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Organo-Photocatalysis Hot Paper

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Light-Driven Organocatalysis Using Inexpensive, Nontoxic Bi_2O_3 as the Photocatalyst**

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Abstract: *The development of enantioselective catalytic processes that make use of sunlight as the energy source and nontoxic, affordable materials as catalysts represents one of the new and rapidly evolving areas in chemical research. The direct asymmetric α-alkylation of aldehydes with α-bromocarbonyl compounds can be successfully achieved by combining bismuth-based materials as low-band-gap photocatalysts with the second-generation MacMillan imidazolidinone as the chiral catalyst and simulated sunlight as a low-cost and clean energy source. This reaction also proceeded with high efficiency when the reaction vial was exposed to the morning sunlight on a clear September day in Tarragona, Spain.*

Chemical transformations that are promoted by sunlight are currently the subject of intense research.[1] Photocatalytic methods have shown promising potential for bulk production and are widely accepted and popular as convenient strategies in the area of asymmetric catalysis.[2] In a pioneering effort, MacMillan and co-workers merged organo- and photoredox catalysis to promote the direct asymmetric α-alkylation of aldehydes[3] through a process catalyzed by $[Ru(bpy)_3]^{2+}$.[4] Since then, much effort has been devoted to the development of more convenient reaction conditions and to the extension of this combined approach to other key asymmetric organic transformations.[5] In view of the future, substantial use of such reactions, the "Achilles' heel" of these methods is their dependence on ruthenium. This is a scarce and expensive metal with rather low production (ca. twelve tons of ruthenium are mined every year) and very limited estimated world reserves (5000 tons). Furthermore, ruthenium compounds are highly toxic and suspected carcinogens. For these reasons, the identification of more convenient visible-light photocatalysts that are suitable for singly occupied molecular orbital (SOMO) activation[6] has become an area of intense research. As a result of these efforts, several reports have appeared where the commonly used $[Ru(bpy)_3]^{2+}$ catalyst is avoided. In this regard, heterogeneous semiconductors[7] as well as organic dyes[8] have been applied to the asymmetric α-alkylation of aldehydes to avoid the use of expensive ruthenium and the presence of traces of ruthenium in the final products.

In a complementary approach, Melchiorre and co-workers have recently shown that for some combinations of aldehyde and alkylating agent, a photocatalyst is not required for the light-driven alkylation to proceed, and that diarylprolinol organocatalysts alone suffice to promote the photochemical activation of the substrates through the transient formation of electron donor–acceptor (EDA) complexes.[9]

Photocatalysts that are based on heterogeneous semiconductors[10] have found some applications in the catalysis of organic reactions.[7,11] Among them, TiO_2 is by far the most used because of its low toxicity, low cost, and high reactivity.[12] However, its wide band gap (>3 eV) makes the use of UV light for its photoexcitation necessary, which should limit its use in visible-light-driven photocatalysis. In spite of this, several carbon–carbon, carbon–hydrogen, or carbon–heteroatom bond formation reactions[13] and even asymmetric α-alkylation reactions of aldehydes that are promoted by visible light in the presence of TiO_2 have been reported, but they proceed with low efficiency.[7] In turn, low-band-gap semiconductors such as $PbBiO_2Br$ have been revealed to be efficient visible-light photocatalysts for the asymmetric α-alkylation of aldehydes when they were employed either as a bulk material or in nanocrystalline form.[7] In any case, the toxicity of this material, associated with the presence of lead, severely limits its practical use.

Inspired by these results, we have focused our research on the identification of photocatalytic materials that fulfill a series of basic requirements in view of large-scale applications: They should be characterized by a low band gap (<1.5 eV) to ensure successful photoexcitation by visible light, and they should be abundant and nontoxic. Among the possible candidates, we identified bismuth sulfide (Bi_2S_3) and bismuth oxide (Bi_2O_3) as the most promising. These compounds are semiconductors with a low band gap (ca. 1.3 eV). Although Bi is ranked as the 69th most abundant element in the earth's crust (Ru is ranked 74th), a large amount of bismuth is obtained each year as a side product in the refining of different metals, such as copper, lead, tin, and tungsten,[14] and the estimated world reserves exceed 320000 tons. Therefore, bismuth and its compounds are rather inexpensive. Moreover, bismuth and most of its derivatives are nontoxic, noncarcinogenic, and non-bioaccumulative, with low solubility in blood and water.[15] Binary bismuth(III) compounds

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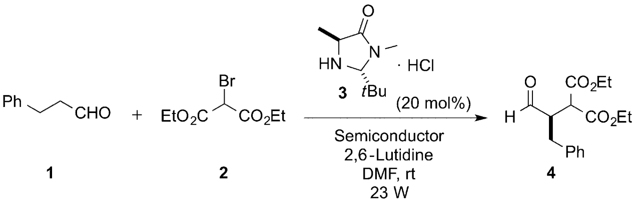
have found applications in organic synthesis,[16] but they have never been used in the context of dual organo-photocatalysis.

We accordingly decided to study the photocatalytic activity of Bi_2S_3 and Bi_2O_3. In particular, we herein report the successful application of these materials, in combination with a second-generation MacMillan catalyst, to promote the asymmetric alkylation of aldehydes with α-bromocarbonyl derivatives. Furthermore, we wanted to evaluate the influence of the physical state of these materials (nanostructured or bulk) on its catalytic behavior.

As the test reaction for process optimization, we selected the α-alkylation of hydrocinnamaldehyde with diethyl bromomalonate in the presence of MacMillan catalyst **3** (Table 1). The use of Bi_2S_3 was studied first (entries 1–4), and a nanostructured material (15 nm long and 5 nm wide) was our initial catalyst of choice (entry 1). Quite gratifyingly, full conversion was achieved in only one hour (entry 1) by irradiating with a 15 W fluorescent-bulb lamp, and the alkylated product **4** was obtained with excellent enantioselectivity (93 % *ee*). Product **4** could be isolated in a slightly improved yield (80 %) with the use of a 23 W lamp (entry 2), which was thus used for the rest of the study. As anticipated, the reaction did not proceed in the dark (entry 3). With respect to the effect of the particle size on the performance of the photoredox catalyst, it was found that a reaction performed with commercial bulk Bi_2S_3 (entry 4) showed only minor erosion in catalytic activity and enantioselectivity.

Table 1: α-Alkylation of hydrocinnamaldehyde with diethyl bromomalonate using a second-generation MacMillan catalyst and semiconductors.[a]



Entry	Semiconductor	*t* [h]	Conv.[b] [%]	Yield[c] [%]	*ee*[d] [%]
1	Bi_2S_3[e]	1	100	71	93
2	Bi_2S_3	1	100	80	93
3	Bi_2S_3[f]	12	2	nd	nd
4	Bi_2S_3[g]	3	98	54	85
5	Bi_2O_3[g]	1	100	86	93
6	Bi_2O_3[f]	48	–	–	–
7	Bi_2O_3[h]	3	99	81	72
8	Bi_2O_3[i]	1	100	80	93
9	TiO_2[j]	1	12	nd	nd
10	Fe_2O_3[g]	72	96	45	78
11	–	1	8	nd	nd

[a] Hydrocinnmaldehyde (0.90 mmol), diethyl bromomalonate (0.45 mmol), 2,6-lutidine (0.90 mmol), **3** (0.09 mmol), semiconductor (0.011 mmol), DMF (1 mL), 23 W fluorescent-bulb lamp as the light source. The reactions were performed in Pyrex glassware, and the reaction mixture was degassed before irradiation. [b] Determined by ^1H NMR spectroscopy. [c] Yield of isolated product. [d] Determined by ^1H NMR analysis of the diastereomeric acetals obtained by derivatization with (2*S*,4*S*)-2,4-pentanediol. [e] A 15 W fluorescent-bulb lamp was used. [f] Reaction carried out in the dark. [g] Commercially available powder. [h] The reaction mixture was not degassed. [i] Reaction promoted by sunlight. [j] P25 Degussa, a mixture of rutile and anatase.

We next explored the use of commercial Bi_2O_3 powder in the reaction (entries 5–8). Under the previously optimized reaction conditions (entry 2), complete conversion was recorded after one hour (entry 5), and the alkylated aldehyde **4** was obtained with excellent yield (86 %) and enantioselectivity (93 % *ee*). Control experiments showed that the reaction did not proceed in the dark (entry 6), and that the presence of dissolved oxygen had a negative effect on the process (entry 7). Most gratifyingly, the reaction proceeded to completion in one hour with high efficiency when the reaction vial was exposed to the morning sunlight on a clear September day in Tarragona, Spain (entry 8).

For comparison, titanium dioxide[7] was tested under the optimized conditions, which are given in entry 5 (entry 9). As anticipated from band-gap considerations, a rather low conversion was recorded (12 %). The even cheaper semiconductor Fe_2O_3 was also tested as a photoredox catalyst of this transformation (entry 10). In this case, a much longer reaction time (72 h) was required for complete conversion, and the alkylated product was obtained with lower yield (45 %) and moderate enantioselectivity (78 % *ee*). Finally, we wanted to test the viability of the reaction in the absence of a photocatalyst.[9] When the reaction mixture was irradiated for one hour in the absence of a semiconductor (entry 11), only 8 % conversion was observed. These last results (entries 9–11) clearly show that the bismuth derivatives employed in this study are real photocatalysts under irradiation with visible light, with efficiencies that are in accordance with their low band gaps.

To establish the scope of the asymmetric α-alkylation of aldehydes enabled by bismuth-based semiconductors as photocatalysts, we selected a representative family of aldehyde substrates and reacted them with dialkyl (methyl or ethyl) bromomalonates and with some α-bromocarbonyl compounds in the presence of either Bi_2S_3 nanoparticles or bulk Bi_2O_3 and the second-generation MacMillan catalyst **3** under the previously optimized reaction conditions. The results are summarized in Figure 1. Although not explicitly shown, the results obtained with Bi_2O_3 showed much higher reproducibility than those obtained with Bi_2S_3 nanoparticles. This is most probably due to the fact that nanostructured Bi_2S_3 is almost completely insoluble in the reaction medium, and changes in aggregation between different batches of this material lead to substantial differences in catalytic behavior. Bismuth oxide, in turn, dissolves in the reaction media as the reaction proceeds. Thus, reactions mediated by Bi_2O_3 are essentially homogeneous and hence are not influenced by the physical state of the photoredox catalyst.

By comparison with the seminal contribution of Nicewicz and MacMillan, which illustrated the potential of $[Ru(bpy)_3]^{2+}$ in this transformation, some important advantages (as well as some limitations) that are associated with the use of bismuth-based semiconductors as photocatalysts became evident. First, the reactions with bromomalonate alkylating agents (products **4**–**9**) are much faster (1–3 h vs. 5–7 h) and slightly more enantioselective with the bismuth-based photoredox catalysts than with $[Ru(bpy)_3]^{2+}$. In contrast, for processes that involve α-bromocarbonyl alkylating agents (products **10**–**14**), the reactions mediated by Bi_2X_3

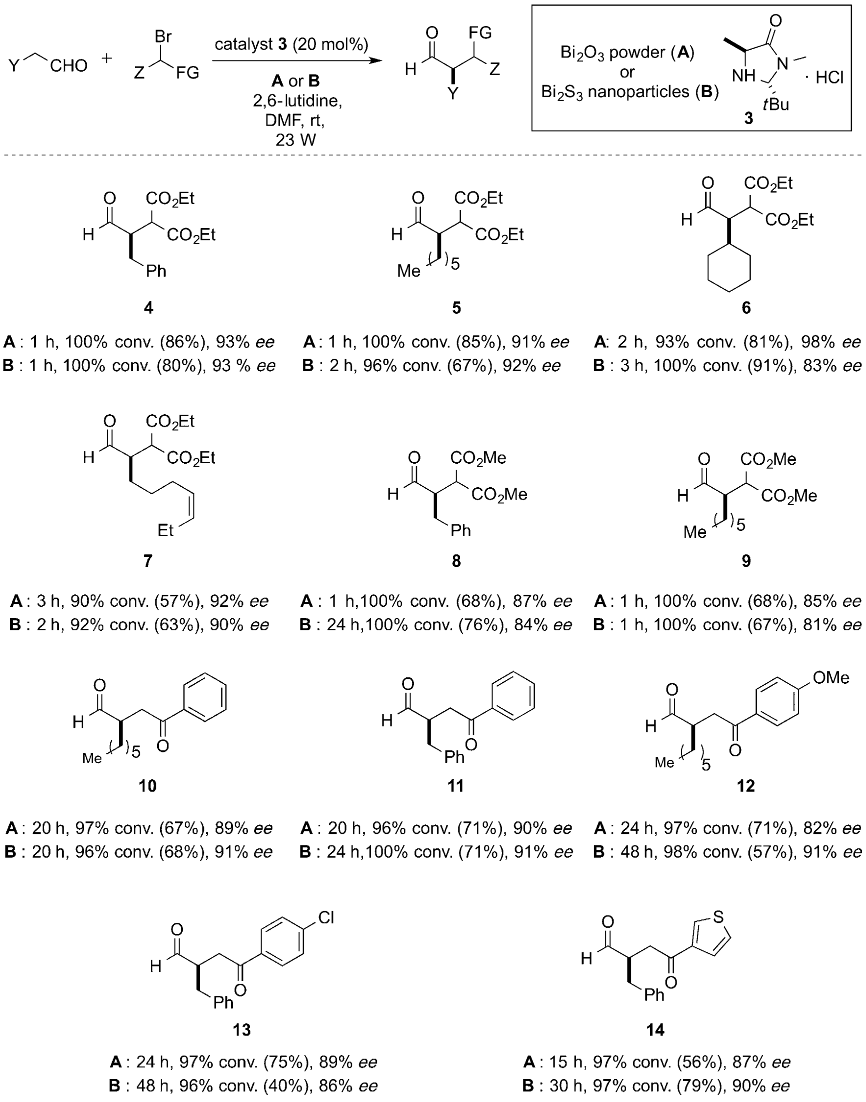


Figure 1. α-Alkylation of aldehydes with α-bromocarbonyl compounds. Conversion determined by ^{1}H NMR spectroscopy. Yields of isolated products are given in parentheses. Enantiomeric excess (*ee*) values were determined by ^{1}H NMR analysis of the diastereomeric acetals obtained by derivatization with (2*S*,4*S*)-2,4-pentanediol or by HPLC analysis on a chiral stationary phase.

required substantially more time to reach completion, although the enantioselectivities remained high (ca. 90% *ee*, with the exception of **12**). Furthermore, for these substrates, both aryl (products **10**–**13**) and heteroaryl substituents (product **14**) were tolerated in the α-bromocarbonyl component. Unfortunately, both Bi_2O_3 and Bi_2S_3 failed to mediate the formation of quaternary centers.

From a mechanistic perspective, a catalytic cycle that involves the promotion of electrons from the valence band (VB) to the conduction band (CB) as a key photochemical step should be considered (Figure 2). This type of mechanism, which has already been proposed by different groups,[7] involves the generation of radicals derived from the alkylating agent ($R^2\cdot$) by semiconductor-mediated single electron transfer (SET) with electrons that have previously been photopromoted to the CB. These radicals in turn react with the rather abundant enantiopure enamine (its concentration is dictated by the amount of organocatalyst used) in the enantiodiscriminating step to afford an α-amino radical that delivers an electron to the semiconductor, which closes the catalytic cycle.

In any case, after the findings by Melchiorre and co-workers, a background photoreaction proceeding through a secondary photocatalytic cycle that involves the formation of an EDA complex and does not require the participation of an external photocatalyst[9] should be considered. Although kinetic considerations tend to indicate that the semiconductor cycle should be much faster than the EDA cycle (the latter involves the coupling of two low-abundance radical species), which was clearly confirmed by our results on the alkylation of 3-phenylpropanal in the presence of Bi_2S_3 and Bi_2O_3 (compare entries 2, 5, and 11 in Table 1), this situation could be reverted when alkylating agents that are prone to the formation of EDA complexes are used in the reaction. To assess the relative importance of the two considered reaction modes under these circumstances, the α-alkylation of butanal with 2,4-dinitrobenzyl bromide leading to **15** was studied under Melchiorre's conditions[9] and in the presence of Bi_2O_3. Very interestingly, even in this case, the semiconductor cycle appears to predominate over the EDA cycle (Scheme 1; see the Supporting Information for the complete reaction profile).

In summary, the feasibility of using Bi_2O_3 and Bi_2S_3 semiconductors as photocatalysts for the direct asymmetric α-alkylation of aldehydes with α-bromocarbonyl compounds under organo-photocatalytic conditions has been established. Aside from the advantages of bismuth compounds in terms of their low cost and nontoxicity, we have found that bulk, commercial Bi_2O_3 is an even more active catalyst of this process than nanostructured Bi_2S_3, which appears to be due to the solubility of the oxide in the reaction medium. Both bismuth compounds are catalytically active at low concentrations under irradiation with white light from a standard-illumination fluorescent bulb or under simple exposure to sunlight. The findings reported in this communication pave the way for future applications of these environmentally friendly materials in photocatalyzed organic reactions.

Experimental Section

General procedure for the α-alkylation of aldehydes: A sealed vial containing **3** (0.09 mmol, 0.2 equiv), the corresponding bromocarbonyl compound (0.45 mmol, 1 equiv), and the photocatalyst

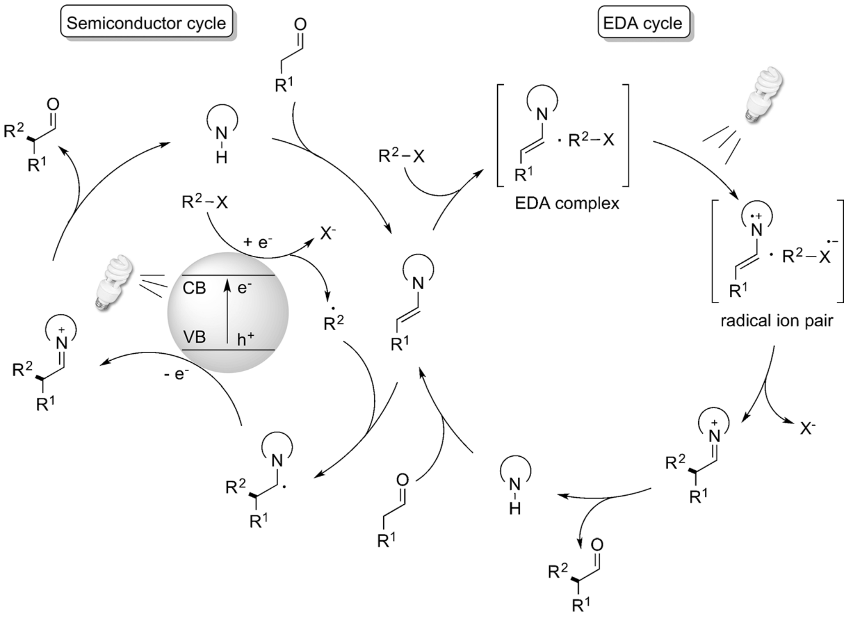
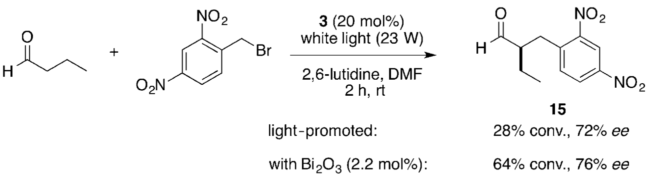


Figure 2. Proposed reaction mechanism for the organo-photocatalyzed α-alkylation of aldehydes in the presence of low-gap semiconductors.



Scheme 1. Photocatalytic α-alkylation of butanal catalyzed by **3** in the presence or in the absence of Bi_2O_3.

(0.01 mmol or 5 mg for Bi_2S_3 nanoparticles) was purged with argon, and anhydrous DMF (1 mL) was added through a septum. The aldehyde (0.9 mmol, 2 equiv) and 2,6-lutidine (0.9 mmol, 2 equiv) were added to this suspension via syringe, and the mixture was degassed for 10 minutes by bubbling argon through the reaction medium. Then, the inlet and outlet needles were removed; the vial was sealed (parafilm) and placed at a distance of 10 cm from a household bulb lamp. When the reaction was complete according to TLC analysis or ^{1}H NMR spectroscopy, the crude reaction mixture was poured into a funnel containing diethyl ether (5 mL) and H_2O (5 mL). The layers were separated; the aqueous phase was extracted with diethyl ether (3 × 5 mL), and the combined organic phases were dried over $MgSO_4$ and concentrated. The resulting residue was purified by column chromatography on silica gel (hexane/EtOAc, 90:10) to afford the corresponding product.

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