Visible Light-Driven Atom Transfer Radical Addition to Olefins using Bi$_2$O$_3$ as Photocatalyst

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Dedicated to Prof. Antonio M. Echavarren on the occasion of his 60th birthday

Abstract: Bismuth oxide, an inexpensive and non-toxic semiconductor, has been successfully used as a visible light photocatalyst for the atom transfer radical addition (ATRA) reaction of organobromides to diversely functionalized terminal olefins. The reaction takes place under very mild conditions, in the absence of any additive, and with low catalyst loading (1 mol%). The corresponding ATRA products are obtained with moderate to excellent yields (up to 95%).
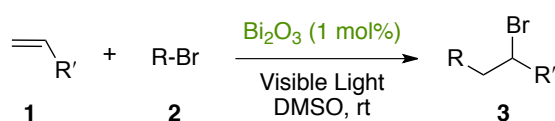
The development of chemical transformations promoted by costless energy, such as sunlight, is at the forefront of research in catalysis.[1] Within this area, the search for greener (non-toxic) and low cost catalysts, suitable for large scale production, has driven the entire field towards the intersection of organic chemistry, nanomaterials science and photochemistry.[2] In particular, much effort has been devoted to the discovery of visible light photocatalysts allowing the replacement of the yet widely used, but economically and toxicologically inconvenient, ruthenium and iridium complexes.[3] In this context, a variety of readily available semiconductors[4] and organic dyes[5] have been evaluated as photocatalysts.

Recently, we have reported the photoinduced enantioselective a-alkylation of aldehydes with a-bromocarbonyl compounds by merging the commercially available, cheap semiconducting oxide Bi$_2$O$_3$ as a photocatalyst and the second generation MacMillan imidazolidinone as an organocatalyst.[6] From a mechanistic perspective, these results strongly suggest that the readily available photoexcited state of Bi$_2$O$_3$ (this semiconductor is characterized by a low band gap of *ca*. 1.3 eV) is appropriate to promote the cleavage of reactive C-Br bonds leading to alkyl radicals. Bearing this in mind, we envisaged that Bi$_2$O$_3$ might be a convenient visible light photocatalyst for other important organic reactions initiated by electron transfer to carbon-halogen bonds.

Pioneered by Kharasch and coworkers,[7] and further studied by Curran[8] and by others,[9] the **A**tom **T**ransfer **R**adical **A**ddition (ATRA) reaction[10] consists in the addition of haloalkanes across C-C double (or triple) bonds promoting the simultaneous formation of a C-X (X = halogen) and a C-C bond. A closely related process, the **A**tom **T**ransfer **R**adical **P**olymerization (ATRP) reaction,[11,12] independently introduced by Sawamoto[12a] and
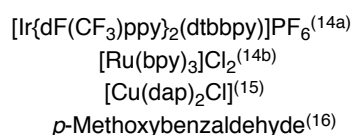
Matyjaszewski,[12b] has evolved into one of the most powerful methodologies to build up well-defined polymers and copolymers.

Typically, the ATRA reaction is accomplished using transition metal complexes and reducing agents under harsh reaction conditions.[13] In this regard, some valuable approaches have been reported involving the use of metal-mediated visible light photoredox catalysis as an alternative for this useful synthetic transformation (Scheme 1).[14] Most often, the photocatalysts employed for the photoinduced ATRA have been expensive metals based on Ir- or Ru- complexes in the presence of a Lewis acid. As an alternative to these expensive metals, Reiser and coworkers demonstrated that a homemade copper complex was also an effective visible-light photocatalyst mediating the formation of ATRA products.[15] In a different approach, Melchiorre and coworkers have very recently reported a photochemical metal-free process to mediate the ATRA reaction.[16]

This work:

Other photocatalysts in previous works:

[Ir{dF(CF$_3$)ppy}$_2$(dtbbpy)]PF$_6$[14a]
[Ru(bpy)$_3$]Cl$_2$[14b]
[Cu(dap)$_2$Cl][15]
p-Methoxybenzaldehyde[16]

Scheme 1. Catalysts for the visible light photoinduced atom transfer radical addition (ATRA) reaction. Where dF(CF3)ppy=2-(2,4-difluorophenyl)-5-trifluoromethylpyridine; dtbbpy=4,4'-di-tert-butyl-2,2'-dipyridyl; bpy=2,2'-bipyridyl, and dap=2,9-bis(para-anisyl)-1,10-phenanthroline.

Herein we report the successful application of the cheap, non-toxic and commercially available Bi$_2$O$_3$ powder as a light-driven photocatalyst to promote the ATRA reaction of a variety of organobromides into activated and non-activated alkenes under very mild reaction conditions involving either simulated or actual sunlight.

Table 1. Bi$_2$O$_3$ photocatalyzed ATRA reaction under different conditions.[a]
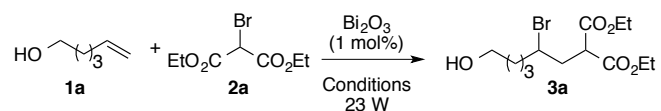
Entry	2a [mmol]	Solvent	Time [h]	Yield [%][b]
1[c]	2	DMF	24	38
2	2	DMF	24	81
3	1.2	DMF	48	63
4	2	DMSO	20	74
5[d]	1.2	DMSO	20	69
6	1.2	DMSO	20	90
7[e]	1.2	DMSO	72	-

8[f]	1.2	DMSO	72	-
9[g]	1.2	DMSO	24	-
10[h]	1.2	DMSO	6[h]	85

[a] Conditions: Bi_2O_3 (5 mg, 0.01 mmol), **1a** (1 mmol), **2a** (1.2 or 2 mmol), degassed solvent (2 mL) at room temperature. [b] Isolated yield after column chromatography. [c] LiBr (2 mmol) was used as an additive. [d] LiBr (0.1 mmol) was used as an additive. [e] Reaction performed without Bi_2O_3. [f] Reaction carried out in the dark. [g] TiO_2 (P25, Degussa) was used instead of Bi_2O_3. [h] Reaction promoted by daylight in Tarragona (41°07'00"N) in the first week of December; daylight hours computed.

To start our investigation, the reaction between 5-hexen-1-ol (**1a**) and diethyl bromomalonate (**2a**) was chosen as a model to test the performance of Bi_2O_3 (1 mol%) in the ATRA reaction under different conditions and using as light source a 23 W household fluorescent bulb lamp (Table 1). We initially studied the use of DMF as solvent, either in the presence or in the absence of LiBr as a Lewis acidic additive (Table 1, entries 1-3). Product **3a** could be isolated in good yield using a twofold amount of the ATRA donor in the absence of additive (Table 1, entry 2) but, in contrast with previous reports,[14] the presence of LiBr had a deletereous effect on the performance of the reaction causing a significant decrease in yield (Table 1, entry 1). In a similar manner, yield also decreased when the reaction was carried out with a lower excess of diethyl bromomalonate (Table 1, entry 3). We next examined the effect on the ATRA reaction of using a slightly more polar aprotic solvent, such as DMSO. Also in this case, poorer outcomes were recorded either using 2 equiv. of **2a** (entry 4) or in the presence of LiBr (entry 5). Gratifyingly, when the reaction was performed in DMSO without any additive and with a 120% molar amount of ATRA donor, a substantial increase in yield was noted (entry 6). Control experiments clearly established that the presence of both Bi_2O_3 and light was essential for the reaction to proceed (entries 7 and 8). For comparison purposes, titanium dioxide was also tested as a photocatalyst under optimized conditions (entry 9), but no conversion was recorded. Finally, the reaction conditions employed in entry 6 were used for an additional experiment promoted by daylight (entry 10). In the first week of December 2014 (partly cloudy weather) in Tarragona, 6 hours of exposure to daylight irradiation (see Supporting Information) sufficed to induce complete conversion of **1a**.

Encouraged by the results achieved in the addition of **2a** to **1a**, we decided to examine the scope of the ATRA reaction promoted by light and catalyzed by Bi_2O_3. The results of this study have been summarized in table 2.
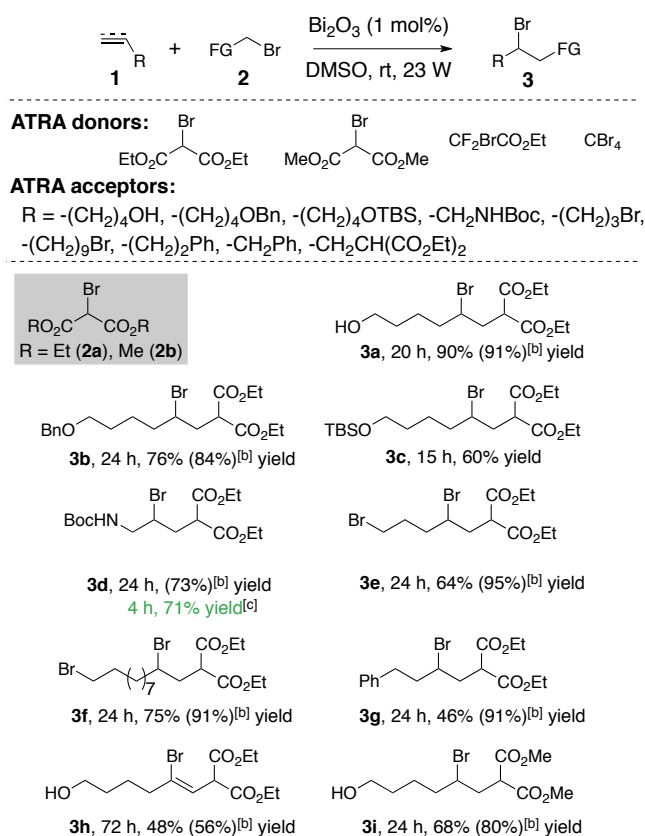
Four different ATRA donors were tested (diethyl and dimethyl bromomalonate, ethyl bromodifluoroacetate, and carbon tetrabromide). Among them, diethyl and dimethyl bromomalonate displayed the highest reactivity in the ATRA reaction promoted by light and Bi_2O_3. For instance, the reaction of diethyl bromomalonate with a variety of functionalized terminal olefins led the expected adducts (**3a-g**) in good to excellent yields (up to 95%) in relative short reaction time (< 24 hours). Interestingly, the highest yields in the preparation of some of these products are recorded when the limiting reagent is the ATRA donor (olefin/ATRA donor = 1.1), a fact not observed in the preparation of **3a**. Alkyne partners could also be used in combination with this ATRA donor leading the compound **3h** as a ca. 60/40 mixture of *Z*/*E* isomers.[17] On the other hand, the use of dimethyl bromomalonate as ATRA
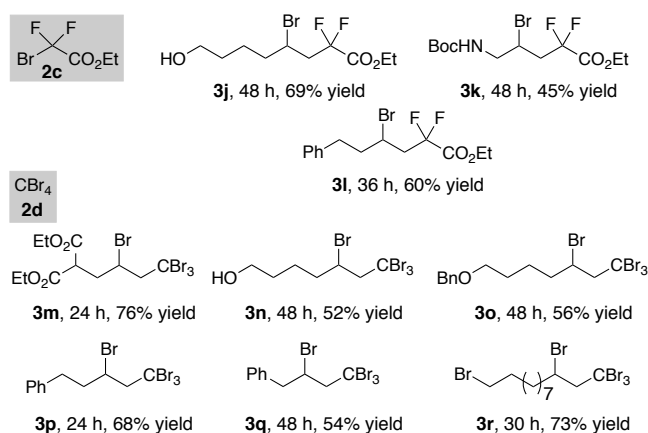
donor appears to involve slightly longer reaction times and leads to somewhat lower yields (compare **3a** and **3i**).

It is worth mentioning that the ATRA additions of **2a** performed by this procedure can be readily scaled up. Thus, **3a** could be prepared at 5 mmol scale (1.52 g, 90% isolated yield) with the same experimental setup and in the same reaction time by linearly scaling the amounts of reactants, solvent and catalyst. As a further example of the robustness of this methodology, the preparation of **3d** was also performed with daylight promotion (71% yield). Remarkably enough, the reactions performed in this manner involved shorter reaction times (4 *vs*. 24 h) than with simulated sunlight (23W lamp). Thus, the use of Bi_2O_3 as a photocatalyst effectively allows performing ATRA reactions promoted by costless sunlight energy.

Optimal conditions for the ATRA reaction of ethyl bromodifluoroacetate (**2c**) involved working with a slight excess of organobromide (**2c/1** = 1.2), as established in the initial screening (Table 1). Thus, while the formation of **3j** took place in 69% yield under these conditions, a significant yield decrease was noted (to 50%) when **2c** and **1** were used in a 1:1.1 molar ratio. A parallel behavior was observed for the formation of **3k** and **3l**.

Table 2. Scope of ATRA reaction using Bi_2O_3 as the photocatalyst.[a]

2c

3j, 48 h, 69% yield

3k, 48 h, 45% yield

3l, 36 h, 60% yield

2d

3m, 24 h, 76% yield

3n, 48 h, 52% yield

3o, 48 h, 56% yield

3p, 24 h, 68% yield

3q, 48 h, 54% yield

3r, 30 h, 73% yield

[a] Conditions: Bi$_2$O$_3$ (5 mg, 0.01 mmol), **1** (1.0 mmol), **2** (1.2 mmol), DMSO (2 mL) at room temperature. [b] Yields in parentheses are for reactions performed with **1** (1.1 mmol) and **2a** or **2b** (1.0 mmol). [c] Reaction promoted by daylight in Tarragona (41º07'00"N) in Dec. 10. Daylight hours computed.

Carbon tetrabromide (**2d**) could also be used as an ATRA donor in front of a variety of terminal olefins (**3m**-**3r**). As with **2c**, the reactions proceeded better when the ATRA donor was used in slight excess with respect to the olefin partner (**2d**/**1** = 1.2). With the aim of verifying whether the reaction catalyzed by Bi$_2$O$_3$ takes place through radical intermediate, the known radical scavenger TEMPO (1.2 mmol per mmol **1a**) was used as an additive in the preparation of **3a** under otherwise optimized conditions. As anticipated, this provoked complete inhibition of the addition reaction (Scheme 2).

Scheme 2. Inhibition by TEMPO of the visible-light-induced atom transfer radical addition (ATRA) reaction.

This fact, along with the semiconducting properties of the photocatalyst, enables us to propose the tentative mechanism shown in Figure 1.[8b,14,18] According to it; the incident photons promote the photoexcitation of electrons on the surface of the semiconductor from the valence to the conduction band, with generation of positive holes (h^+). The photoexcited electrons induce reductive cleavage of the organobromide to generate the electrophilic radical R· (**I**). Then, this photogenerated radical undergoes addition to the partner olefin-giving raise to the radical intermediate **II**. From this point, two routes are possible. In *route a* (a radical-polar crossover), the radical intermediate **II** delivers an electron to the semiconductor to neutralize a positive hole and to provide a carbocation intermediate, which ultimately reacts with bromide leading to the ATRA product **3**. In *route b,* a radical chain propagation pathway is proposed. Radical **II** subtracts a bromine atom from the starting material leading directly to **3** and regenerating radical **I** that continues the chain. Likewise, routes *a* and *b* operate in a concomitant manner. While *route b* is well established in the context of the ATRA reaction,[8b,14] the nature of Bi$_2$O$_3$ (solid semiconductor particles) could importantly favor *route a*.[19]
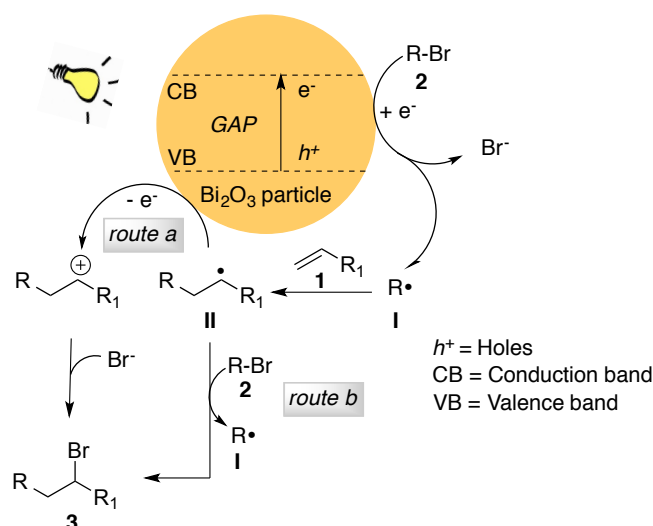
Figure 1. Proposed mechanism for the Bi_2O_3 catalyzed, visible light photoinduced atom transfer radical addition (ATRA) reaction.

In conclusion, a simple catalytic system composed of a non-toxic, commercially available Bi_2O_3 powder operating at low loading (1%) under visible light irradiation in DMSO displays excellent performance in the ATRA reaction between a variety of olefins and organobromides. The photocatalytic reaction works specially well for dialkyl bromomalonate ATRA donors, and allows using costless daylight to promote the process. Interestingly, the present methodology does not require the use of any additive for the reaction to proceed and offers advantages in cost and atom economy over previously reported methods involving the use of expensive metals or large amounts of organic materials.

Experimental Section

General procedure for ATRA reaction: To a sealed vial filled with argon, containing Bi_2O_3 powder (5 mg, 0.01 mmol), the corresponding organobromide (1.2 mmol, 1.2 equiv) and degassed dimethylsulfoxide (2 mL) was added through a septum. To this suspension, the alkene (1 mmol, 1.0 equiv) was added via syringe, and the mixture was degassed for 10 min by bubbling argon through the reaction medium. Inlet and outlet needles were removed; the vial was sealed (parafilm) and placed at a distance of 10 cm from a household bulb lamp (26 W). When the reaction was complete according to TLC or ^1H NMR, the crude was poured into a funnel containing ethyl acetate (5 mL) and H_2O (5 mL). The layers were separated; the organic phase was extracted with ethyl acetate (3 x 5 mL), washed with brine, dried over $MgSO_4$ and concentrated. The resulting residue was purified by column chromatography on silicagel (cyclohexane/ethyl acetate) to afford the corresponding product.

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[17]   Diastereomeric ratios were determined by ^{1}H NMR analysis. The *E* and *Z* configurations were unambiguously assigned by 2D [1]H-^{1}H NOESY experiments.

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[19]   The participation in the process of solid semiconductor particles could allow that all the events involved in the generation of radical intermediate **II** and its conversion into **3** through *route a* could take place in solvent cages containing **1** and **2** on the surface of Bi_2O_3 particles. As a consequence, *route a* would benefit from a very favorable entropy factor.

Let the sunshine in: Bismuth oxide, a cheap and non-toxic semiconductor, efficiently converts sunlight into chemical energy. The ATRA addition of organobromides to terminal olefins is efficiently promoted by Bi_2O_3 (1 mol%) under the influence of actual or simulated sunlight.