Bismuth(III)-Catalyzed Hydration of Terminal Alkynes: Sustainable Synthesis of Methyl Ketones in Batch and Flow

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ABSTRACT: Environmentally benign synthesis of methyl ketones is demonstrated via unprecedented bismuth(III)-catalyzed activation and Markovnikov-type hydration of terminal acetylenes. Besides a batch process operating under reasonably mild conditions, a chemically intensified high-temperature continuous-flow methodology has also been developed using a coil reactor. The preparative capabilities of the flow process were demonstrated with multigram-scale alkyne hydrations. The methods presented rely on readily available bismuth(III) salts as “green” catalysts and exhibit less environmental concerns than earlier methods.

KEYWORDS: Alkynes, Bismuth, Flow chemistry, Hydration, Ketones

INTRODUCTION

In the past few years, synthetic applications of bismuth(III) compounds have received an upsurge of interest, which is mainly due to the recognition of bismuth as a “green element.” This favorable reputation arises from the fact that bismuth and its compounds are considered to be nontoxic and noncarcinogenic. 1,2 Which is in sharp contrast to other heavy metals located nearby in the periodic table. 3 Another very important point is that bismuth(III) compounds are relatively cheap, which is mainly due to the fact that bismuth is typically obtained as a byproduct of lead, tin, and copper manufacturing. As a result of these beneficial properties, bismuth(III) salts are nowadays increasingly investigated as environmentally benign catalysts in a wide array of synthetic transformations. 5–11

Although it is somewhat surprising for a group 15 element, bismuth(III) salts exhibit significant Lewis acidic behavior, and they are capable of activating a large variety of substrates of both π- and σ-donor characters. 9–11 Among σ-donors, the activation of alcohols and amines are especially well established. 6,7 For example, bismuth(III)-catalyzed Friedel–Crafts alkylation of (hetero)arenes and benzylation of 2,4-pentanediones both with benzyl alcohols as electrophiles were described by Rueping and co-workers. 13,14 Besides alcohols, the activation of carbon—nitrogen bonds using alkenes as nucleophiles is also extensively studied by using bismuth(III) salts as σ-acceptors. 15 For example, efficient procedures were developed for C-alkylations and arylation with diversely substituted olefins as reaction partners. 15–17 Moreover, bismuth(III)-catalyzed hydroaminations are increasingly popular for the formation of carbon—nitrogen bonds using alkenes as nucleophiles. 18–20

In contrast, the activation of alkynes with the use of bismuth(III) salts is much less explored. 1,5–11 There are only a few examples, which typically include intramolecular annihilations of alkenyl esters, ketones, amides, and carboxylic acids with bismuth(III) serving as a dual σ-/π-activator. 11–25 In most of these studies, Bi(OTf)₃ was employed as catalyst with the involvement of Ti(OH)₃ generated in situ playing an important role in the catalytic cycles. 26,27

Markovnikov-type hydration of alkynes is a valuable transformation for the atom-economical synthesis of carbonyl compounds. 28,29 Because of the stability and ease of introduction of the acetylene moiety, the direct alkyne hydration has become especially popular to provide ketones in total syntheses and late-stage manipulations of complex structures. 30,31 However, the classical procedure raises significant environmental concerns as it employs catalytic amounts of mercuric salts in strongly acidic media (Kucherov HgO—H₂SO₄, Hennon—Nieuwland HgO—BF₃). 32–37 Extensive efforts have therefore been made for the development of alternative synthetic procedures. 38–40 In the last few decades, many other metals have been reported as catalysts for alkyne hydrations, including salts and/or complexes of gold, 41–45 silver, 46–49 platinum, 50 palladium, 51 copper, 52,53 rhodium, 54 ruthenium, 55 and cobalt. 56,57 These alternative catalysts are...
typically less harmful than mercuric salts, but, in some cases, serious environmental concerns are still involved.4,58 On the other hand, most of the above-mentioned metals and their compounds are quite expensive, and they frequently necessitate the use of special ligands which involves further disadvantages as concerns process costs and environmental impacts. Metal-free approaches have also been reported for Markovnikov-type alkyne hydrations,59−63 but these methods generally involve harmful substances, such as strong acids and halogenated reagents.

In spite of recent developments in alkyne hydration chemistry, there is an excessive need for an uncomplicated and cheap catalyst which operates under mild reaction conditions without any additives (e.g., ligands or acids) and, importantly, with the least possible environmental concerns involved. Due to their potentials in \( \pi \)-activation and also because of their beneficial environmental properties, we speculated that certain bismuth(III) salts may satisfy these expectations. Thus, we are presenting our results on the bismuth(III)-catalyzed Markovnikov-type hydration of alkyynes for the sustainable synthesis of carbonyl compounds. Besides a conventional batch process employing reasonably mild conditions, we also aimed to investigate the utilization of a high-temperature continuous-flow reactor environment in order to exploit extended parameter spaces for chemical intensification and easily realize large-scale syntheses.64−76

### RESULTS AND DISCUSSION

We initiated our study by investigating the catalytic activity of various bismuth(III) salts in the hydration of \( p \)-methoxyphenylacetylene as a model substrate. MeOH was selected as solvent, and the reaction mixture, containing the alkyne (0.25 M) and 10 mol % of the catalyst, was stirred at 65 °C for 24 h.

### Table 1. Investigation of Various Catalysts in the Markovnikov-Type Hydration of \( p \)-Methoxyphenylacetylene

| no. | name                  | purity (%) | price (EUR/g)\(^a\) | conv (%)\(^b\) | selectivity (%) | 1 | 2 | 3 |
|-----|-----------------------|------------|---------------------|---------------|----------------|---|---|---|
| 1   | Bi(NO\(_3\))\(_3\)·5H\(_2\)O | 98         | 0.17                | 100           | 100            | 0 | 0 | 0 |
| 2   | Bi(OTF)\(_3\)            | 99         | 17.24               | 100           | 100            | 0 | 0 | 0 |
| 3   | BiBr\(_3\)             | ≥98        | 2.15                | 8             | 100            | 0 | 0 | 0 |
| 4   | Bi(OTf)\(_3\)          | ≥98        | 0.32                | 8             | 100            | 0 | 0 | 0 |
| 5   | Bi powder (100 mesh)    | 99         | 0.33                | 5             | 100            | 0 | 0 | 0 |
| 6   | CuSO\(_4\)·5H\(_2\)O  | ≥98        | 0.13                | 92            | 68             | 2 | 30|
| 7   | AgNO\(_3\)             | 99         | 5.02                | 90            | 96             | 0 | 4 | 0 |
| 8   | Bi(NO\(_3\))\(_3\)·5H\(_2\)O | ≥99.99    | 1.72                | 100           | 100            | 0 | 0 | 0 |

\(^a\)Data obtained from www.sigmaaldrich.com. \(^b\)Determined by \(^1\)H NMR analysis of the crude product.

### Table 2. Effects of Various Reaction Conditions on the Markovnikov-Type Hydration of \( p \)-Methoxy Phenylacetylene

| no. | solvent | reaction time (h) | catalyst loading (mol %) | T (°C) | added \( H_2O \) (equiv) | conv (%)\(^a\) | select (%)\(^a\) | 1 | 2 |
|-----|---------|-------------------|--------------------------|-------|-------------------------|---------------|-----------------|---|---|
| 1   | MeOH    | 24                | 10                       | 65    | 0                       | 100           | 100             | 0 | 0 |
| 2   | MeOH    | 12                | 10                       | 65    | 0                       | 98            | 100             | 0 | 0 |
| 3   | MeOH    | 6                 | 10                       | 65    | 0                       | 89            | 100             | 0 | 0 |
| 4   | MeOH    | 1                 | 10                       | 65    | 0                       | 65            | 100             | 0 | 0 |
| 5   | MeOH    | 24                | 10                       | 10    | 25                      | 8             | 100             | 0 | 0 |
| 6   | MeOH    | 24                | 5                        | 65    | 0                       | 92            | 80              | 20|
| 7   | MeOH    | 24                | 2                        | 65    | 0                       | 85            | 78              | 22|
| 8   | MeOH    | 24                | 10                       | 65    | 1                       | 63            | 100             | 0 |
| 9   | MeOH    | 1                 | 10                       | 65    | 2                       | 64            | 100             | 0 |
| 10  | MeOH    | 1                 | 10                       | 65    | 5                       | 62            | 100             | 0 |
| 11  | MeOH    | 24                | 5                        | 65    | 1                       | 91            | 84              | 16|
| 12  | MeOH    | 24                | 5                        | 65    | 5                       | 91            | 83              | 17|
| 13  | MeOH    | 24                | 10                       | 65    | 0                       | 80            | 100             | 0 |
| 14  | EtOH    | 24                | 10                       | 65    | 0                       | 12            | 100             | 0 |
| 15  | iPrOH   | 24                | 10                       | 65    | 0                       | 81            | 100             | 0 |
| 16  | H\(_2\)O | 24                | 10                       | 65    | 0                       | 77            | 100             | 0 |

\(^a\)Determined by \(^1\)H NMR analysis of the crude product. \(^b\)Under an argon atmosphere.
AgNO₃ proved to be more expensive. Among the investigated materials, only CuSO₄·5H₂O were also explored as cheap and relatively harmless catalysts. Besides bismuth(III) salts and Bi powder, AgNO₃ and CuSO₄·5H₂O were also explored as cheap and relatively harmless catalysts. Although, both gave conversions of ≥90%, the chemoselectivity was lower than in bismuth-catalyzed reactions (entries 6 and 7). In the case of CuSO₄·5H₂O, besides the desired hydration product (1), the competing copper-mediated alkyne homocoupling yielded a significant amount of diyne 3,77,78 and even a small amount of dimethyl acetal 2 was found in the crude product mixture (1/2/3 ratio was 68:2:30). AgNO₃ proved to be more efficient as hydration catalyst, since only some diyne 3 was detected as side product (1/3 ratio was 96:4). Note that silver-mediated alkyne homocoupling is known from the literature.79 Gold(III) salts are also promising catalysts for reactions involving alkyne activation,39 but none of them were tested herein because of their incomparably high price.

In order to exclude the possibility of any contamination contributing significantly to the catalytic activity observed with Bi(NO₃)₃·5H₂O, direct comparison was carried out by using salts of 98 and ≥99.99% purity at different reaction times. The same catalytic results were registered with both materials (Table 1, entry 1 vs 8, and Table S1), which eliminates the incidental cocatalytic role of any contaminations.

To evaluate the above results for sustainable method development, the price and purity of the catalytic materials should also be taken into account. The purity of the catalysts employed was in the range of 98–99% (Table 1). Among them, Bi(NO₃)₃·5H₂O and Bi(OTf)₃ gave similarly excellent catalytic results (entries 1 and 2), but Bi(OTf)₃ is much more expensive than Bi(NO₃)₃·5H₂O (17.24 vs 0.17 EUR/g). Other bismuth compounds and AgNO₃ performed less effectively (entries 3−5 and 7). Moreover, they are more expensive than Bi(NO₃)₃·5H₂O with prices in the range 0.32−5.02 EUR/g.

Among the investigated materials, only CuSO₄·5H₂O (0.13 EUR/g) is cheaper than Bi(NO₃)₃·5H₂O, but it was not selective as a hydration catalyst (entry 6). These facts readily made Bi(NO₃)₃·5H₂O the catalyst of choice for our batch method development.

To explore more details on the nature of the Bi(NO₃)₃·5H₂O-catalyzed alkyne hydration, next, the effects of various reaction conditions were examined carefully (Table 2). On investigating the effects of the reaction time, almost 90% of the starting material was consumed in the first 6 h of the reaction and the conversion reached 98% after 12 h (entries 1−4). It was also observed that replacing the aerobic atmosphere with argon did not bring about any significant changes in conversion or selectivity (entry 5), which excludes the oxidative nature of the reaction. Gentle heating was found to be crucial for effective alkyne hydration, since a mere 8% conversion occurred at ambient temperature (entry 6). We attempted to lower the catalyst loading to 5 and then to 2 mol %, but it resulted in a conversion decrease (to 92 and 85%, respectively) and, more importantly, dimethyl acetal 2 appeared as a side product to an extent of around 20% (entries 7 and 8).

To account for the formation of 2, a possible reaction mechanism is depicted in Scheme 1.30,57,80 After bismuth(III)-mediated alkyne activation, a two-step hydroalkoxylation with methanol gives dimethyl acetal 2 as an intermediate, which is subsequently hydrolyzed to yield methyl ketone 1 as the desired product. Bismuth(III)-catalyzed deprotection of acetals is known from the literature,81 which may explain the appearance of dimethyl acetal 2 upon reducing the catalyst loading (entries 7 and 8). For the demethoxylation of the acetal intermediate, the intervention of small amounts of H₂O may be necessary. H₂O traces may arise from the solvent, from moisture present in the air and/or from the catalyst itself. Hydration of p-methoxyphenacylencylene was next repeated with 1, 2, or 5 equiv. H₂O as additive in the presence of 5 or 10 mol % catalyst. With added H₂O, no reaction rate enhancement occurred, conversions were similar to that without deliberately added H₂O (Table 2, entries 9−11 vs entry 4; entries 12 and 13 vs entry 7). It was observed, however, that, when catalyst loading was 5 mol %, a slightly lesser amount of acetal 2 was formed in the presence of added H₂O (entries 12 and 13 vs entry 7).

When EtOH, iPrOH, and H₂O were explored as reaction medium, significant decreases in conversions occurred as compared to MeOH as solvent (Table 2, entries 14−16 vs entry 1). Theoretical calculations suggest that the rate-determining step of the hydration process is the addition of a second nucleophile to the enol ether intermediate.30 Therefore, decreased conversions observed with the use of bulkier alcohols may be explained by steric hindrance. In the case of H₂O as a solvent, electronic effects may also be operative. In further solvents, such as DMSO, hexane, THF, and EtOAc, no conversion was detected.

Attempts were made for catalyst recycle and reuse. As the bismuth(III) salt was partially dissolved in MeOH during the reactions, we first attempted to quantitatively precipitate it from the reaction mixture. Unfortunately, it was not possible by adding various cosolvents (such as CH₂Cl₂ or diethyl ether). However, by means of simple centrifugation, we...
managed to recover approximately 40% of the material which could subsequently be reused in a next cycle.

After getting familiar with the conditions of the model reaction, the scope and applicability of the batch methodology was next tested. Various aromatic alkynes with diverse substitution patterns were thus submitted to the optimized reaction conditions (24 h stirring in MeOH at 65 °C) in the presence of 10 mol % Bi(NO₃)₃·5H₂O as catalyst. We were pleased to find conversions in the range of 81–100% and excellent selectivities of ≥95% toward the desired acetophenone derivatives in the reactions of phenylacetylene and its substituted derivatives containing methyl, methoxy, or tert-butyl substituents (Table 3, entries 1–5). Even multi-substituted phenylacetylenes (entries 6 and 7), 3-ethynyl-3-phenylbutyrapropene (entries 8 and 9) gave outstanding results. Aliphatic alkynes are known to display their reactions were investigated in the presence of 30 mol % Bi(NO₃)₃·5H₂O as catalyst, and the reaction time was extended to 72 h. Under these conditions, good and excellent conversions were observed for nonbranched aliphatic alkynes dec-1-yne and oct-1-yne (63% and 100%, respectively, entries 10 and 11).

However, in the case of 3-cyclohexyl-1-propyne, a mere 21% conversion was found (entry 12), which maybe due to steric hindrance of the triple bond. In the reactions of aliphatic alkynes, the corresponding ketones were formed with 100% chemoselectivities. Reactivities of internal alkynes were also explored (diphenylacetylene and oct-4-yne were tested); however, conversion was not detected.

In order to access extended parameter spaces for chemical intensification and also to conveniently achieve large scale production, we continued our investigations by translating the bismuth(III)-catalyzed alkyne hydration into a continuous-flow process. As Bi(NO₃)₃·5H₂O is only partly soluble in MeOH, we speculated that it may serve as a simple catalytic source in a filled catalyst column. However, after a few preliminary experiments, it turned out that the application of solid Bi(NO₃)₃·5H₂O is not practical due to its low melting point and/or its intense leaching from the catalyst bed which led to frequent clogging issues. Bi powder (100 mesh) was also investigated as a solid catalytic source, but even a column filled with 25 g of the material exhibited unsatisfactory results at temperatures >200 °C. (Continuous-flow results with solid Bi(NO₃)₃·5H₂O and Bi powder are shown in Table S2.)

With the aim of creating a robust synthesis system without uncontrollable leaching issues, we finally decided to investigate soluble bismuth(III) sources. Due to the low solubility of Bi(NO₃)₃·5H₂O in MeOH, DMSO was added as a cosolvent. A MeOH/DMSO ratio of 8:1 was found to be optimal to dissolve 10 mol % of the bismuth(III) catalyst, while the starting alkyne was utilized in a concentration of 0.25 M. The hydration of p-methoxyphenylacetylene was employed as a model reaction, similarly as in the batch experiments. Reactions were carried out in a 13 mL stainless steel coil equipped with a backpressure regulator (BPR) to prevent solvent boil-over. The effects of the reaction temperature were investigated at a fixed flow rate of 0.1 mL min⁻¹, which corresponds to a residence time of 130 min. Upon increasing the temperature from 100 to 250 °C, the conversion was gradually improved from 55% until it finally reached completion at 230 °C (Figure 1A). Formation of intermediary dimethyl acetal 2 was not detected in this set of experiments. The effects of the residence time were next screened at 230 °C (Figure 1B). We were delighted to find that 65 min (corresponding to 0.2 mL min⁻¹ flow rate) was sufficient to maintain complete alkyne conversion and 100% chemoselectivity toward the desired p-methoxyacetophenone, which is particularly appealing as compared with the batch reaction time of 24 h (see Table 2, entry 1). Higher flow rates (lower residence times) led to incomplete conversions, and traces of dimethyl acetal intermediate 2 appeared at flow rates of ≥0.5 mL min⁻¹.

Table 3. Substrate Scope of Alkyne Hydration Catalyzed by Bi(NO₃)₃·5H₂O in MeOH as a Solvent under Batch Conditions

| #  | Alkyne | Product | Conv. (%)a | Sel. (%)a |
|----|--------|---------|------------|-----------|
| 1b | [Alkyne structure] | [Product structure] | 90         | 95        |
| 2b | Me- [Alkyne structure] | Me- [Product structure] | 100        | 100       |
| 3b | MeO- [Alkyne structure] | MeO- [Product structure] | 100        | 100       |
| 4b | tBu- [Alkyne structure] | tBu- [Product structure] | 81         | 100       |
| 5b | [Alkyne structure] | [Product structure] | 92         | 100       |
| 6b | MeO- [Alkyne structure] | MeO- [Product structure] | 100        | 100       |
| 7b | [Alkyne structure] | [Product structure] | 100        | 98        |
| 8b | [Alkyne structure] | [Product structure] | 100        | 100       |
| 9b | [Alkyne structure] | [Product structure] | 91         | 96        |
| 10b | [Alkyne structure] | [Product structure] | 100        | 100       |
| 11b | [Alkyne structure] | [Product structure] | 63         | 100       |
| 12b | [Alkyne structure] | [Product structure] | 21         | 100       |

“Determined by ¹H NMR or GC-MS analysis of the crude product.

bReaction conditions: c_{alkyne} = 0.25 M in MeOH, 10 mol % Bi(NO₃)₃·5H₂O as catalyst, stirring for 24 h at 65 °C. cReaction conditions: c_{alkyne} = 0.25 M in MeOH, 30 mol % Bi(NO₃)₃·5H₂O as catalyst, stirring for 72 h at 65 °C.”

substituted phenylacetylenes (entries 6 and 7), 3-ethynylthiophene and ethynylferrocene (entries 8 and 9) gave outstanding results. Aliphatic alkynes are known to display lower reactivities in such transformations.⁶⁰,⁴⁷,⁵⁷ Therefore, their reactions were investigated in the presence of 30 mol % catalyst, and the reaction time was extended to 72 h. Under these conditions, good and excellent conversions were observed for nonbranched aliphatic alkynes dec-1-yne and oct-1-yne (63% and 100%, respectively, entries 10 and 11).
to 0.3 mL min$^{-1}$ (43 min residence time), only a slight decrease of conversion to 96% occurred. When the reaction temperature was raised to 230 °C, complete alkyne conversion and 100% chemoselectivity were detected even at a residence time as low as 32.5 min (0.4 mL min$^{-1}$ flow rate, Figure 2B).

Next, a range of alkynes were studied under the best continuous-flow conditions. The reactions were attempted by using both Bi(NO$_3$)$_3$·5H$_2$O (10 mol %) and BiBr$_3$ as catalysts (10 or 20 mol %). All experiments were performed with an alkyne concentration of 0.25 M at a temperature of 230 °C. In the Bi(NO$_3$)$_3$·5H$_2$O-mediated reactions MeOH/DMSO (8:1) was used as solvent at 0.1 mL min$^{-1}$ flow rate (Method A), whereas in the case of BiBr$_3$ as catalyst, MeOH was used as the sole solvent at 0.2 mL min$^{-1}$ flow rate (Method B). Upon investigating diversely substituted aromatic alkynes, the flow methods worked comparably well to the batch reactions. Complete conversions and full chemoselectivities were achieved in most of the examples (Table 4, entries 1−3, 5−7, 9, and 10), only the 4-tert-butyl- and 3-methyl-substituted phenylacetylene derivatives gave somewhat lower conversions (82 and 52%, respectively; entries 4 and 8). In some of the reactions, we even managed to outperform the batch results (entries 1, 5, and 10). Aliphatic alkynes performed poorer than aromatic ones with conversions of 6−69% with Method A and 15−80% with Method B (20 mol % BiBr$_3$; entries 11−13). In these cases, the flow conversions were slightly lower than those registered under batch conditions for aliphatic alkynes, but the results are still intriguing taken into account the batch reaction times of 72 h vs the flow residence times of 65 or 130 min.

Conversions and selectivities achieved under flow conditions A and B were practically similar. However, with some of the substrates (e.g., phenylacetylene and its 4-tert-butyl- and 3-methyl-substituted derivatives), precipitation occurred in the presence of Bi(NO$_3$)$_3$·5H$_2$O and the reactions could not be fulfilled reproducibly under conditions A. For the flow reactions, BiBr$_3$ proved to be a more reliable and more general catalyst without precipitation issues. Furthermore, pure MeOH as solvent had a remarkable advantage in terms of process sustainability. Preparative-scale continuous-flow alkyne hydrations were therefore attempted under conditions B using BiBr$_3$ as catalyst. In these experiments, the solution of the appropriate starting materials was continuously pumped for 5 h after reaching steady state. The formation of the corresponding acetophenone derivatives was successfully achieved in multigram scales with isolated yields of around 90%. Importantly, the methodology proved to be highly productive affording >0.40 g pure product per h in each reaction (Figure 3).

In conclusion, novel methodologies were developed for the atom-economical synthesis of carbonyl compounds via the Markovnikov-type hydration of terminal acetylenes. Bi(NO$_3$)$_3$·5H$_2$O was found readily applicable as catalyst for a diverse set of aromatic and aliphatic alkynes under reasonably mild batch conditions. In order to exploit extended parameter spaces, the reactions were investigated under high-temperature continuous-flow conditions. The flow reactions were carried out by...
Catalytic sources. BiBr₃ was found to be a more reliable and added. The application of continuous—which could be employed in MeOH without any cosolvent more robust homogeneous catalyst for the reactions, which were carried out with mixtures of Bi(NO₃)₃·5H₂O and Bi(NO₃)₃·5H₂O as catalyst, 0.1 mL min⁻¹ flow rate, 230 °C. Method B: calkyne = 0.25 M, MeOH as solvent, 10 mol % Bi(NO₃)₃·5H₂O as catalyst, 0.1 mL min⁻¹ flow rate, 230 °C. Method A: calkyne = 0.25 M, MeOH/DMSO 8:1 as solvent, 10 mol % Bi(NO₃)₃·5H₂O as catalyst, 0.1 mL min⁻¹ flow rate, 230 °C. Method B: calkyne = 0.25 M, MeOH as solvent, 10 mol % BiBr₃ as catalyst, 0.2 mL min⁻¹ flow rate, 230 °C. Determined by ¹H NMR or GC-MS analysis of the crude product. '20 mol % catalyst.

Figure 3. Preparative-scale alkyne hydrations under continuous-flow conditions.

using both Bi(NO₃)₃·5H₂O and BiBr₃ as readily available catalytic sources. BiBr₃ was found to be a more reliable and more robust homogeneous catalyst for the flow reactions, which could be employed in MeOH without any cosolvent added. The application of continuous-flow conditions offered a marked chemical intensification in comparison with batch reactions (65 min residence time vs 24 or 72 h reaction time) and ensured time-efficient syntheses. The preparative capabilities of the flow methodology were demonstrated with the gram-scale synthesis of three acetophenone derivatives.

The processes developed exhibit major advances in points of sustainability which are summarized as follows: (i) application of cheap, nontoxic catalysts; (ii) no need for special additives and/or harmful reagents, (iii) use of environmentally benign solvents; (iv) selective syntheses with a low amount of waste generation; (v) mild conditions for conventional batch reactions; (vi) high-temperature flow conditions for safe chemical intensification.

### EXPERIMENTAL SECTION

**General Information.** Reagents and materials were commercially available and used as received. Analytical thin-layer chromatography was performed on Merck silica gel 60 F254 plates and flash column chromatography on Merck silica gel 60. Compounds were visualized by means of UV or KMnO₄. ¹H NMR and ¹³C NMR spectra were recorded on a Bruker Avance NEO 500 MHz spectrometer equipped with a Prodigy BBO 5 mm CryoProbe, in CDCl₃ as solvent, with TMS as internal standard. GC-MS analyses were performed on a Thermo Scientific Trace 1310 Gas Chromatograph coupled with a Thermo Scientific ISQ QD Single Quadrupole Mass Spectrometer using a Thermo Scientific TG-SQC column (15 m x 0.25 mn ID x 0.25 μm film). Measurement parameters were as follows: column oven temperature from 50 to 300 °C at 15 °C min⁻¹; injection temperature 240 °C; ion source temperature 200 °C; electrospray ionization 70 eV; carrier gas He at 1.5 mL min⁻¹; injection volume 2 μL; split ratio 1:33:3; and mass range 50–500 m/z.

**General Procedure for Batch Reactions.** A reaction mixture containing the appropriate alkyne (c = 0.25 M) and Bi(NO₃)₃·5H₂O (10 mol %) in MeOH was compiled in an oven-dried Schlenk tube equipped with a magnetic stir bar. The mixture was stirred for 24 or 72 h at 65 °C. After completion, the mixture was cooled to room temperature, water was added and the organic product was extracted with EtOAc (3 x). The combined organic phases were washed with brine, dried over Na₂SO₄ and concentrated in vacuo. The crude products were analyzed by NMR or GC-MS to determine conversion and selectivity. If necessary, column chromatographic purification was carried out with mixtures of n-hexane/EtOAc as eluent.

**General Procedure for Flow Reactions.** Reactions were performed in a homemade flow reactor consisting of a Jasco PU-2085 Plus HPLC pump, a 13 mL stainless steel coil (internal diameter 0.75 mm, length 30 m) and a 10-bar BPR purchased from IDEX. The reaction coil was placed into a GC oven (CE Instruments GC 8000) for heating purposes. The parts of the system were connected with stainless steel and PEEK capillary tubing (0.25 mm internal diameter, both) in combination with stainless steel unions.

For each reaction, a mixture consisting of the alkyne (c = 0.25 M) and the corresponding bismuth(III) catalyst (10 or 20 mol %) in MeOH was compiled in an oven-dried Schlenk tube equipped with a magnetic stir bar. The mixture was stirred for 24 or 72 h at 65 °C. After completion, the mixture was cooled to room temperature, water was added and the organic product was extracted with EtOAc (3 x). The combined organic phases were washed with brine, dried over Na₂SO₄ and concentrated in vacuo. The crude products were analyzed by NMR or GC-MS to determine conversion and selectivity. If necessary, column chromatographic purification was carried out with mixtures of n-hexane/EtOAc as eluent.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acssuschemeng.9b02520.

Additional batch and flow reaction data. Analytical data of the reaction products. Collection of NMR spectra (PDF)
Notes
The authors declare no competing financial interest.

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