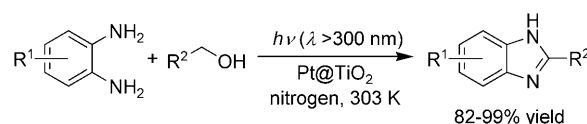


One-Pot Synthesis of Benzimidazoles by Simultaneous Photocatalytic and Catalytic Reactions on Pt@TiO₂ Nanoparticles**

Yasuhiro Shiraishi,* Yoshitsune Sugano, Shunsuke Tanaka, and Takayuki Hirai

Benzimidazole and its derivatives occupy pivotal positions in the synthesis of natural products and pharmaceutical materials. These compounds have been studied extensively because of their biological activities as bactericides,^[1] anticarcinogens,^[2] and peptic ulcer agents.^[3] There is particular interest in their activity against several viruses such as HIV,^[4] herpes (HSV-1),^[5] and influenza.^[6] The classical method for benzimidazole synthesis is the coupling of *ortho*-arylenediamines with carboxylic acids or their derivatives,^[7] which requires strongly acidic conditions and high temperatures (> 200 °C). The other method is the oxidation of benzimidazoline intermediates that are generated from the condensation of *ortho*-arylenediamines and aldehydes.^[8] This method produces benzimidazoles at relatively low temperatures (approx 100 °C), but requires unstable aldehydes as reactants and stoichiometric or excess amounts of strong oxidants such as DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone). Recent advances in this method have allowed the use of molecular oxygen as an oxidant,^[9] but these processes require homogeneous catalysts, such as metal triflates, and a free radical. Alternative methods that proceed under mild reaction conditions with stable reactants, such as alcohols and carboxylic acids, and easy-to-handle heterogeneous catalysts are therefore desirable for economically and environmentally benign benzimidazole production.

Herein, we present a new strategy for the acid- and oxidant-free synthesis of benzimidazoles using *ortho*-arylenediamines and alcohols as the reactants at room temperature under photoirradiation conditions ($\lambda > 300$ nm; Scheme 1). This process employs nanoparticles that comprise of a TiO₂ semiconductor loaded with platinum (Pt@TiO₂) as a heterogeneous catalyst. This catalyst promotes two different transformations in one pot by employing both photocatalytic and catalytic actions: the conversion of alcohols into aldehydes through a platinum-assisted photocatalytic oxidation on the



Scheme 1. One-pot synthesis of benzimidazole using a Pt@TiO₂ catalyst under photoirradiation.

TiO₂ surface,^[10] and the catalytic dehydrogenation of benzimidazoline intermediates that are generated from the condensation of *ortho*-arylenediamines and aldehydes on the platinum particle surface. Various catalytic systems that enable one-pot organic transformations have been proposed.^[11] However, there are only two reports of one-pot systems that combine photocatalysis and catalysis;^[12] both systems use a homogeneous photocatalyst (photoredox catalyst) and an organocatalyst to effect the one-pot transformations.

Pt(*x*)@TiO₂ samples, containing different platinum loadings [*x* (wt %) = Pt/(TiO₂ + Pt) 100; *x* = 0.05, 0.1, 0.2, 0.5, 1.0], were prepared by a conventional photodeposition method,^[13] in which photoirradiation of an aqueous solution that contains JRC-TiO-4 TiO₂ particles (equivalent to Degussa P25) and H₂PtCl₆ afforded gray powders of the Pt@TiO₂ catalyst. The transmission electron microscopy (TEM) image of Pt-(0.2)@TiO₂ (Figure 1) shows a spherical platinum particle

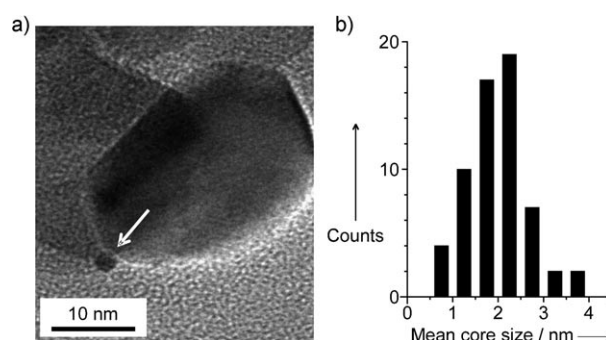


Figure 1. a) TEM micrograph of Pt(0.2)@TiO₂ and b) size distribution of platinum particles on Pt(0.2)@TiO₂.

with an average diameter of 2.0 nm. The platinum particle size increased with an increase in the platinum loading on TiO₂: where *x* = 0.5 and 1.0, the platinum particle size was 4.0 nm and 9.3 nm, respectively (see the Supporting Information, Figure S1). Furthermore, the catalysts with higher platinum loading showed an increased absorbance at $\lambda > 300$ nm owing to light scattering by the platinum particles^[14]

[*] Dr. Y. Shiraishi, Y. Sugano, Prof. T. Hirai
Research Center for Solar Energy Chemistry
and Division of Chemical Engineering
Graduate School of Engineering Science, Osaka University
Toyonaka 560-8531 (Japan)
Fax: (+81) 6-6850-6273
E-mail: shiraish@cheng.es.osaka-u.ac.jp

Dr. S. Tanaka
Department of Chemical, Energy and Environmental Engineering
Kansai University (Japan)

[**] This work was supported by a Grant-in-Aid for Scientific Research (No. 19760536) from the Ministry of Education, Culture, Sports, Science and Technology (Japan) (MEXT).

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/anie.200906573>.

(see the Supporting Information, Figure S2), although the band gap energies of the catalysts are similar (3.2–3.3 eV).

The catalytic activity of Pt@TiO₂ for the synthesis of benzimidazoles was investigated for the reaction of *ortho*-phenylenediamine (**1**) with ethanol. The change in the concentrations of **1** and the product, 2-methylbenzimidazole (**2**), of an EtOH solution containing **1** under photoirradiation ($\lambda > 300$ nm) in a nitrogen atmosphere were determined over time (Figure 2). Using pure TiO₂ (Figure 2a), 24 h photo-

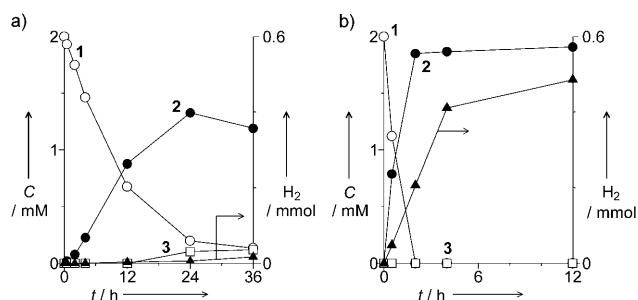
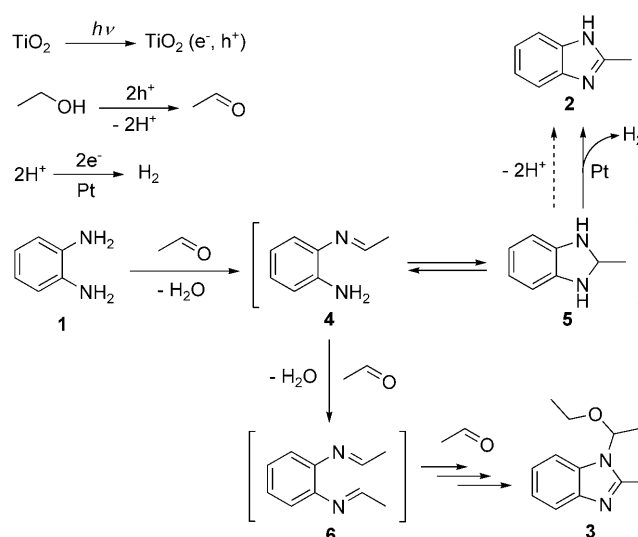


Figure 2. Time-dependent change in the concentrations of substrate and products during photoirradiation of **1** in EtOH with a) TiO₂ or b) Pt(0.2)@TiO₂ catalyst. Reaction conditions: catalyst (10 mg), **1** (20 μ mol), EtOH (10 mL), nitrogen (1 atm), $\lambda > 300$ nm, 303 K, where 10 mg Pt(0.2)@TiO₂ contains 0.10 μ mol platinum. $\circ$ = **1**, $\bullet$ = **2**, $\square$ = **3**, $\blacktriangle$ = evolution of H₂ (right hand axis).

irradiation was required to achieve > 90 % consumption of **1**, affording **2** in only circa 60 % yield. The major by-product was determined by ¹H and ¹³C NMR spectroscopy, and EI-MS analysis to be 1-(1-ethoxyethyl)-2-methyl-1*H*-benzimidazole (**3**; see the Supporting Information, Figures S3–S5), which was obtained in 5.2 % yield after 36 h irradiation. In contrast, Pt(0.2)@TiO₂ promoted the rapid and selective production of **2**; achieving > 99 % consumption of **1** after only 2 h irradiation to afford **2** in > 93 % yield (Figure 2b). This indicates that Pt@TiO₂ promotes rapid and selective benzimidazole production.

The formation of **2** was achieved by tandem photocatalytic and catalytic reactions on Pt@TiO₂ (Scheme 2). The reaction is initiated by the photoexcitation of TiO₂ particles. The excited TiO₂ produces electron (e[−]) and positive hole (h⁺) pairs. The h⁺ oxidizes EtOH to acetaldehyde on the TiO₂ surface.^[15] Spontaneous condensation of the aldehyde with **1** produced a monoimine intermediate (**4**).^[16] The rapid consumption of **1** during the reaction with Pt@TiO₂ (Figure 2b) is because the platinum particles efficiently trap e[−] on the excited TiO₂ and enhance the charge separation between e[−] and h⁺; this trapping accelerates the oxidation of the alcohol (and produces large amounts of aldehyde), and thus facilitates the rapid condensation between **1** and the aldehyde. The amount of H₂ produced after 12 h irradiation with Pt@TiO₂ was 486 μ mol, whereas pure TiO₂ produced only 3 μ mol H₂ (Figure 2). This indicates that the e[−] formed on TiO₂ was trapped by the platinum particles and consumed efficiently by the reduction of H⁺ that is formed during the oxidation of the alcohol.^[15] These results suggest that the enhanced photocatalytic transformation of the alcohol into



Scheme 2. Proposed mechanism for the one-pot synthesis of benzimidazole promoted by a Pt@TiO₂ catalyst under photoirradiation.

the aldehyde on Pt@TiO₂ allows the efficient production of intermediate **4**.

The product (**2**) is formed by cyclization of **4** followed by the oxidation of benzimidazoline intermediate **5** with the release of H⁺,^[18] where **4** and **5** are in equilibrium.^[19] Imine **4** readily reacts with a second aldehyde molecule to produce a diimine intermediate (**6**), which leads to the formation of by-product **3**.^[20] Therefore, in the classical reaction between *ortho*-arylenediamines and aldehydes,^[8,9] oxidants that promote the rapid transformation of **5** into **2** are necessary for the selective formation of **2** whilst suppressing the formation of by-products. In the Pt@TiO₂-catalyzed process, platinum particles promote the rapid and selective transformation of **5** into **2** via a catalytic dehydrogenation pathway (Scheme 2). This mechanism is confirmed by the reaction of **1** with equimolar amounts of acetaldehyde in the dark. Figure 3 shows the time-dependent change in the amounts of **1** and the products at 303 K. The rate of decrease of **1** with Pt@TiO₂ (Figure 3c) is similar to that obtained without the catalyst

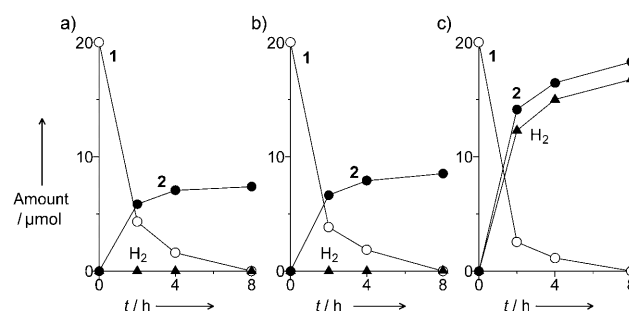


Figure 3. Time-dependent change in the amount of **1** ($\circ$), **2** ($\bullet$), and H₂ ($\blacktriangle$) during the reaction of **1** with 1 equivalent of acetaldehyde in the dark, a) without catalyst, b) with TiO₂, and c) with Pt(0.2)@TiO₂. Reaction conditions: catalyst (10 mg), **1** (20 μ mol), acetaldehyde (20 μ mol), EtOH (10 mL), nitrogen (1 atm), 303 K, where 10 mg Pt(0.2)@TiO₂ contains 0.10 μ mol Pt.

(Figure 3a) and with pure TiO_2 (Figure 3b), which indicates that the rate of condensation of **1** with the aldehyde is comparable. The yields of **2** obtained without a catalyst and with TiO_2 only were low ($<40\%$), but the addition of Pt@TiO_2 afforded **2** in quantitative yield, which indicates that the platinum particles successfully promote the transformation of **5** into **2**. In this case, a comparable amount of H_2 gas to **2** was produced, whereas other systems did not produce H_2 . This suggests that the platinum particles successfully catalyze the dehydrogenation of **5**. Therefore, the rapid transformation of **5** into **2** in the Pt@TiO_2 system leads to a shift of the equilibrium between **4** and **5** towards **5** (Scheme 2). Thus, this allows the selective formation of **2** whilst suppressing the formation of by-products. The high activity of platinum particles for dehydrogenation at room temperature is probably due to the strong affinity of the amine nitrogens of **5** to the platinum surface, as observed for the dehydrogenation of ethylenediamine on the platinum surface.^[21]

The amount and size of platinum particles are important factors in the rapid and selective benzimidazole production. Figure 4 shows the conversion of **1** and the selectivity of **2**

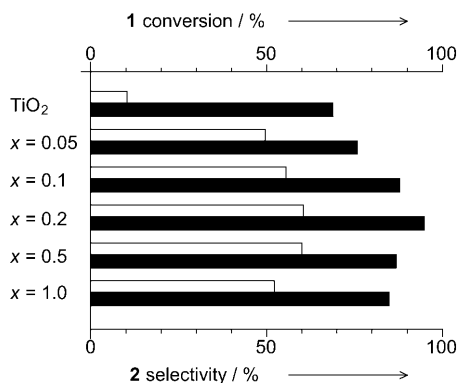


Figure 4. The conversion of **1** (□) and selectivity of **2** (■) obtained from the photoirradiation of an EtOH solution containing **1** with TiO_2 or $\text{Pt}(x)\text{@TiO}_2$ catalysts for 4 h. Reaction conditions: EtOH (10 mL), **1** (0.1 mmol), catalyst (10 mg), nitrogen (1 atm), $\lambda > 300$ nm, 303 K.

during the 4 h photoirradiation of an EtOH solution of **1** with their respective catalysts. The conversion of **1** increases with the platinum loading on TiO_2 because larger amounts of platinum allow an efficient charge separation on the photo-excited TiO_2 . The highest conversion was obtained with $\text{Pt}(0.2)\text{@TiO}_2$, and the catalysts with larger platinum loading show lower conversion. This is because excess amounts of platinum suppresses the incident light absorption by TiO_2 .^[22]

The selectivity of **2** is also affected by the amount of platinum particles; the selectivity increases with an increase in the platinum loading, but the catalysts with >0.2 wt% platinum showed lower selectivities (Figure 4). This is because the larger sized platinum particles have a lower dehydrogenation activity. As previously reported,^[23] the dehydrogenation activity of platinum particles increased with a decrease in their size; in particular, particles with a diameter of <4 nm showed very high activity. The size of platinum particles on $\text{Pt}(0.2)\text{@TiO}_2$ was 2.0 nm, whereas

when $x = 0.5$ and 1.0 the particle sizes were 4.0 and 9.3 nm, respectively. The reaction of **1** with an equimolar amount of acetaldehyde with $\text{Pt}(0.2)\text{@TiO}_2$ (4 h, 303 K) in the dark produced **2** in a 91 % yield, along with 82 % H_2 formation (see the Supporting Information, Table S1). In contrast, catalysts where $x = 0.5$ or 1.0 showed lower yields of **2** ($<80\%$) and H_2 ($<48\%$). This indicates that smaller platinum particles with a <4 nm diameter have higher dehydrogenation activities and are responsible for efficient benzimidazole formation. TEM analysis of $\text{Pt}(0.2)\text{@TiO}_2$ that had been recovered after a 12 h photoreaction for the synthesis of **2** (Figure 2b) revealed that the platinum particle size scarcely changed during the reaction (Supporting Information, Figure S6). Furthermore, the catalyst was reusable at least three times without a loss of activity (Supporting Information, Table S2).

This process is tolerant for the synthesis of various substituted benzimidazoles. Photoirradiation of alcohol solutions that contained various *ortho*-arylenediamines and the $\text{Pt}(0.2)\text{@TiO}_2$ catalyst successfully afforded the corresponding benzimidazoles (Table 1). Both 2-alkyl- and 2-aryl-substituted benzimidazoles were successfully produced in very high yields. Furthermore, 5- and/or 6-substituted derivatives were also produced successfully.

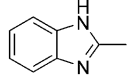
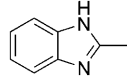
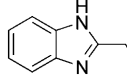
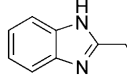
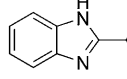
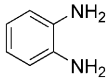
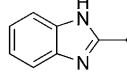
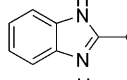
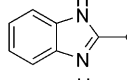
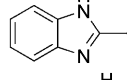
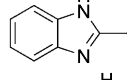
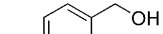
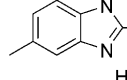
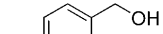
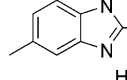
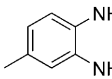
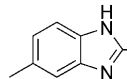
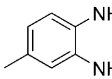
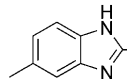
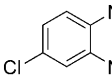
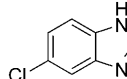
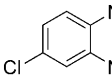
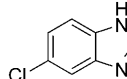
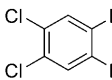
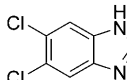
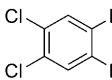
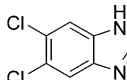
In conclusion, Pt@TiO_2 enables efficient benzimidazole production under photoirradiation conditions. This is promoted by one-pot multiple catalytic transformations on Pt@TiO_2 , which involve a platinum-assisted photocatalytic oxidation on TiO_2 and a catalytic dehydrogenation on the surface of the platinum particles. This process has significant advantages when compared with other methods:^[24] 1) a cheap and stable reactant (alcohol), 2) it does not require the use of acids or oxidants, 3) the by-products formed are harmless (only water and H_2 form during the reaction), and 4) the reaction proceeds under milder ambient conditions. Therefore, this process has the potential to enable a more sustainable benzimidazole synthesis. Organic transformations using semiconductor photocatalysts has attracted much recent attention^[25] but successful examples are still scarce. The combination of photocatalytic and catalytic reactions presented here may help to develop a new strategy towards the development of photocatalysis-based organic synthesis.

Experimental Section

JRC-TIO-4 TiO_2 (anatase/rutile = 8:2) was supplied from the Catalyst Society of Japan. The $\text{Pt}(x)\text{@TiO}_2$ [x (wt %) = 0.05, 0.1, 0.2, 0.5, and 1.0] catalysts were synthesized as follows: TiO_2 (0.1 g) and H_2PtCl_6 (0.11, 0.21, 0.42, 1.06, and 2.12 mg) were added to a water/MeOH (24:1, v/v) mixture (10 mL) in a Pyrex glass tube (20 cm³) and purged with nitrogen gas. The tube was photoirradiated using a high-pressure mercury lamp (300 W; Eikohsha Co. Ltd.; light intensity at 300–400 nm, 19.1 W m⁻²) under magnetic stirring at 303 K for 30 min. The product was recovered by filtration, washed thoroughly with water, and dried in vacuo at 353 K for 12 h. The platinum loadings were determined by X-ray fluorescence spectrometry.

Photoreaction procedure: *ortho*-arylenediamine, alcohol, and catalyst were added to a Pyrex glass tube (20 cm³). The tube was purged with nitrogen gas and photoirradiated using a xenon lamp (2 kW; Ushio Inc.; light intensity, 18.2 W m⁻² at 300–400 nm) under

Table 1: Synthesis of benzimidazoles from *ortho*-arylenediamines and alcohols.^[a]

Entry	Diamines	Amount [μmol]	Alcohol	t [h]	Catalyst	Diamine conversion [%]	Product	GC yield [%]
1		20		4	TiO_2	27		11
2		20		4	$\text{Pt}(0.2)@\text{TiO}_2$	> 99		93
3		20		4	TiO_2	56		34
4		20		4	$\text{Pt}(0.2)@\text{TiO}_2$	> 99		> 99
5		20		4	TiO_2	54		37
6		20		4	$\text{Pt}(0.2)@\text{TiO}_2$	> 99		> 99
7		20		4	TiO_2	62		43
8		20		4	$\text{Pt}(0.2)@\text{TiO}_2$	> 99		95
9 ^[b]		10		24	TiO_2	93		1.8
10 ^[b]		10		24	$\text{Pt}(0.2)@\text{TiO}_2$	> 99		89
11 ^[c]		10		12	TiO_2	> 99		57
12 ^[c]		10		12	$\text{Pt}(0.2)@\text{TiO}_2$	> 99		82
13		20		4	TiO_2	43		23
14		20		4	$\text{Pt}(0.2)@\text{TiO}_2$	> 99		94
15		20		4	TiO_2	63		11
16		20		4	$\text{Pt}(0.2)@\text{TiO}_2$	> 99		> 99
17		20		4	TiO_2	64		20
18		20		4	$\text{Pt}(0.2)@\text{TiO}_2$	> 99		83

[a] Reaction conditions: catalyst (10 mg), alcohol (10 mL), nitrogen (1 atm), $\lambda > 300$ nm; [b] catalyst (80 mg), alcohol (5 mL); [c] catalyst (5 mg), alcohol (750 μmol), MeCN (5 mL).

magnetic stirring at 303 K. The reactant and product concentrations were determined by GC equipped with FID or TCD.

Received: November 21, 2009

Revised: December 25, 2009

Published online: January 28, 2010

Keywords: dehydrogenation · photocatalysis · photooxidation · platinum · titanium

- [1] P. S. Charifson, A.-L. Grillot, T. H. Grossman, J. D. Parsons, M. Badia, S. Bellon, D. D. Deininger, J. E. Drumm, C. H. Gross, A. LeTiran, Y. Liao, N. Mani, D. P. Nicolau, E. Perola, S. Ronkin, D. Shannon, L. L. Swenson, Q. Tang, P. R. Tessier, S.-K. Tain, M. Trudeau, T. Wang, Y. Wei, H. Zhang, D. Stamos, *J. Med. Chem.* **2008**, *51*, 5243–5263.
- [2] A. W. White, R. Almassy, A. H. Calvert, N. J. Curtin, R. J. Griffin, Z. Hostomsky, K. Maegley, D. R. Newell, S. Srinivasan, B. T. Golding, *J. Med. Chem.* **2000**, *43*, 4084–4097.
- [3] K.-Fr. Sewing, *Trends Pharmacol. Sci.* **1984**, *5*, 262–263.
- [4] M. L. Morningstar, T. Roth, D. W. Farnsworth, M. K. Smith, K. Watson, R. W. Buckheit, Jr., K. Das, W. Zhang, E. Arnold, J. G. Julias, S. H. Hughes, C. J. Michejda, *J. Med. Chem.* **2007**, *50*, 4003–4015.
- [5] Z. Zhu, B. Lippa, J. C. Drach, L. B. Townsend, *J. Med. Chem.* **2000**, *43*, 2430–2437.
- [6] I. Tamm, *Science* **1954**, *120*, 847–848.
- [7] a) J. B. Wright, *Chem. Rev.* **1951**, *48*, 397–541; b) P. N. Preston, *Chem. Rev.* **1974**, *74*, 279–314; c) P. N. Preston in *Chemistry of Heterocyclic Compounds*, Vol. 40 (Eds.: A. Weissberger, E. C. Taylor), Wiley, New York, **1981**, part 1, pp. 6–60.
- [8] a) K. J. Lee, K. D. Janda, *Can. J. Chem.* **2001**, *79*, 1556–1561; b) P. L. Beaulieu, B. Haché, E. Von Moos, *Synthesis* **2003**, 1683–1692; c) K. Bahrami, M. M. Khodaei, I. Kaviani, *Synthesis* **2007**, 547–550.
- [9] a) Y.-X. Chen, L.-F. Qian, W. Zhang, B. Han, *Angew. Chem.* **2008**, *120*, 9470–9473; *Angew. Chem. Int. Ed.* **2008**, *47*, 9330–9333; b) R. Trivedi, S. K. De, R. A. Gibbs, *J. Mol. Catal. A* **2006**, *245*, 8–11; c) M. Curini, F. Epifano, F. Montanari, O. Rosati, S. Taccone, *Synlett* **2004**, 1832–1834.
- [10] B. Ohtani, M. Kakimoto, S. Nishimoto, T. Kagiya, *J. Photochem. Photobiol. A* **1993**, *70*, 265–272.
- [11] a) J. M. Lee, Y. Na, H. Han, S. Chang, *Chem. Soc. Rev.* **2004**, *33*, 302–312; b) H. C. Kolb, M. S. VanNieuwenhze, K. B. Sharpless, *Chem. Rev.* **1994**, *94*, 2483–2547.
- [12] a) D. A. Nicewicz, D. W. C. MacMillan, *Science* **2008**, *322*, 77–80; b) D. A. Nagib, M. E. Scott, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2009**, *131*, 10875–10877.
- [13] J. Lee, W. Choi, *Environ. Sci. Technol.* **2004**, *38*, 4026–4033.
- [14] E. Kowalska, H. Remita, C. Colbeau-Justin, J. Hupka, J. Belloni, *J. Phys. Chem. C* **2008**, *112*, 1124–1131.
- [15] a) Y. Z. Yang, C.-H. Chang, H. Idriss, *Appl. Catal. B* **2006**, *67*, 217–222; b) S.-I. Nishimoto, B. Ohtani, T. Kagiya, *J. Chem. Soc. Faraday Trans. 1* **1985**, *81*, 2467–2474.
- [16] H. Sharghi, M. H. Beyzavi, M. M. Doroodmand, *Eur. J. Org. Chem.* **2008**, 4126–4138.

- [17] B. Ohtani, K. Iwai, S. Nishimoto, S. Sato, *J. Phys. Chem. B* **1997**, *101*, 3349–3359.
- [18] H. Chikashita, S. Nishida, M. Miyazaki, Y. Morita, K. Itoh, *Bull. Chem. Soc. Jpn.* **1987**, *60*, 737–746.
- [19] G. Speier, L. Párkányi, *J. Org. Chem.* **1986**, *51*, 218–221.
- [20] D. Yang, D. Fokas, J. Li, L. Yu, C. M. Baldino, *Synthesis* **2005**, 47–56.
- [21] D. H. Kang, M. Trenary, *Surf. Sci.* **2000**, *470*, L13–L19.
- [22] Z.-G. Zhao, M. Miyauchi, *Angew. Chem.* **2008**, *120*, 7159–7163; *Angew. Chem. Int. Ed.* **2008**, *47*, 7051–7055.
- [23] a) M. A. Aramendía, J. A. Benítez, V. Boráu, C. Jiménez, J. M. Marinas, A. Moreno, *React. Kinet. Catal. Lett.* **1997**, *62*, 23–31; b) R. M. Rioux, B. B. Hsu, M. E. Grass, H. Song, G. A. Somorjai, *Catal. Lett.* **2008**, *126*, 10–19.
- [24] There is one report of a photocatalytic benzimidazole production process, which describes the photoirradiation of an alcohol solution containing *ortho*-dinitrobenzenes with pure Degussa P25 TiO₂: H. Wang, R. E. Partch, Y. Li, *J. Org. Chem.* **1997**, *62*, 5222–5225. However, the benzimidazole selectivity is only circa 25% (see the Supporting Information, Figure S7).
- [25] a) A. Maldotti, A. Molinari, R. Amadelli, *Chem. Rev.* **2002**, *102*, 3811–3836; b) G. Palmisano, V. Augugliaro, M. Pagliaro, L. Palmisano, *Chem. Commun.* **2007**, 3425–3437; c) Y. Shiraishi, T. Hirai, *J. Photochem. Photobiol. C* **2008**, *9*, 157–170; d) S. Yurdakal, G. Palmisano, V. Loddo, V. Augugliaro, L. Palmisano, *J. Am. Chem. Soc.* **2008**, *130*, 1568–1569.