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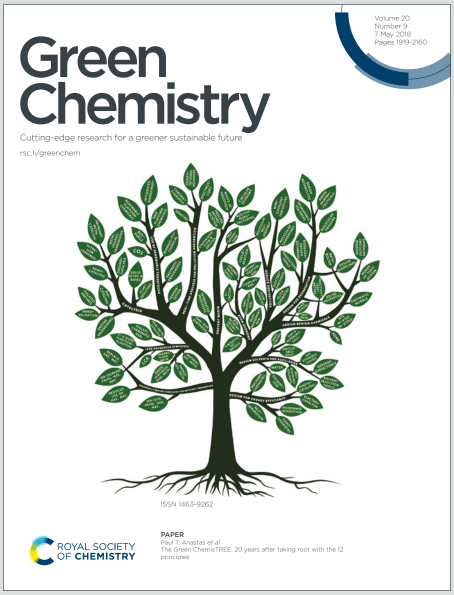

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Continuous flow processing of bismuth-photocatalyzed atom transfer radical addition reactions using an oscillatory flow reactor

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Metal oxides represent an abundant and non-toxic class of photocatalysts for organic transformations. However, their use in larger scale processes is complicated by incompatibilities with continuous flow processing – a proven scale-up route for photochemistry. We detail the development of an efficient atom transfer radical addition protocol using a sustainable solvent system (acetone:PEG 400) and a low loading (2 mol%) of Bi_2O_3, which can be handled in an oscillatory flow reactor. Optimization of the reaction and oscillatory parameters led to high throughput (36 g in 4 h, 89% yield, 599 g L^{-1} h^{-1}), with a process mass intensity (PMI) of just 8.5. The process also facilitates high recyclability (3 cycles with no loss of yield), and was demonstrated to be applicable to a range of other substrates on multigram scale, in moderate to excellent yields.

Introduction

Bismuth, the 83rd element of the periodic table, is a metal which is increasingly considered for catalysis because of its low cost, non-toxic nature, large reserves and good availability.[1] Among bismuth species, the semiconductor bismuth oxide (Bi_2O_3) has gained some interest as a photocatalyst in recent years. This is, in part, owing to its lower bandgap compared to the other commonly used metal oxide semiconductor photocatalysts, such as titanium oxide (Bi_2O_3 = 2.6 eV vs 3.0 eV or 3.2 eV for TiO_2 in its rutile or anatase forms, respectively). This advantage enables the use of visible light irradiation in place of high energy UV wavelengths.[2] A small number of synthetically useful transformations using Bi_2O_3 as a photocatalyst have already been demonstrated, in particular by Pericàs et al.[3]

Performing visible-light-driven reactions is appealing since it can enable mild conditions, selectivity, sustainability, and catalytic amounts of the light-absorbing species. Therefore, various photocatalysts have been developed for a broad range of organic reactions.[4] Atom transfer radical addition (ATRA) reactions have received substantial attention as a photocatalyzed synthetic transformation, whereby a substrate R-X inserts across an unsaturated compound, resulting in complete atom incorporation. The addition of haloalkyl, aminoperfluoroalkyl, hydroperfluoroalkyl, or haloperfluoroalkyl moieties, to name a few, have been successfully performed upon light irradiation.[5]

Among these reactions, the use of organobromide substrates has interested researchers because of their safer profile than HBr or Br_2. Since bromination is also an important reaction in organic synthesis,[6] these transformations are attractive from a sustainability viewpoint. Accordingly, less toxic, more abundant, and cheaper catalysts than iridium or ruthenium complexes have been proposed for such reactions, Bi_2O_3 being one of these candidates.[3a]

Despite the attractive profile of visible light-driven reactions, the requirement for efficient light penetration to homogeneously irradiate the reaction vessel renders them difficult to manage, especially at synthetically useful concentrations. As described by the Beer-Lambert law, increasing the size of a batch vessel leads to drastic light attenuation, potentially leading to degradation and side-product formation. To tackle this issue, continuous flow has been proven as a powerful alternative processing method.[7] The small dimensions of the reactor channels ensure a short irradiation path length (which allows quasi homogeneous irradiation), thus eliminating potential dark zones and increasing the efficiency and scalability of these reactions. Surprisingly, despite the well-explored benefits of flow photochemistry, relatively few ATRA reactions in flow have been reported.[8]

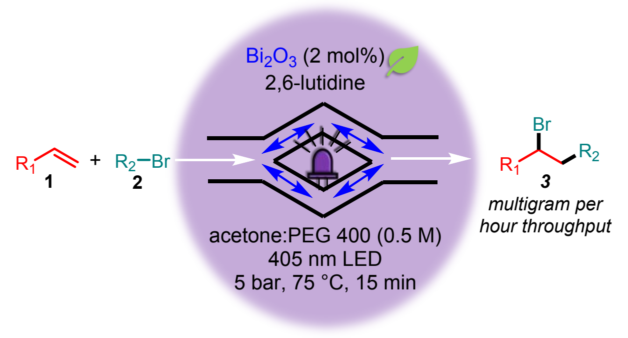

Fig 1. General scheme of the bismuth-photocatalyzed ATRA across unsaturated compounds in flow.

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The use of continuous flow reactors, however, can raise numerous issues, particularly when handling solids. Depending on the flow rate, the properties of the reactor and the reaction medium, settling and even clogging will occur unless preventative measures are taken.[9] An appealing development for efficiently handling solids in flow is that of oscillatory flow reactors (OFRs). The use of a superimposed pulsation (meaning the addition of a symmetric pulse on top of the net flow rate) enhances mixing, hence ensuring a stable suspension of the solids along the reactor. Other advantages of this technology include: mixing independent of the net flow rate, ease of scale-up, and improved heat transfer.[10] Interest in this promising strategy has grown significantly over the last 20 years, facilitating the development of various oscillatory flow processes for multiphase and/or slow reactions, which are difficult to handle using conventional flow reactors.[11] Specifically, an OFR using static mixing elements (the HANU reactor commercialized by Creaflow)[12] has recently been demonstrated as an effective flow reactor for photochemical reactions containing solids,[13] or two immiscible liquid phases.[14] This reactor has previously been characterized actinometrically, demonstrating a high volumetric photon flux of 1.97 × 10^{-3} mol L^{-1} s^{-1}.[13b]

In this work, the inherent assets of an OFR were combined with the potential of Bi_2O_3 as a sustainable and non-toxic visible light photocatalyst, to provide an efficient protocol for ATRA reactions of organobromides **2** with terminal olefins **1** (Fig. 1). The OFR used in this study has previously been exploited for handling two different solids in flow, a carbon nitride derivative (density = 2.34 g cm^{-3})[13a] and Na_2CO_3 (density = 0.86 g cm^{-3}).[13b] The innovative process, presented here, pushes the limit of this reactor setup in terms of handling solid particles and enables processing of a homogeneous suspension of the much denser solid, Bi_2O_3 (density = 8.90 g cm^{-3}).[15]

Results and discussion

Batch optimization

For the purpose of reaction optimization, the reaction between 1-hexene **1a** and diethyl bromomalonate **2a** was chosen as a model (Fig. 2). A few observations regarding the physicochemical properties of Bi_2O_3 were first considered. Firstly, Bi_2O_3 can react with HBr to form BiOBr or $BiBr_3$, depending on the content of HBr in the medium.[16] Starting material **2a** contains ~5% HBr due to debromination into diethyl malonate. Furthermore, HBr can be formed during elimination as a side reaction following the ATRA,[17] leading to acidification of the reaction mixture and reaction of the bismuth species. The resulting complexes are far more soluble and possess different optical properties than Bi_2O_3.[18] It is, therefore, recommended to add an organic base to the medium, such as 2,6-lutidine to keep Bi_2O_3 intact (see Fig. S5a). As proposed in other studies, this base may also interact with the alkyl halide substrate, activating the C-Br bond to cleavage.[8b]

Another important point to consider is the observation of black solids, attributed to Bi_2O_3 reduction to Bi^0 through a radical process promoted by light. This transformation strongly depends on the solvent properties (see Fig. S5b). However, this reduction is hypothesized to be slower than the ATRA reaction, since it was only observed after complete reaction conversion (i.e. by overirradiation of the reaction medium), further emphasizing the benefits of continuous flow to prevent such phenomena.

Finally, Bi_2O_3 has a bandgap that depends on the size and morphology of the particles.[19] Between the particles of 90-210 nm diameter and the ones of 10 µm diameter that were commercially available, the larger ones were chosen, owing to their significantly higher reactivity (see Fig. S5c and Table S1). Incidentally, these were also more readily available (EUR55 / 100 g).[20]

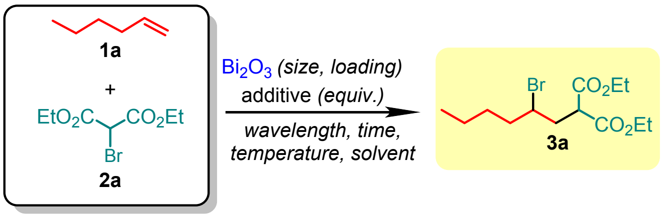

Fig. 2 Bismuth-photocatalyzed ATRA reaction model between 1-hexene (**1a**) and diethyl bromomalonate (**2a**).

It has been decided to use visible light (λ >380 nm) instead of UV since it is less harmful and less energetic, hence fitting within the context of greenness and improved substrate compatibility. LEDs of 405 nm and 460 nm were available for the flow setup (or 400 nm and 455 nm for batch experiments). The 400 nm and 405 nm wavelengths were selected, since the absorption profile of Bi_2O_3 decreases drastically between 400 and 500 nm.[19b] This choice was reinforced with comparative experiments in batch, which showed that the reaction was much faster at 400 nm than at 455 nm (5 h instead of 20 h; see Table S1 for initial reaction scoping experiments in batch).

The context of sustainability requires a conscientious choice of solvent, considering its impact on health, safety, and environment.[21] Furthermore, its inert profile towards the photocatalyst, as well as performance in the ATRA reaction must be considered. As an additional parameter for this application, a high solvent viscosity may significantly decrease the potential settling of the catalyst particles. A screen of solvents was, therefore, performed and the corresponding results are presented in Table 1, alongside the solvent's properties.

The only way to fulfill all these requirements was to mix two solvents. Dimethylsulfoxide, dimethylformamide, acetonitrile, and dimethylacetamide (entries 1, 2, 4 and 12) enabled good conversion, but are considered as hazardous or problematic solvents. The use of ester (ethyl acetate and isopropyl acetate; entries 3 and 9) or alcohol (ethanol, isopropanol, ethylene glycol, and polyethylene (PEG); entries 7, 8, 10 and 11) solvents provided a slow reaction, aside from benzyl alcohol, which strongly reduced Bi_2O_3 particles (entry 13). No conversion was obtained with water (entry 6). Acetone (entry 5) was a promising solvent in terms of its reaction efficiency and

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Table 1 Solvent screening for the bismuth-photocatalyzed ATRA reaction between **1a** and **2a** [a]

Entry	Solvent	Greenness[b]	Price for 1 L[c] (EUR)	Viscosity (cP)	Bi_2O_3 reduction	Conv.[d] (%)	Yield[d] (%)
1	Dimethylsulfoxide	Problematic	42.3	1.99	Slow	>99	97
2	Dimethylformamide	Hazardous	22.5	0.92	Slow	97	95
3	Ethyl acetate	Recommended	17.7	0.46	Slow	11	5
4	Acetonitrile	Problematic	22.3	0.37	Medium	>99	98
5	Acetone	Recommended	13.5	0.32	Slow	>99	98
6	Water	Recommended	/	1.00	Fast	<1	<1
7	Ethanol	Recommended	18.5 (denaturated)	1.10	Slow	7	4
8	Isopropanol	Recommended	21	2.86	Medium	19	16
9	Isopropyl acetate	Recommended	36.1	0.52	Slow	2	1
10	Ethylene glycol	Recommended	42.4	16.10	Fast	3	1
11	Polyethylene (PEG) 400	Recommended	26.7	109.42	Slow	30	25
12	Dimethylacetamide	Hazardous	37.6	0.95	Slow	>99	94
13	Benzyl alcohol	Problematic	20.2	5.47	Fast	>99	95
14	Acetone:ethylene glycol (8:2)	Recommended	19.28	3.48	Fast	24	20
15	**Acetone:PEG 400 (8:2)**	**Recommended**	**16.14**	**22.14**	**Slow**	**>99**	**95**

[a] Conditions: [**1a**] = 0.675 M, [**2a**] = 0.5 M and [2,6-lutidine] = 0.5 M, reaction volume = 2 mL, Bi_2O_3 loading = 1 mol%, 400 nm LED irradiation, room temperature, 5 h; [b] according to Prat et al.[21]; [c] from VWR (for technical grade when available, accessed on 3rd September 2020); [d] consumption of starting material **2a** and yield of desired product **3a**, based on GC-FID area with decane as the internal standard.

greenness (according to the *CHEM21 selection guide*,[21] exemption from "volatile organic compound" classification,[22] and general non-toxic and biodegradable character) but was not viscous enough to suspend the solid particles. It was therefore decided to add a small portion of PEG to increase the viscosity of the mixture.

The choice of the PEG chain length and its content in the mixture was determined through laser diffraction experiments. In these experiments, the mixture was stirred, then stirring ceased and the resulting optical density was recorded over 20 seconds, as a measure of how quickly the solids settle (see section B.1.3 in the ESI). Such experiments showed that a high amount of PEG was advantageous and that short chain lengths were more effective in improving particle suspendability. However, the higher content of Bi^0 obtained upon irradiation of a reaction mixture with PEG 200 than PEG 400 restricted the choice to the latter (see Fig. S5b). Therefore, the mixture of acetone and PEG 400 (8:2 in volume) was selected as the best candidate for the next experiments (entry 15). The selectivity towards **3a** was slightly reduced, when compared with pure acetone (entry 5), but the yield remained high (95%).

Having considered all of these aspects, some further optimization experiments and control reactions were carried out (Table 2). Increasing the Bi_2O_3 loading showed no improvement in reaction performance, likely owing to a higher amount of Bi^0 particles produced, or to a more turbid suspension with poor light transmission (entry 1, see also Table S1 entries 5 vs 6). An excess of olefin **1a** was also required to ensure complete conversion (entries 2, 3, and 4). Usually the limiting reagent during ATRA reaction is the olefin but, as in the method reported by Pericàs, the opposite trend can occur.[3a]

High conversion and yield were obtained with Bi_2O_3 and lutidine upon visible light irradiation (entry 5), whilst no reaction occurred without irradiation (entry 6). With irradiation, but no Bi_2O_3 or 2,6-lutidine, the reaction proceeded (albeit very slowly) in the mixture of acetone:PEG 400 (entry 7), but not in pure acetone (entry 8). Nevertheless, the selectivity towards **3a** was far lower than during the photocatalyzed reaction (81% for entry 7, compared with 95% for entry 5). By the addition of 2,6-lutidine, the reaction slowed down drastically (entry 9), perhaps due to the basic rather than acidic conditions.

Table 2 Batch optimization of the bismuth-photocatalyzed ATRA reaction between **1a** and **2a** [a]

Entry	Solvent	Bi_2O_3 loading (mol%)	Additive (equiv.)	[1a] (M)	[2a] (M)	$\lambda_{irr.}$ (nm)	Conv. (%)[b]	Yield (%)[b]
1	acetone	5	lutidine (1)	0.675	0.5	400	97	93
2	acetone	1	lutidine (1)	0.675	0.5	400	>99	98
3	acetone	1	lutidine (1)	0.5	0.5	400	83	82
4	acetone	1	lutidine (1)	0.44	0.5	400	49	49
5	**acetone:PEG 400 (8:2)**	**1**	**lutidine (1)**	**0.675**	**0.5**	**400**	**>99**	**95**
6	acetone:PEG 400 (8:2)	1	lutidine (1)	0.675	0.5	none	<1	<1
7	acetone:PEG 400 (8:2)	none	none	0.675	0.5	400	36	29
8	acetone	none	none	0.675	0.5	400	<1	<1
9	acetone:PEG 400 (8:2)	none	lutidine (1)	0.675	0.5	400	2	2

[a] Reaction volume = 2 mL, room temperature, 5 h; [b] consumption of starting material **2a** and yield of desired product **3a**, based on GC-FID area with decane as the internal standard.

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As an additional control experiment to determine whether this catalysis is truly heterogeneous, an experiment was carried out whereby the reaction was started, then filtered after 2 h, and initiated again. This serves to determine whether a homogeneous catalytic species is formed as the reaction progresses. At 2 h reaction time, 5% conversion was observed, then after filtration and a further 3 h reaction, the level of conversion increased to 76%. This result suggests that the reaction's initiation period is likely caused by the formation of homogeneous species over time, by either dissolution, or derivatization of Bi_2O_3.

Transition to continuous flow

The main challenge during the transposition to continuous flow conditions was to avoid the settling and deposition of the dense Bi_2O_3 particles along the reactor. To overcome such an issue and benefit from the sustainable profile of continuous flow technology, a few considerations had to be taken. It was hypothesized that the particle suspendability would be enhanced with a viscous solvent mixture, a high particle loading, and a small particle diameter. Therefore, the viscous mixture of acetone and PEG 400 (8:2 in volume) was maintained and an increase of Bi_2O_3 loading from 1 to 2 mol% was applied. However, the low reactivity of the smaller particles discouraged their use in the flow process, so the large particles (10 µm diameter) were kept.

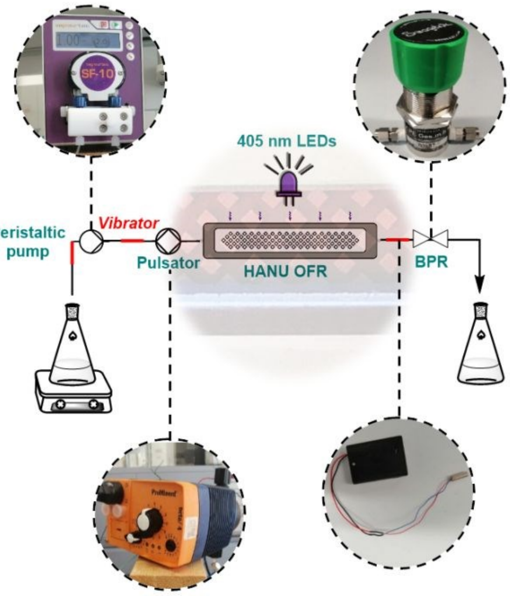

Fig. 3 Schematic of the oscillatory flow setup for the bismuth-photocatalyzed ATRA reaction.

The design of the oscillatory flow setup was also paramount to avoid particle settling (Fig. 3). The OFR used for this study, the HANU reactor,[12] includes a series of cubic static mixing elements. When combined with a pulsator pump, with tuneable oscillation character, the split-and-recombine mixing obtained by the cubic elements can be generated during each pulsation. Furthermore, the resulting narrow channels (2 mm x 2 mm) ensure homogeneous irradiation and reinforce stable particle suspension, even at low flow rates. In addition to the pulsator, the use of thin tubes and strategically placed vibrator motors ensured better particle suspension in the auxiliary tubing (outside the photoreactor itself). It was also important to use a back-pressure regulator (BPR, Swagelok) and pump (Vapourtec SF-10) capable of solid handling (see section B.2.1. in the ESI).

After compiling the oscillatory flow setup, and optimizing the parameters that enable a homogeneous solid suspension, a brief optimization study in flow was performed, to achieve similar results to batch experiments (Table 3). Despite the more efficient irradiation in flow, keeping room temperature with a short residence time was not enough to overcome the reaction's induction period (entry 1) and the observation was the same at 50 °C (entry 2).

By increasing the temperature to 70 °C and the Bi_2O_3 loading to 5 mol%, a conversion of 46% was obtained (entry 3). However, to minimize Bi^0 formation, the Bi_2O_3 loading was reduced to 2 mol% and both the temperature and residence time were increased to 75 °C and 15 min, respectively, to provide excellent conversion and selectivity (entry 4). From that point, it was considered necessary to perform additional control reactions, since the light irradiation and the temperature have changed. No conversion was observed without irradiation at 75 °C (entry 5) or without Bi_2O_3 (entry 6).

Table 3 Flow optimization of the bismuth-photocatalyzed ATRA reaction between **1a** and **2a** [a]

Entry	Bi_2O_3 loading (mol%)	Irradiation (nm)	Residence time (min)	Temperature (°C)	Conv. (%)[d]	Yield (%)[d]
1[b]	2	405	7.5	25	<1	<1
2[b]	2	405	7.5	50	<1	<1
3[b]	5	405	7.5	70	46	42
4[b]	2	405	15	75	99	94
5[c]	2	none	15	75	<1	<1
6[c]	none	405	15	75	<1	<1

[a] [**1a**] = 0.675 M, [**2a**] = 0.5 M and [2,6-lutidine] = 0.5 M, solvent = acetone:PEG 400 (8:2), processed reaction volume = 25 mL, pressure = 5 bar; [b] oscillation parameters: 2.4 Hz frequency, 0.265 mL amplitude; [c] oscillation parameters: 1.5 Hz frequency, 0.12 mL amplitude; [d] consumption of starting material **2a** and yield of desired product **3a**, based on GC-FID area with decane as the internal standard.

Preliminary experiments were in accordance with studies in the literature, which demonstrated a stronger effect of the oscillation amplitude than the frequency on the RTD (see section B.2.2. in the ESI).[13,23] A low oscillation amplitude was required to maintain a similar profile for both reaction phases. By setting the frequency to 1.5 Hz (50%) and the amplitude to 0.12 mL (20%), it was possible to observe a similar response profile (Fig. 4). An increase in conversion at the end of the process was also observed, owing to a higher catalyst loading present at that time point (different residence time profile for the solid phase compared to the liquid phase).[24]

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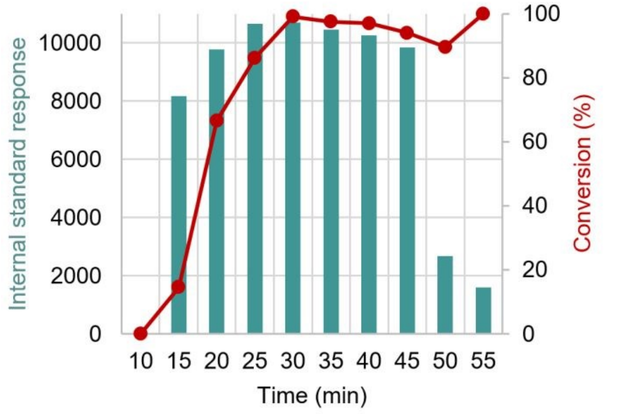

Fig. 4 Distribution of conversion and reaction concentration over time, when working under continuous flow conditions. Conditions: [**1a**] = 0.675 M, [**2a**] = 0.5 M and [2,6-lutidine] = 0.5 M, solvent = acetone:PEG 400 (8:2), processed volume = 50 mL, Bi_2O_3 loading = 2 mol%, 405 nm LED irradiation, pressure = 5 bar, temperature = 75 °C, residence time = 15 min, flow rate = 1 mL min^{-1}, frequency = 1.5 Hz (50%), amplitude = 0.12 mL (20%)**.** Conversion was determined by GC-FID using decane as the internal standard.

Scale-out, Bi_2O_3 recycling and substrate scope

The likelihood of clogging and settling increases with the time of processing, so a long run experiment was tested to show the stability of this process. The reaction was run for 4 h (250 mL reaction mixture processed) without any issues. Following a simple workup, 35.9 g of the model substrate **3a** was obtained, corresponding to an 89% yield (accounting for 92.5% purity by GC-FID analysis). This corresponds to a process mass intensity (PMI: total mass involved in the reaction, divided by the product mass) of 8.5, without taking into account any solvent recyclability, which is low for a photochemical process such as this.

During the scale-out experiment, 97% conversion was observed, with a fluctuation of only ±2% conversion, demonstrating the stability of the protocol (Fig. 5). The space-time yield of this experiment (productivity divided by 15 mL reactor volume) was calculated to be 599 g L^{-1} h^{-1}. This high productivity, achieved by high concentration, high conversion and short residence time, demonstrates new possibilities for industrial scale processing of ATRA reactions.

Since the use of solid catalysts is advantageous in terms of cost and time needed for downstream purification, the reuseability of Bi_2O_3 particles was assessed. After centrifugation and washing (acetone, water, then acetone, with centrifugation between each solvent wash; 5000 rpm for 15 min) and drying overnight (105 °C in an oven), high amounts of Bi_2O_3 were recovered (89%, 94% and 90% of the input mass, for three cycles). This high recovery demonstrates minimal solid settling or dissolution along with the flow setup, and only minor losses in the particle recovery process.

Since the Bi_2O_3 loading was kept at 2 mol% to minimize settling issues, some fresh Bi_2O_3 (~20 mg per cycle) was added to replace the mass lost during the previous cycle. As previously demonstrated, a homogeneous bismuth species is likely to be involved in the reaction, but the lost mass from each recycle represents <10% of the initial Bi_2O_3 loading. After recycling the solid 3 times, no loss of activity was observed (Fig. 6), representing another promising feature for the sustainability profile of this methodology.

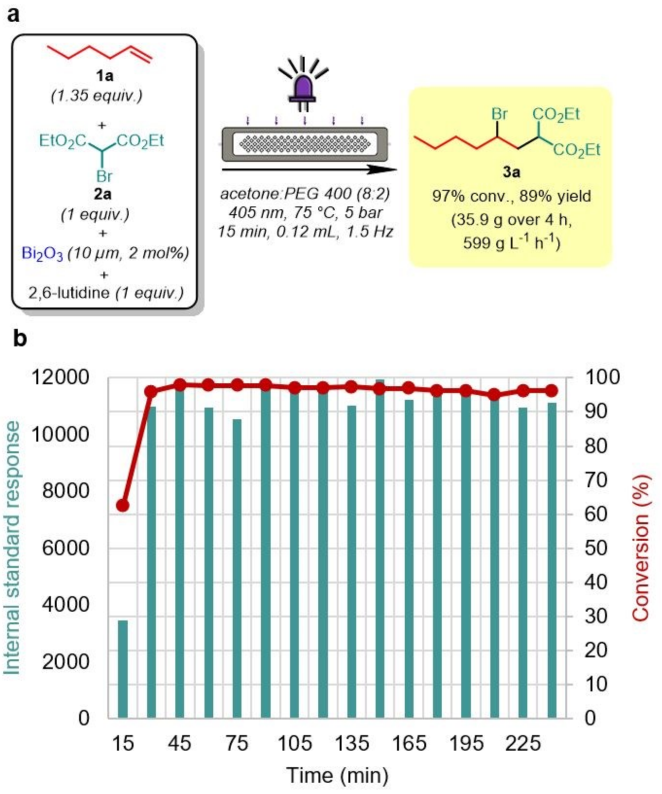

Fig. 5 Long run experiment of the ATRA procedure under continuous flow conditions. Conditions: [**1a**] = 0.675 M, [**2a**] = 0.5 M and [2,6-lutidine] = 0.5 M, solvent = acetone:PEG 400 (8:2), processed volume = 250 mL, Bi_2O_3 loading = 2 mol%, 405 nm LED irradiation, pressure = 5 bar, temperature = 75 °C, residence time = 15 min, flow rate = 1 mL min^{-1}, oscillation frequency = 1.5 Hz, amplitude = 0.12 mL. **(a)** Reaction scheme. **(b)** Stability of the long run experiment over time. Conversion was determined by GC-FID using decane as the internal standard.

The protocol was extended to other substrates (Fig. 7, see ESI for procedures and characterization data). In this reaction scope, a selection of olefins were reacted with **2a** as the brominated donor, under the optimized conditions (75 °C and 20 min residence time). Increasing the residence time (30 min) and temperature (80 °C) was, however, required to facilitate complete reaction with allyl benzene **1b** (93% conv.), allyl alcohol **1c** (97% conv.), and 1-hexyne **1d** (79% conv.). The selectivity towards the brominated product **3** depends on the olefin **1** and was lower for **3c** and **3d** than for **3a** and **3b**. In these cases, the major side product was proposed to be from elimination of the desired product. Moderate to excellent isolated yields were obtained for **3a** (94%), **3b** (90%), **3c** (66%), and **3d** (55%), all of which were performed on multigram scale.

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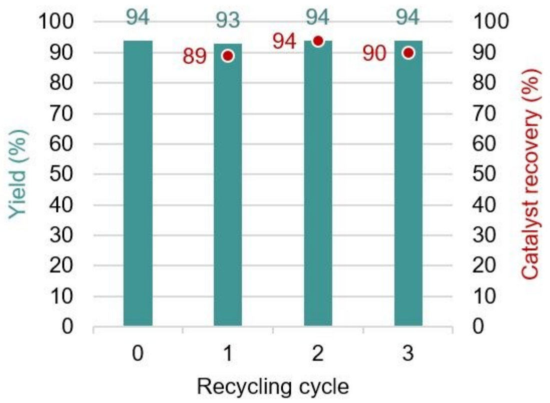

Fig. 6 Recycling experiments of the ATRA procedure under the optimized flow conditions. Conditions: [**1a**] = 0.675 M, [**2a**] = 0.5 M and [2,6-lutidine] = 0.5 M, solvent = acetone:PEG 400 (8:2), processed volume = 50 mL, Bi_2O_3 loading = 2 mol%, 405 nm LED irradiation, pressure = 5 bar, temperature = 75 °C, residence time = 20 min, flow rate = 0.75 mL min^{-1}, frequency = 2.1 Hz, amplitude = 0.12 mL. Conversions were determined by GC-FID using decane as the internal standard.

The applicability of different ATRA donors was also examined. Bromoacetonitrile **2b** and carbon tetrabromide **2d** were assessed for new bromofunctionalization reactions and perfluorohexyl iodide **2c** was tested for an iodoperfluoroalkylation.[8b,25] An excellent yield was obtained for the iodoperfluoroalkylation under the less forcing set of conditions, owing to the weaker C-I bond. In this case, the desired compound **3f** was the only product detected (97% yield, with no chromatography required). Iodoperfluoroalkylation is another interesting ATRA transformation since perfluorinated compounds play a key role in different fields such as medicinal chemistry.[26]

Using the more forcing conditions (80 °C and 30 min residence time) facilitated an excellent yield of **3e** (95%). The selectivity towards **3g** and **3h** was, however, much lower, due to the high propensity for elimination from the desired product. This decreased further at higher temperature and residence time. Moderate yields were obtained for **3g** and **3h** under the optimized conditions at 75°C and 20 min residence time (52% and 57% respectively). These results were similar to those reported in the literature,[3a] but it must also be stated that photocatalyst-free ATRA reactions of CBr_4 have been reported.[26]

As a comparison of reaction productivity, the protocol of Pericàs et al. performed the synthesis of **3h** in 54% yield after 48 h irradiation, leading to a space-time yield of 2.5 g L^{-1} h^{-1}.[3a] Although not directly comparable (different light intensity, for example), the space-time yield of **3h** using this flow protocol was determined as 385 g L^{-1} h^{-1}, showing far higher productivity than previously reported. Such an increase of this throughput reinforces the green profile and larger scale applicability of this continuous flow procedure.

Conclusions

An oscillatory flow process has been designed for the bromofunctionalization of terminal unsaturated compounds through a metal oxide photocatalyzed ATRA reaction. The added species, Bi_2O_3, fulfills the expectations of a green catalyst since it is cheap, widely available, easy to procure, non-toxic and in the solid state (allowing straightforward reuse). Furthermore, the activation of the radical reaction has been promoted by visible light, less energetic and harmful than UV irradiation. The choice of the solvent, a mixture of acetone and PEG 400, has a low cost, minimal safety concerns, negligible extent of bismuth reduction, and no reaction quenching. The use of oscillatory flow technology enables experiments at larger scale, with better control of the photochemical process and efficient handling of the dense Bi_2O_3 species (d = 8.9 g cm^{-3}).

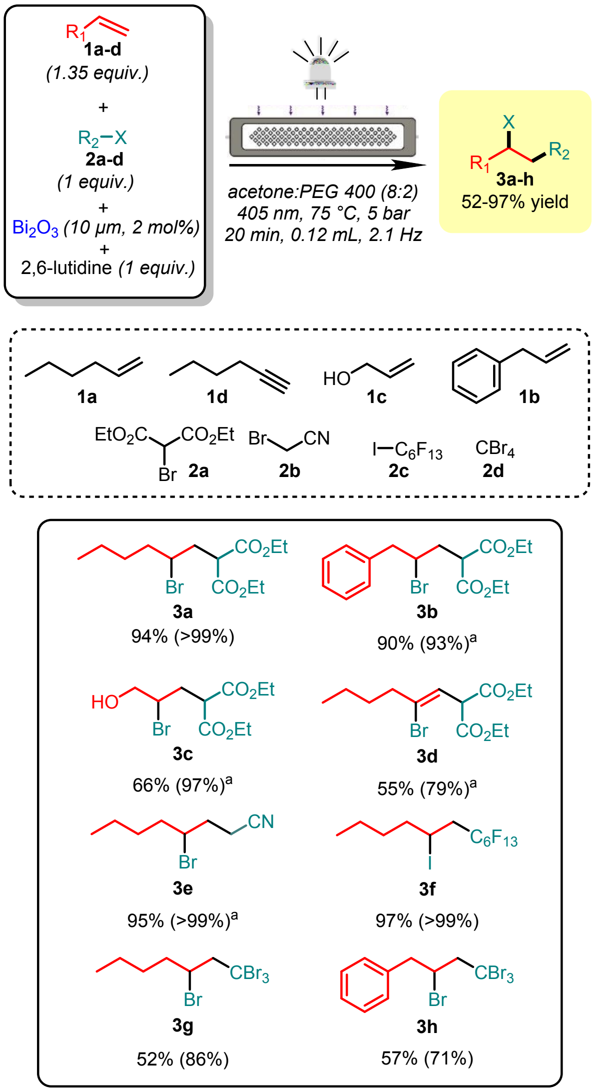

Fig. 7 Substrate scope of the ATRA procedure under continuous flow conditions. Processed volume = 25 mL except for **3a** (50 mL). Isolated yield of the desired product on multigram scale is displayed. Value in parentheses shows consumption of starting material **2**, based on GC-FID area with decane as the internal standard. [a] reaction performed at 80 °C, with 30 min residence time.

Careful optimization of the flow setup, oscillation parameters, and chemical conditions (in batch and flow) avoids clogging or settling of the particles, while maintaining a narrow RTD. In this way, the model product was synthesized in high

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yield after 4 h of processing without any reactor clogging (35.6 g, 89% yield, 599 g L^{-1} h^{-1}). To our knowledge, this is the highest throughput obtained for a photochemical ATRA bromination. No loss of activity was observed after recycling the solid Bi_2O_3 3 times, with high recovery. Finally, a substrate scope was performed, with moderate to excellent yields on multigram scales. It is envisaged that the success demonstrated here will serve to encourage the use of metal oxide semiconductors, and other sustainable inorganic photocatalysts, in continuous flow.

Experimental section

General information

Bismuth(III) oxide, 2,6-lutidine, decane (internal standard), 1-hexene **1a**, diethyl bromomalonate **2a**, allylbenzene **1b**, allyl alcohol **1c**, 1-hexyne **1d**, bromoacetonitrile **2b**, perfluorohexyl iodide **2c**, carbon tetrabromide **2d**, polyethylene glycol 400 and acetone (technical grade) were received from commercial sources and used without further purification. Conversion and optimization yields were determined by gas chromatography coupled to a flame ionization detector (GC-FID) or by ^{1}H NMR spectroscopy, with decane or 1,3,5-trimethoxybenzene respectively as the internal standards. Structural characterization was performed by ^{1}H and ^{13}C NMR spectroscopy (300 MHz Bruker spectrometer) in $CDCl_3$ (see ESI). Product masses were confirmed by high-resolution mass spectrometry (HRMS). Particle size and suspendability measurements were carried out using laser diffraction (LD) analysis (see ESI).

Experimental oscillatory flow setup

Flow experiments were carried out in a commercially available plug flow HANU reactor from Creaflow[12] (Hastelloy C276, 15 mL internal volume, containing of 2 x 2 x 2 mm cubic static mixers and irradiated at the top by a Peschl Ultraviolet module composed of 36 x 405 nm LEDs). The feed mixture was pumped using a Vapourtec SF-10 peristaltic pump, while the oscillations were delivered by a Creaflow customized ProMinent Beta/4 pump (PTFE/carbon pump head). Pressure was applied by a Swagelok back pressure regulator (KCB Series, up to 25.8 bar). Thermal regulation was managed with a Huber CC304 thermostat. All connections between the parts of the setup were achieved with 1/8’’ (1.6 mm i.d.) or 1/16’’ (0.8 mm i.d.) o.d. PTFE/PFA tubes with PEEK or stainless steel (Swagelok) fittings.

Representative batch procedure: A sealed vial containing 1 mol% of Bi_2O_3 (5 mg, 0.01 mmol), 1 mmol of **2a** (1 equiv.), 1 mmol of 2,6-lutidine (1 equiv.), 0.5 mmol of decane (50 mol%) and 2 mL of a degassed mixture of acetone:PEG 400 (8:2 in volume) was purged with argon for 10 min. 1.35 mmol of **1a** was added through the septum via a syringe. The vial was then irradiated for 5 h at room temperature at 10 cm from the 400 nm LEDs. After reaction completion, 100 µL of the yellow turbid solution was taken and filtered (0.45 µm syringe filter). The organic phase was extracted from 2 mL of brine by 2 mL of ethyl acetate, dried over Na_2SO_4, diluted with MeCN (100 µL in 1 mL), and submitted for GC analysis (optimized conditions provided conv. >99%, yield 95%).

Representative flow procedure: A sealed Duran bottle containing 2 mol% of Bi_2O_3 (233 mg, 0.5 mmol), 25 mmol of **2a** (1 equiv.), 25 mmol of 2,6-lutidine (1 equiv.), 5 mmol of decane (20 mol%) and 50 mL of a degassed mixture of acetone:PEG 400 (8:2 in volume) was purged with argon for 20 min. A sample of 33.7 mmol (1.35 equiv.) of **1a** was added through the septum via a syringe. The feed was then pumped at a flow rate of 0.75 mL min^{-1} through the flow reactor pressurized at 5 bar, heated to 75 °C and irradiated at 405 nm (residence time = 20 min). During the reaction, the pulsator was set to 20% (0.12 mL) pulsation amplitude and 70% (2.1 Hz) pulsation frequency. The collected yellow turbid suspension was then centrifuged for 15 min at 5000 rpm. PEG 400 was removed by extraction with 50 mL of water and 50 mL of diethyl ether. The aqueous phase was washed with 3 × 50 mL of diethyl ether. The combined organic fractions were washed with 50 mL of water and then dried over Na_2SO_4 before being concentrated on a rotary evaporator. Although product purity was generally high, to obtain analytically pure samples, the obtained oil was purified by flash chromatography on silica gel (40-60 petroleum ether:ethyl acetate, 95:5) to afford the corresponding product (>99% conv., 94% yield, 7.6 g). In the meantime, the solid particles were washed with acetone, then water and finally with acetone, with centrifugation steps in between (15 min at 5000 rpm), before being dried overnight in an oven at 105 °C.

For the scale-out experiment, this procedure was repeated, but with a total solution volume of 250 mL.

Conflicts of interest

There are no conflicts to declare.

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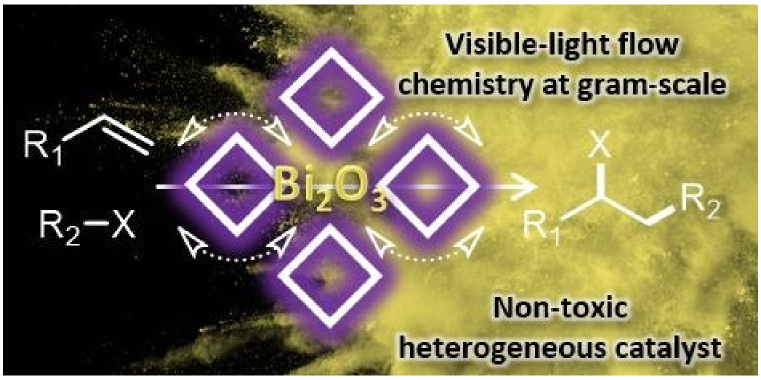

An oscillatory flow photoreactor facilitates the use of Bi_2O_3 as a green and recyclable photocatalyst for ATRA reactions.