Initially, the amine probably loses an electron, thus producing the carbocationic-radical-type intermediate. The superoxide radical anion then abstracts a proton and a hydrogen atom to form the corresponding imine, and seems to be the rate-determining step for the oxidation reaction as demonstrated by the k_H/k_D value of intramolecular deuterium isotope effects. As we never observe molecular H_2O_2, we assume the existence of a second, similar two-electron cycle on mpg-C_3N_4 that leads to the formation of water and an imine.[6] The positively charged hole can coordinate to the imine and thereby make it more prone to nucleophilic attack by the amine to form the aminal. The aminal group will then undergo hole-assisted elimination of ammonia to afford the final coupled product.



Scheme 2. Proposed mechanism for aerobic oxidative coupling of amines.

A one-pot synthesis of benzoxazoles, benzimidazoles, and benzothiazoles was also explored, in which the initial imines generated from the oxidative coupling reaction underwent intramolecular cycloaddition and subsequent oxidation to the target compounds, as depicted in Table 3. As classical methods for the synthesis of benzoxazoles, benzimidazoles, and benzothiazoles usually need rigorous conditions (i.e. high temperature) or hazardous oxidants,[15] the proposed process would represent an interesting and economically efficient catalytic strategy. Indeed, the use of 2-aminophenol, 2-aminothiophenol, and o-phenylenediamine as starting materials, respectively, gave the corresponding cascade products in moderate to high conversions (Table 3, entries 1–3). The presence of intermediate imine (detected and confirmed by GC-MS analysis) during the reaction procedures,[16] regardless of the different starting substrates, also provides strong proof for the proposed mechanism. Unfortunately, relatively low selectivities (ca. 70%) were obtained in the synthesis of benzoxazoles, with the main side product being benzaldehydes (Table 3, entries 1–4). In contrast, high conversions

Table 3: One-pot aerobic coupling synthesis of benzoxazoles, benzimidazoles, and benzothiazoles.[a]



Entry	R	X	t [h]	Conv. [%][b]	Sel. [%][b]
1	CH_3	O	5	99	69
2	H	O	5	99	75
3[d]	H	O	5	99	24
4	Cl	O	5	70	74
5	CH_3	NCH_3	4	97	92
6	H	NCH_3	5	99	98
7	Cl	NCH_3	5.5	98	91
8	OCH_3	S	4	96	97
9	H	S	5	91	92
10	Cl	S	5.5	97	93

[a] Reaction conditions: substituted benzylamine (1 mmol), mpg-C_3N_4 catalyst (50 mg), 2-aminophenol (2-aminothiophenol or o-phenylenediamine) (3 mmol), CH_3CN (10 mL), 100 °C, O_2 (0.5 MPa. [b] Conversion and selectivity were based on benzylamines. [d] 80 °C; using the main product of 2-hydroxybenzoimine.

were observed in the synthesis of benzimidazoles and benzothiazoles using substituted benzylamines (OCH_3, CH_3, H. and Cl; Table 3, entries 5–10).

To conclude, we have developed a metal-free, heterogeneous catalysis protocol for the aerobic oxidation of amines into imines using carbon nitride and visible light. This photocatalytic process avoided the employment of any metal derivative or organic oxidizing agents, and the catalyst was found to be stable and reusable. Specifically, a simple and efficient synthesis of benzoxazoles, benzimidazoles, and benzothiazoles could be realized through a one-pot synthesis by this photocatalytic cascade reaction with notably high yields. The clean and mild synthetic method described here is expected to be extended to a variety of compounds possessing these core structures.

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