Communication

Visible Light-Promoted Arylation Reactions Photocatalyzed by Bismuth(III) Oxide

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Abstract: Bismuth(III) oxide has been successfully applied as a photocatalyst in the arylation of heteroarenes starting from diazonium salts. With a low catalyst loading (1 to 5 mol%), this cheap and non-toxic semiconductor could efficiently promote the formation of the aryl radical under visible light irradiation. The phenylated products were obtained in moderate to good yields, even in a 10 mmol scale. In two cases, the diazonium salt was generated *in situ* and directly used in catalysis. Besides heteroarenes, Bi_2O_3 proved also to catalyze the arylation of differently substituted alkenes and alkynes, thus representing a viable and practical alternative to the more commonly used ruthenium complexes and organic dyes.

In the latest years, photocatalyzed transformations have been receiving increasing attention.[1] Especially when promoted by visible light-sources, photocatalysis represents an important pillar in the development of greener synthetic strategies.[2] On the other hand, the common use of metals like ruthenium and iridium as catalysts in those processes constitutes a significant limitation, because of their high cost and toxicity. For this reason, the quest for cheaper, environmentally benign and non-toxic photocatalysts constitutes a fundamental challenge in synthetic chemistry. Organic dyes[3] and inorganic semiconductors[4,5] can efficiently substitute metal complexes in many photocatalytic transformations. In 2014, our laboratory pioneered the use of bismuth(III) oxide as an efficient photocatalyst. Bismuth(III) oxide has the advantage to be not only very cheap, but also non-toxic.[6] Moreover, differently from titanium(IV) oxide, it possesses a smaller band gap (2.1 – 2.8 eV), so it is able to absorb light in the visible region.[7] Till now, it has been successfully used in the photocatalyzed enantioselective α-alkylation of aldehydes,[8] as well as in atom transfer radical addition (ATRA) reactions,[9] and in photopromoted radical thiol-ene reactions using Bi_2O_3.[10] Looking for new applications for this semiconductor, we focused our attention on processes initiated by the formation of phenyl radicals starting from phenydiazonium salts **1**.
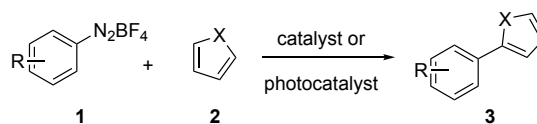
Scheme 1. Arylation reaction with diazonium salts **1**.

Particularly, the arylation of heteroarenes represents an appealing reaction since it provides access to important heterobiaryl structures which can find applications in several scientific fields, for their biological[11] and optical[12] properties. Thanks to their characteristics (a weak and labile C-N bond),[13] diazonium salts have been widely exploited in arylation reactions.[14] The copper-catalyzed version of this transformation (the Meerwein arylation) has been known since the 1930s, but it suffers from some important drawbacks, such as the usually low yields and the high catalyst loading required.[15] Since then, many variations of the original procedure have been reported (Scheme 1), involving both thermal[17-21] and photochemical[22-27] reaction conditions.[16] König and coworkers proved that this transformation can be photocatalyzed by eosin Y,[22a] and that under visible light irradiation the phenyl radical is formed from the diazonium salt **1**. In the field of inorganic photocatalysts, initial work dealing with the use of Ru(II) complexes as visible-light photocatalysts[25] has been followed by the use of the more convenient titanium(IV) oxide,[26] in spite of its larger band gap. In fact, TiO_2 can form a diazoether together with **1**, which absorbs light in the visible spectrum.[27] Although stoichiometric amounts of TiO_2 were often necessary, the problem was partially overcome by the immobilization of the semiconductor in the microchannels of a continuous-flow reactor.[28]

Herein, we report the successful application of inexpensive, commercially available, and non-toxic bismuth(III) oxide to promote the photocatalyzed α-arylation of heteroarenes (Table 1). To optimize conditions, the reaction of furan (**2a**) with 4-bromobenzenediazonium tetrafluoroborate (**1a**) was selected as a benchmark. The light source was in all cases a household 23 W compact fluorescence lamp (CFL, see Supporting Information).[29]

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Table 1. Optimization of reaction conditions.
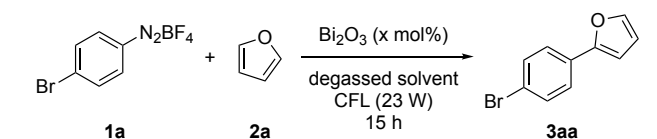
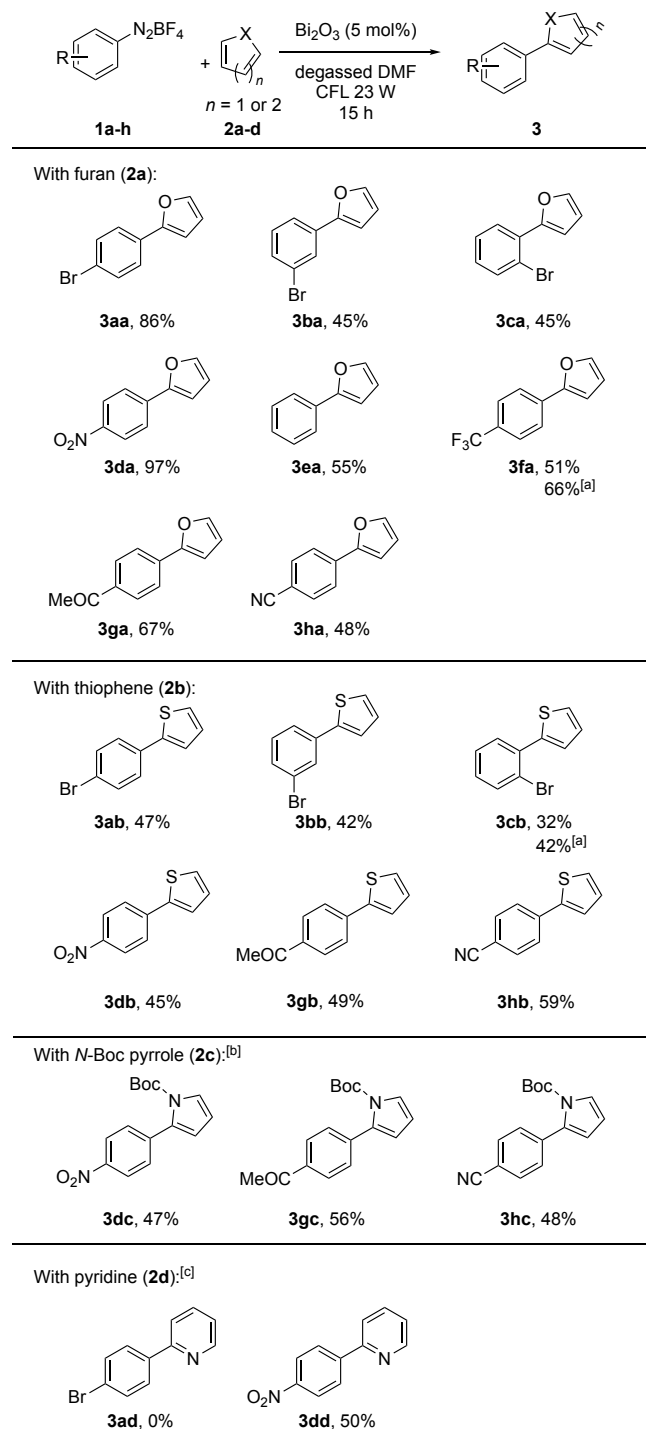| Entry[a]	Catalyst loading (mol%)	**2a** (equiv.)	Solvent	Yield (%)[b]
1	5.0	27	DMSO	64
2[c]	5.0	27	DMSO	20
3[d]	0	27	DMSO	25
4	5.0	27	CH3CN	15
5	5.0	27	EtOH	–
6	**5.0**	**27**	**DMF**	**86**
7	10[e]	27	DMF	50
8	5.0[f]	27	DMF	54
9	5.0	10	DMF	36
10	10	10	DMF	36
11[g]	1.0	27	DMF	70
12[h]	1.0	27	DMF	74

[a] **1a** (0.25 mmol), **2a** (27 equiv.), Bi_2O_3 (5 mol%), degassed DMF (1 ml), visible light (CFL, 23 W), 15 h. [b] After column chromatography. [c] The reaction was performed in the dark. [d] The reaction was carried out for 65 h. [e] $BiVO_4$ (10 mol%) was used instead of Bi_2O_3. [f] Bi_2S_3 (5.0 mol%) was used instead of Bi_2O_3. [g] The reaction was carried out on 1 mmol scale (0.27 g of **1a**). [h] The reaction was carried out on 10 mmol scale (2.7 g of **1a**).
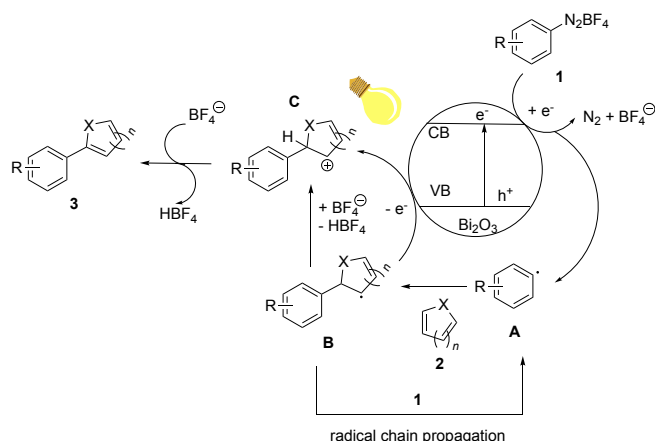
To our delight, in degassed DMSO and with 5 mol% of catalyst, the corresponding product **3a** was obtained in 64% yield (Table 1, entry 1). When performing the reaction either in dark conditions (entry 2) or in the absence of the catalyst (entry 3), **3a** was isolated in low yields, even after prolonged reaction time. From the screening of different solvents (entries 4 – 6), DMF emerged as the optimal one. In ethanol, in turn, only degradation products could be observed by ^{1}H NMR in the reaction crude (entry 5).[30] $BiVO_4$ and Bi_2S_3 proved not to be as efficient as Bi_2O_3, even though using the double catalyst loading (entries 7 and 8). Decreasing the excess of furan used in the reaction (from 27 to 10 equivalents), led to a substantial drop in yield (entry 9). On the other hand, increasing the amount of Bi_2O_3 loading did not cause any yield improvement (entry 10). Interestingly, only 1 mol% of catalyst is sufficient to catalyze the arylation, as it was proved scaling-up the reaction to 1 mmol or even up to 10 mmol (entries 11 and 12). In this way, it was possible to isolate 1.65 g of product **3aa**. With the optimized conditions in hand, we started to explore the substrate scope (Scheme 2). The reactions were performed on 0.25 mmol scale and, for practical reasons, a 5 mol% of Bi_2O_3 was used. Not only furan (**2a**), but also thiophene (**2b**), N-Boc-pyrrole (**2c**, with only 12 equivalents), and pyridine (**2d**) were

tested in the reaction. The substitution pattern partially affects the outcome of the transformation. In fact, when *metha-* and *ortho-* substituted diazonium salts (**1b** and **1c**, respectively) were reacted with furan, the yields dropped down (compare **3aa**, **3ba** and **3ca**), whereas the corresponding reactions with thiophene were not affected (compare **3ab**, **3bb**, and **3cb**).

Scheme 2. Substrate scope. [a] The reaction was promoted by sunlight for 8 h in Tarragona (Spain; 41.11º N) in the second week of May. [b] With 12 equiv. of **2c**. [c] With 1.2 equiv. of DIPEA.

The presence of electron-withdrawing group in the diazonium salt seems to have an influence on the reaction outcome. However, even the electron-neutral diazonium salt **1e** delivered the corresponding product **3ea** in moderate yield (55%). 4-Nitrophenyl derivatives **3da**, **3db**, **3dc**, **3dd** were isolated in moderate (45-50%) to excellent (97%) yields. Particularly, in order to obtain the pyridine derivative **3dd**, it was necessary to modify the standard conditions by addition of 1.2 equivalents of diisopropylethylamine (DIPEA). This base is probably necessary to neutralize the tetrafluoroboric acid formed during the reaction progress, which likely protonates the pyridine moiety, leading to deactivation in the absence of a base. On the other hand, **3ad** was not obtained even in the presence of added base. 4-Trifluoromethyl-, 4-acetyl-, and 4-cyanophenyldiazonium tetrafluoroborate (**1f**, **1g**, and **1h**, respectively) were all well tolerated and furnished the corresponding products in moderate yields, irrespectively of the heteroarene partner (see products **3fa**–**3ha**, and **3gb**–**3hc**). It was possible to improve the yields of the transformation, by exposing the reaction vessell to solar irradiation for 8 hour, instead of CLF. This was proved with products **3fa** and **3cb**, where yields increased of 15% and 10%, respectively. Interestingly, it is also possible to generate the starting material *in situ*, as demonstrated by Ranu and coworkers (Scheme 3).[22b] Starting from the corresponding aniline **4**, *tert*-butyl nitrite works as a diazotizing agent to form **1**. In the presented instance, the heterobiaryl compounds **3ha** and **3hb** were obtained in yields comparable to the ones of the standard procedure. This indicates the non-interference of *tert*-butyl nitrite with the reaction pathway triggered by Bi$_2$O$_3$.

Scheme 3. *In situ* generation of diazonium salt and concomitant photocatalytic arylation mediated by Bi$_2$O$_3$.

In order to prove the efficiency of bismuth(III) oxide in related photocatalytic arylations, we also studied the addition of phenyl radicals to non-aromatic, yet unsaturated systems. (Scheme 4). The three studied reactions had been previously reported with ruthenium(II) complexes as photocatalysts. In the first case (Scheme 4-A),[31] Bi$_2$O$_3$ works as a co-catalyst together with a gold(I) complex: whereas the semiconductor likely promotes the formation of the phenyl radical, the gold activates the propargyl alcohol **5**, allowing the formation of the desired product **6** in high yield. The photocatalytically-generated aryl radical can also efficiently attack enol acetate **7**, affording **8** in 90% yield, a result that favorably compares with the one reported with [Ru(bpy)$_3$]Cl$_2$ (Scheme 4-B) and the same substrate.[32] Moreover, 3,3-disubstituted oxindole **10** could be isolated in 46% yield starting from *N*-arylacrylamide **9** and **1b** (Scheme 4-C).[33] Although the yield achieved in this case is somewhat lower than the one reported with ruthenium(II), the result is still exciting since no transition metal is employed.

Scheme 4. Other applications of Bi$_2$O$_3$-photocatalyzed arylations. Conditions: (a) Bi$_2$O$_3$ (2.5 mol%), Ph$_3$PAuCl (2.5 mol%), degassed MeOH, CFL (23 W), 20 h; b) Bi$_2$O$_3$ (5.0 mol%), degassed DMF, CFL (23 W), 20 h; c) Bi$_2$O$_3$ (5.0 mol%), degassed DMSO, CFL (23 W), 20 h.

In accordance with literature precedents,[22,27] we proposed a mechanism involving first the photoinduced excitation of Bi$_2$O$_3$. (Scheme 5). In this way, one electron gets promoted from the valence band (VB) to the conduction band (CB), generating positive holes (h$^+$). Thanks to the low gap of bismuth oxide, only visible light is required for this promotion, which is followed by electron transfer to the diazonium salt. After that, the diazonium salt **1** is transformed into the phenyl radical **A**, with evolution of nitrogen gas and tetrafluoroborate anion. The so-formed species **A** would then attack the heteroarene **2**, affording the radical **B**. From this point, two possible pathways are possible: i) a radical crossover, where the catalyst is re-generated, by abstraction of an electron from the intermediate radical **B**, furnishing the cation species **C**; and ii) a situation where **B** directly reacts with the diazonium salt **1** yielding the radical **A**, which starts the cycle again, following a radical chain propagation mechanism. In any

case, **C** gets deprotonated by the tetrafluoroborate, giving rise to the desired phenylated product **3**.

Scheme 5. Proposed mechanism of the transformation photocatalyzed by Bi_2O_3 (VB = valence band, CB = conductive band, h^+ = hole).

In summary, we have found a new use for Bi_2O_3 as a photocatalyst in Meerwein-type arylation reactions. This cheap and non-toxic semiconductor can catalyze the formation of aryl radicals starting from easily available diazonium salts. At a difference from titanium(IV) oxide, only 5 mol% of catalyst is necessary to prepare a wide range of differently-substituted α-arylated heteroarenes, and the catalyst loading can be reduced up to 1 mol% for experiments in larger scales. In this way, it is possible to perform the reaction up to a 10 mmol scale, without any significant loss of yield. The process tolerates *in situ* generation of the diazonium salts from the corresponding anilines. Yields vary from moderate to excellent, the combination of electron-rich heteroarenes with electron-poor diazonium salts usually leading to optimal yields. Interestingly, the use of sunlight to promote the reaction can shorten reaction times and improve the outcome of the transformation, probably as the result of more homogeneous illumination. As an extension of this chemistry, bismuth(III) oxide has also been successfully applied to promote the aryl addition to different unsaturated systems.

Experimental Section

Diazonium salt **1** (0.25 mmol, 1.0 equiv.) and Bi_2O_3 (6 mg, 5 mol%) were solved in DMF (1.5 ml) under argon. The solution was degassed with an argon flow during 10 minutes. Afterwards, the heterocycle **2** (27 equiv.) was added. The reaction mixture was sealed and placed at 10 cm from a 23 W CFL. After 15 hours, the mixture was poured into water (5 ml). The organic phase was extracted with Et_2O (3 x 5 ml) and washed with water and brine. After drying it with $MgSO_4$, the reaction mixture was filtered and concentrated under vacuum. The desired product was purified by silica gel column chromatography.

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[30] This fact is remarkable, since Rueping *et al.* selected ethanol as the solvent for the same transformation catalyzed by TiO_2, whereas no product was observed in other solvents. Ethanol was necessary in their case in order to form a diazoether, which was the species absorbing the visible light.[27] Thanks to its smaller band gap, Bi_2O_3 does not require the formation of the diazoether species (see UV-visible spectra in the Supporting Information), so the reaction proceeds well without alcoholic solvents.

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