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Copper-Catalyzed Huisgen 1,3-Dipolar Cycloaddition under Oxidative Conditions: Polymer-Assisted Assembly of 4-Acyl-1-Substituted-1,2,3-Triazoles

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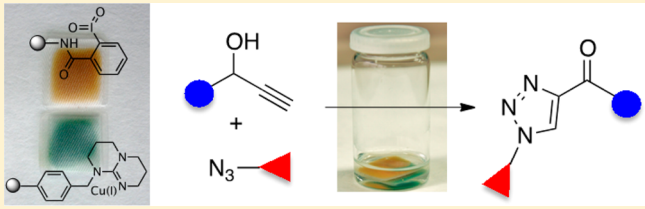
Supporting Information

ABSTRACT: We herein document the first example of a reliable copper-catalyzed Huisgen 1,3-dipolar cycloaddition under oxidative conditions. The combined use of two polymer-supported reagents (polystyrene-1,5,7-triazabicyclo[4,4,0]dec-5-ene/Cu and polystyrene-2-iodoxybenzamide) overcomes the thermodynamic instability of copper(I) species toward oxidation, enabling the reliable Cu-catalyzed Huisgen 1,3-dipolar cycloadditions in the presence of an oxidant agent. This polymer-assisted pathway, not feasible under conventional homogeneous conditions, provides a direct assembly of 4-acyl-1-substituted-1,2,3-triazoles, contributing to expand the reliability and scope of Cu(I)-catalyzed alkyne−azide cycloaddition.



INTRODUCTION

By virtue of its regiospecificity, reliability, and experimental simplicity, the Cu(I)-catalyzed alkyne−azide cycloaddition (CuAAC)[1] has emerged as the flagship of click chemistry,[2] a synthetic paradigm of remarkable practical and environmental significance that has found applications in diverse areas.[3] Independently, Medal[4] and Sharpless[5] introduced the copper-catalyzed Huisgen cycloaddition, highlighting its regiospecificity, substrate scope, and tremendous acceleration of the reaction. These seminal papers proposed alternative approaches to overcome the thermodynamic instability of Cu(I), thus providing the currently established experimental procedures to perform CuAAC:[1] by employing Cu(I) salts [e.g., copper(I) iodide] in combination with ligands and/or bases, or the in situ generation of Cu(I) from copper(II) salts [e.g., copper(II) sulfate pentahydrate], either by comproportionation with copper metal or employing a sacrificial reducing agent (typically sodium ascorbate) that constantly reduces Cu(II) to Cu(I), maintaining high levels of catalytically active species. The simplicity and robustness of the reaction, notwithstanding the instability of Cu(I) oxidation state, generally impose strict experimental conditions aimed to minimize the impact of oxidant species. Accordingly, reliable CuAAC protocols, employing Cu(I) halides, are performed under anaerobic conditions, while those taking place under a weakly reductive reaction medium (sodium ascorbate) do not require an inert atmosphere. Despite extensive practical validation of the transformation,[1,3] the development of CuAACs in the presence of oxidant agents remains a methodological challenge.

Although CuAAC is effectively catalyzed under "ligand-free" conditions,[1] diverse ligands, particularly some heterocyclic derivatives, have shown to preserve the reliability of the reaction in challenging applications.[1,6] These agents stabilize Cu(I) (shielding catalytic species from interactions that lead to degradation), thus enabling the reaction to work under aerobic conditions, thereby reducing the catalyst loading and preventing oxidative damage of biomolecules.[1] Such a scenario has stimulated the emergence of copper-immobilized catalytic systems, particularly of those based on polymeric matrices incorporating Cu(I)-stabilizing chelates.[1,7]

In the context of a program to develop polymer-assisted methodologies enabling the rapid assembly of privileged structures, libraries of pharmacologically relevant 4-acyl-1-substituted-1,2,3-triazoles (**5**)[8] were required. CuAAC-based approaches targeting this chemotype (Figure 1) employ azides (**2**) and either acetylenic carbinols (**1**) or ynones (**3**) as dipolarophiles, both strategies requiring an additional oxidation step to generate the ketone function (either at the starting propynol **1** or the 1,2,3-triazolic intermediate **4**) that must necessarily be carried out as a separate step.[8] Accordingly, we speculated on the feasibility of a direct pathway to access 4-acyl-1-substituted-1,2,3-triazoles (**5**) starting from azides **2** and propynols **1** by performing CuAAC in the presence of an oxidant reagent that is able to selectively transform the hydroxyl group into a ketone function, without affecting the performance of the catalytic process. Being aware that instability of Cu(I) species precluded the viability of such a strategy employing conventional homogeneous catalysts, and building upon Cohen's "wolf and lamb" principle,[9] which states that resins

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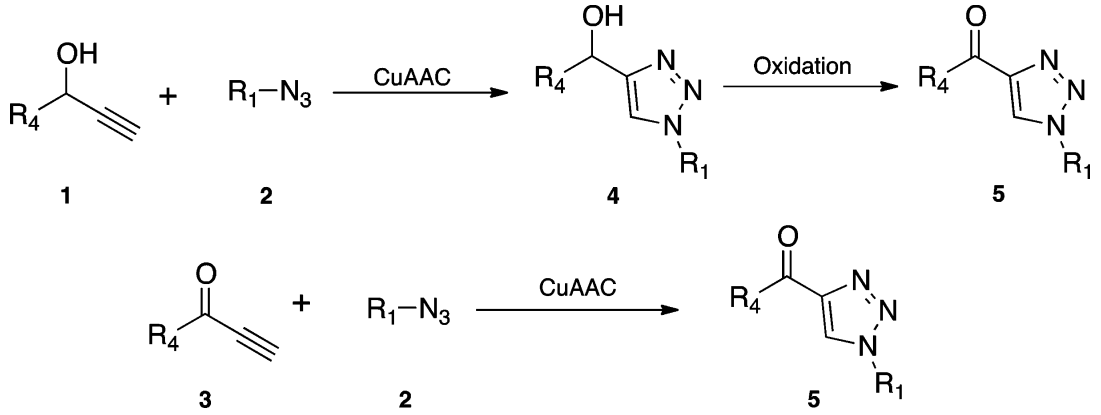

Figure 1. CuAAC-based pathways targeting 4-acyl-1-substituted-1,2,3-triazoles (**5**).[8]

with mutually incompatible functionality do not interact with each other and may be used together to achieve one-pot transformations that would not be possible employing their soluble phase counterparts, it was reasoned that the combined use of two polymer-supported reagents[10] (e.g., a heterogenized Cu(I) chelating catalytic system and a mild oxidant reagent grafted to a polymeric matrix) would be able to overcome the previously stated limitations.

Herein, we document a polymer-assisted approach enabling reliable Cu(I)-catalyzed alkyne–azide cycloadditions under oxidative conditions. Our findings, in addition to providing an efficient, environmentally friendly, and shortened pathway to access 4-acyl-1-substituted-1,2,3-triazoles **5**, emphasize the potential of heterogeneous CuAACs in comparison to their homogeneous counterparts, reveal novel facets of the transformation, and consequently, expand their scope. To the best of our knowledge, this is the first report describing a Cu(I)-catalyzed alkyne–azide cycloaddition in the presence of an oxidant reagent, and the implementation of such a transformation provides theoretical, as well as practical, connotations that go beyond the direct access to 1,2,3-triazoles **5** starting from azides (**2**) and propynols (**1**).

RESULTS AND DISCUSSION

Because the feasibility and practical interest of the proposed pathway rely heavily on the robustness and compatibility of the polymer-supported reagents employed, particularly for the CuAAC catalyst, we have focused on a comprehensive survey of candidates exhibiting not only excellent efficiency and selectivity but also optimal performance on challenging reaction environments and the recyclability criteria. Among the plethora of heterogeneous catalysts described for CuAAC,[11] it became apparent that copper chelates derived from amine-based heterocyclic ligands grafted to polymeric matrices[6,7] were ideally suited for this application. These catalytic systems have been shown to prevent oxidative dimerization pathways when performing CuAAC under oxidative environments.[1,12] The heterocyclic moiety stabilizes catalytically active copper species, shielding them from interactions that lead to degradation, simultaneously exhibiting significant efficacy as copper scavengers. Attending to its effectiveness, robustness, and polyvalent roles, the polystyrene-based 1,5,7-triazabicyclo-[4,4,0]dec-5-ene (TBD) framework-copper chelate [PS-TBD-Cu, (**6**)][13] seemed to us to be a good candidate for proof of concept (Figure 2). While the presence of homogeneous copper species was detected during CuAAC experiments with

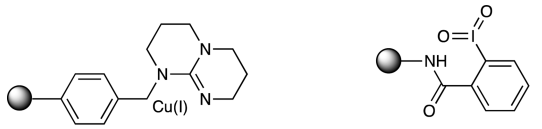

Figure 2. Structure of herein employed polymer-supported reagents.

PS-TBD-Cu(I),[13] negligible leaching of the metal was verified by ICP-MS analysis (of solvent and isolated products), confirming that the excellent stabilizing/chelating profile of the TBD framework guarantees that copper species remain fixed on the solid support, which would enable minimizing its exposition to oxidant agents. A search among supported reagents able to efficiently oxidize alcohols under mild conditions highlighted the tailored reactivity and selectivity profiles elicited by polymeric matrices incorporating the 2-iodoxybenzoic acid scaffold (IBX).[14] Among this reagent's family, polystyrene IBX amide[15] (**7**, 0.5–1.0 mmol/g) was selected (Figure 2), which is a stable (air- and moisture-tolerant) and highly efficient reagent that is able to rapidly (2–5 h) and selectively transform activated alcohols into the corresponding ketones or aldehydes at room temperature.[15c]

The first stage of the study consisted of a brief verification that candidates **6** and **7** constitute highly competent supported reagents for each single step; to this end, 1-phenylprop-2-yn-1-ol (**1a**), 1-phenylprop-2-yn-1-one (**3a**), and benzyl azide (**2a**) were employed as model substrates (Scheme 1). These experiments were also aimed at exploring the key experimental parameters in order to reach proof of concept (e.g., solvent compatibility, reaction temperature, as well as the equivalents of each supported reagent required for optimal performance in reasonable reaction times). The obtained results were consistent with previous data, validating the robustness of the supported reagents (**6** and **7**) for the tested transformations [alcohol oxidation (**1a** → **3a**, **4a** → **5a**), as well as CuAAC (**1a** + **2a** → **4a**, **3a** + **2a** → **5a**)], affording 1,2,3-triazoles **4a** and **5a** in nearly quantitative yields. The optimized conditions (Scheme 1) require a slight excess of both polymer-supported reagents [2 equiv of PS-TBD/Cu (≈3 mol % Cu) and 3 equiv for PS-IBX-amide] to ensure a complete conversion of the reactants at room temperature in reasonable times (8–10 h for CuAAC and 2–5 h for alcohol oxidation). Although the effect of the solvent does not seem to be particularly critical (DMF, $CHCl_3$, and DCM are eligible), DMF was preferred for further optimization due to its generality and excellent swelling of

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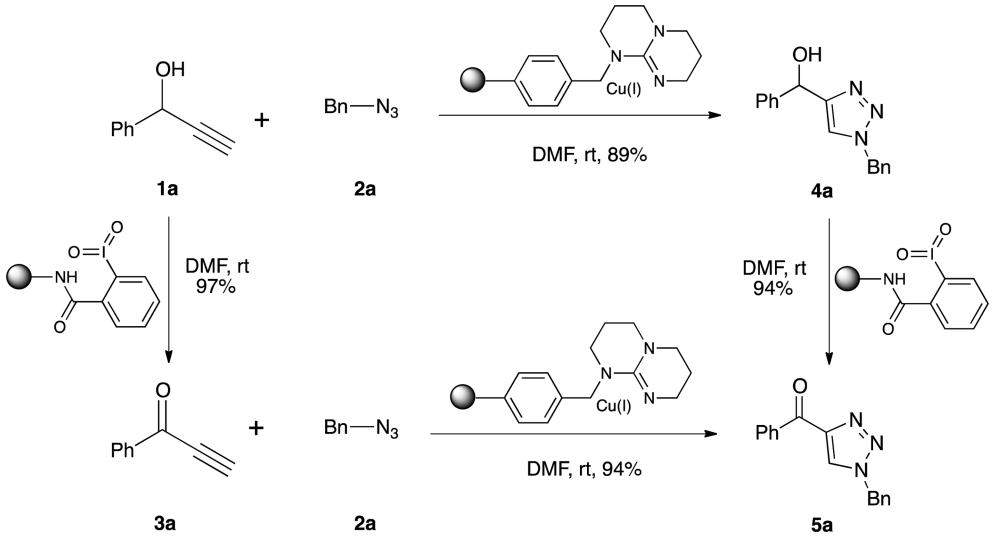
Scheme 1. Polymer-Assisted Step-Wise Synthesis of 4-Acyl-1-benzyl-1,2,3-triazoles



polystyrene-based matrices. When the superior reactivity profile exhibited by electron-deficient acetylenes toward 1,3-dipolar cycloadditions,[16] and particularly some precedents describing its participation in the Huisgen reaction,[16] were taken into account, the role of the polymer-supported copper catalyst within the transformation was validated. With this aim, 1-phenylprop-2-yn-1-one (**3a**) and benzyl azide (**2a**) were combined under identical experimental conditions to those previously studied (but in the absence of the catalyst). These experiments failed to afford the 4-benzoyl-1-benzyl-1,2,3-triazole (**5a**), verifying conversion levels below 10% after 48 h of reaction, which unequivocally validated that the supported copper species (PS-TBD/Cu) play a key role during the observed transformation. It should be noted that, as expected, attempts to perform the tandem process delivering **5a** under conventional homogeneous conditions [employing Dess–Martin or IBX reagents as oxidants and Cu(I) species in combination with established CuAAC ligands (e.g., DIPEA or TBTA)][1] failed, producing complex mixtures.

Equipped with robust polymer-supported candidates (**6** and **7**), putatively fulfilling the requirements of the designed pathway, we proceeded to assess the feasibility of the Cu(I)-catalyzed alkyne–azide cycloaddition under oxidative conditions. Equimolecular amounts (0.5 mmol) of 1-phenylprop-2-yn-1-ol (**1a**) and benzyl azide (**2a**) were added to a preincubated solution (DMF) containing PS-IBX-amide (3 equiv) and PS-TBD/Cu (2 equiv, i.e. 3 mol % Cu)[13], and the mixture was submitted to orbital stirring at room temperature under either anaerobic or aerobic conditions. Gratifyingly, it was verified that complete consumption of the reactants occurred within 24 h, and the reaction regioselectively afforded 4-benzoyl-1-benzyl-1,2,3-triazole (**5a**) in excellent yields (90–92%), irrespective of whether the cycloaddition was performed under aerobic or anaerobic atmosphere. Full conversion and high purity were observed for the transformation in the following solvents: DMF, $CHCl_3$, and acetonitrile.

A brief screening of the reaction to assess the effect of lowering copper loadings (1.5 and 2 mol %) revealed a similar performance, albeit requiring longer reaction time (24–48 h), while a similar study for the equivalents of PS-IBX-amide confirmed that a minimum of 3 equiv is required. An exhaustive scrutiny of the reaction mixture revealed the nonappearance of byproducts derived from oxidative coupling pathways (e.g., bis-acetylenic compounds, 5,5′-bistriazoles, or 5-alkynyl-1,2,3-triazoles)[12] when CuAAC was performed under oxidant conditions, thus confirming the appropriateness of the herein documented approach. The absence of bis-acetylenic compounds or enynes (derived from Glaser or Strauss reactions) suggests that, notwithstanding the presence of polymer-supported oxidant (PS-IBX-amide), cupric species are not substantially formed. This is likely due to the excellent chelating profile of the TBD framework that scavenges copper species from solution and shields catalytic species from degradation. The polymeric nature of the catalyst could also contribute to such a chemoselective behavior because the formation of copper acetylides on the solvated polymeric matrix thoroughly prevents the occurrence of cross-coupling reactions.[1] In a similar fashion, the nonappearance of oxidative dimeric compounds 5,5′-bistriazoles or 5-alkynyl-1,2,3-triazoles, which are byproduct compounds generally afforded when performing CuAAC transformations under mild oxidative conditions,[12] should be necessarily related to the following: (a) the use of two polymeric reagents effectively prevents capture and oxidative pathways on triazolyl copper intermediates [since both reactive species are linked to different resins], and (b) as recently demonstrated,[12] the use of catalytic systems consisting of copper coordination forms a complex with nitrogenated ligands, inhibits oxidative dimerization exclusively, and affords targeted 1,2,3-triazoles.

The availability of authentic samples of 1-phenylprop-2-yn-1-one (**3a**) and triazole **4a** enabled us to detect both intermediates in the reaction mixture, which confirmed that both pathways are simultaneously operating during the tandem process (Figure 3). Briefly, the CuAAC of azide (**2**) and the 1-substituted-prop-2-yn-1-ol (**1**) afforded the triazolic carbinol intermediate (**4**) that was subsequently oxidized and generated the target structure (**5**). Alternatively, the oxidation of the starting 1-substituted-prop-2-yn-1-ol (**1**) generated an ynone intermediate (**3**) that was transformed into 4-acyl-1-benzyl-1,2,3-triazole **5** by the CuAAC with benzyl azide.

In an attempt to evaluate the importance of the supported ligand (PS-TBD/Cu) on the tandem process, 1-phenylprop-2-yn-1-ol (**1a**) and benzyl azide (**2a**) were reacted under previously optimized experimental conditions (Scheme 1),

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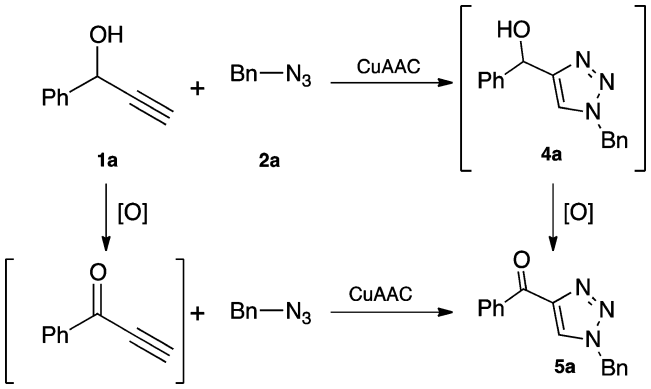
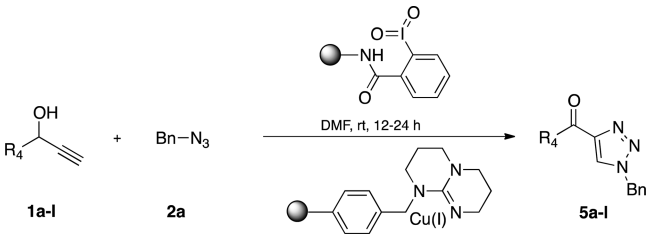


Figure 3. Alternative operating pathways.

but we used the polymeric version of two established ligands for CuAAC (TBTA[7a] and DIPEA[1]), instead of using PS-TBTA/Cu. These experiments highlighted the supreme stabilization provided by heterocyclic ligands (TBD and TBTA), both of which exhibited similar reactivity and comparable yields (87−90%). Conversely, the use of PS-DIPEA/Cu produced lower yields (46%) and the concomitant formation of byproducts.

Having established the feasibility of the proposed method for the model system, a preliminary assessment of the robustness and scope of the developed methodology was performed by recurring to a set of assorted dipolarophiles (**1a−l**) and benzyl azide (**2a**). We were pleased to observe that the conditions described in Scheme 2 led to a smooth cycloaddition, which

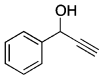
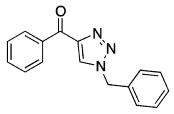
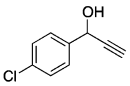
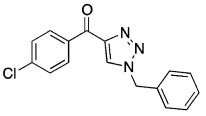
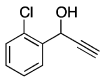
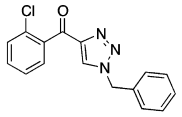
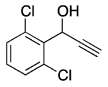
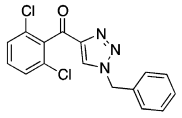
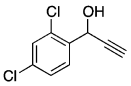
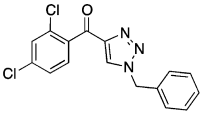
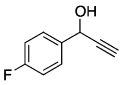
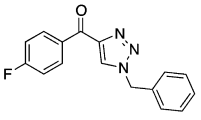
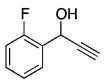
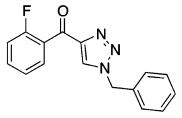
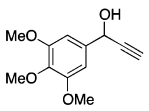
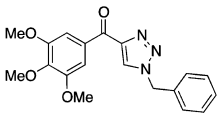
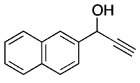
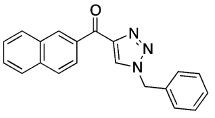
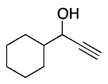
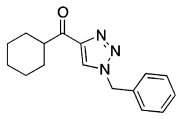
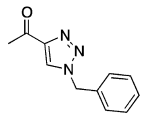
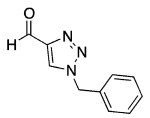
Scheme 2. Polymer-Assisted One-Pot Synthesis of 4-Acyl-1-benzyl-1,2,3-triazoles



exclusively afforded 4-acyl-1-benzyl-1,2,3-triazoles (**5**). The structures of the obtained compounds are depicted in Table 1. It can be seen that the reaction allows a thorough variation (electronic as well as steric) in the acetylenic partner, thus generating 1,2,3-triazoles incorporating diverse acyl residues at position 4 (compounds **5a−l**). It is noteworthy to highlight that the reaction remains successful for dipolarophiles incorporating hindered aromatic residues (e.g., 2-Cl or 2,6-Cl). The use of propargyl alcohol was similarly successful, enabling the introduction of a formyl group at position 4 of the heterocycle without observing the formation of overoxidation products. The purity of the crude isolated adducts was generally higher than 90%, as determined by LC-MS analysis, and the compounds that did not reach this level were purified by preparative chromatography.

A serious limitation of the copper-mediated Huisgen cycloaddition in drug discovery programs arises from the relatively low abundance of commercially available azides.[1] Such a drawback is generally overcome by developing three-component transformations, [17] where the dipolarophile is

Table 1. Representative 1,2,3-Triazoles Obtained Employing Optimized Conditions

Comp.	*Dipolarophile (1a-l)*	*Product (5a-l)*	*Yield (%)*
5a			**90**
5b			**89**
5c			**83**
5d			**87**
5e			**85**
5f			**88**
5g			**92**
5h			**85**
5i			**80**
5j			**92**
5k			**82**
5l			**79**

captured by an organic azide that is generated in situ from an appropriate halide and sodium azide. Encouraged by the efficiency of the new pathway herein described (Scheme 2), and to further evaluate its potential conceptual and practical connotations, we wondered if it would be possible to observe a polymer-assisted three-component assembly of 4-acyl-1-

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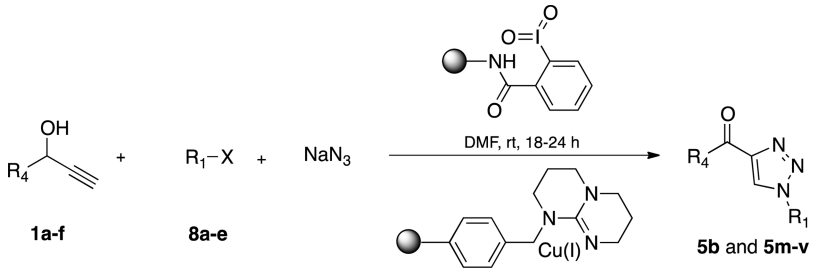
Scheme 3. Polymer-Assisted One-Pot Synthesis of 4-Acyl-1-substituted-1,2,3-triazoles



substituted-1,2,3-triazoles (**5**), starting from acetylenic carbinols (**1**), halides (**8**), and sodium azide (Scheme 3). Such a transformation would combine, in a one-pot sequence, the in situ generation of the organic azide (**2**), a copper-mediated Huisgen 1,3-dipolar cycloaddition, and the oxidation of the alcoholic residue [either at the starting propynol (**1**) or the heterocycle (**4**)]. While the dual role of PS-TBD/Cu [consisting of copper species immobilized on a highly effective chelating/stabilizing basic residue (TBD)] facilitates the implementation of three-component approaches,[13] some studies have described the IBX ability to transform halides into their corresponding carbonyl compounds[18] (DMSO, 65 °C). We anticipated a critical issue that could have potentially affected the feasibility of the projected pathway (Scheme 3). To address a potential issue, the reaction of two representative halides (**8a, b**) with PS-IBX-amide (3−5 equiv) in DMF was studied (at room temperature and 40 °C, respectively). We were pleased to observe that halides **8a, b** remained unaltered under the evaluated conditions, even when combining a large excess (4 equiv) of PS-IBX-amide at 40 °C. These results provided a solid foundation for the feasibility of the planned reaction sequence.

The feasibility of the designed polymer-assisted three-component transformation (Scheme 3) was assessed employing 1-(4-chlorophenyl)prop-2-yn-1-ol (**1b**), sodium azide, and two model halides [benzyl bromide (**8a**) and ethyl bromoacetate (**8b**)]. Process optimization involved a study examining the optimal alkyne/halide/sodium azide ratio, solvent, and temperature, as well as variable equivalents of the polymeric reagents (**6** and **7**). All reactions were performed under aerobic conditions by adding the reactants to a preincubated slurry of the polymer-supported reagents and submitting the reaction mixture to vigorous orbital stirring at room temperature. A slight excess of sodium azide, in combination with DMF as reaction medium, was critical to achieve a complete conversion in reasonable reaction times (18−24 h). After we refined the experimental parameters, it was verified that, in the presence of PS-TBD/Cu (3 equiv) and PS-IBX-amide (5 equiv), 1-(4-chlorophenyl)prop-2-yn-1-ol (**1b**), sodium azide, and the selected halides were smoothly and regiospecifically converted to the corresponding 4-(4-chlorobenzoyl)-1-substituted-1,2,3-triazoles (**5b** and **5m**), resulting in a satisfactory yield (79 and 70%, respectively, Table 2). The reaction performed well at room temperature, and the optimal alkyne/halide/azide ratio was 1.0/1.0/1.5. As observed in previous experiments (Scheme 1), a scrutiny of the reaction mixture confirmed excellent selectivity with an absence of subproducts derived from Glaser-type homocoupling or oxidative dimerization.

Having optimized the performance of the catalytic system for the model examples, the scope of the three-component reaction on a number of assorted substrates was examined. As observed in Table 2, the reaction was not influenced by either the electronic or steric variations of the reacting substrates, being broadly successful for both variable components (i.e., dipolarophiles and halides). A significant structural variation was well-tolerated in the halide, as exemplified by a range of alkyl, benzyl, and heteroaryl halides, as well as dipolarophiles (covering aliphatic and aromatic series). It should be noted that the transformation was not limited to aryl or alkylpropynols, but it also tolerated propargyl alcohol as the acetylenic partner (that successfully afforded carbaldehydes with somewhat satisfactory yield). The information contained in Table 2 enabled the scope of this mild and efficient procedure to be evaluated, exemplifying its contribution in terms of rapid access to hitherto unexplored diversity spaces. This simple method preserves the reliability of the previously developed approach, while maximizing the diversity space for position 1 of the 1,2,3-triazole core.

The success achieved (Schemes 2 and 3) provides unequivocal validation of the reliability of the herein proposed Cu(I)-catalyzed alkyne−azide cycloaddition under oxidative conditions. Nonetheless, a critical analysis reveals that the practical implementation of the concept underexploits advantages derived from the polymeric nature of **6** and **7**. According to one of the basic principles of Green Chemistry,[19] catalytic or recyclable reagents are superior to stoichiometric reagents. Thus, in addition to its efficacy and robustness, the recyclability of polymer-supported reagents constitutes a remarkable feature, with practical and environmental implications. Although efficiently affording targeted compounds, the experimental protocols described in Schemes 2 and 3 [consisting of the addition of reactants to a mixture of both supported reagents (**6** and **7**) in DMF] precluded the separation, regeneration, and potential reuse of **6** and **7** in newer transformations; accordingly, we focused on the development of practical protocols enabling us to recycle and reuse **6** and **7**. The polymer-supported reagents herein employed elicit different recycling potentials, while PS-TBD/Cu (**6**) can be recycled after a simple washing and drying protocol;[13] conversely, the reuse of PS-IBX-amide (**7**) requires an oxidative activation step.[15b] Two alternative scenarios achieving this goal were devised: the first one is based on the compartmentalization of the polymer-supported reagents, and the second is based on the implementation of a continuous-flow process. Considering its versatility and experimental simplicity, we have chosen the compartmentalization approach, in which one of the reactants (or catalysts) remains physically separated by permeable containers (e.g., membranes or capsules), guaranteeing retention of the encapsulated substrate, while allowing smooth transport of solvent, reactants, and products. Such a strategy has recently become an attractive approach pursuing the largely elusive goal of recycling homogeneous catalysts (i.e., function-

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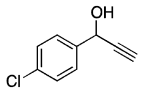
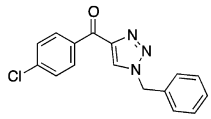
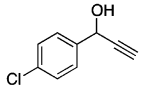
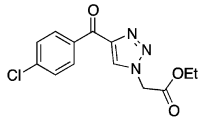
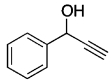
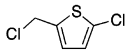
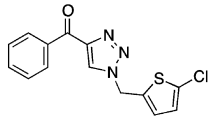
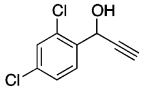
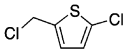
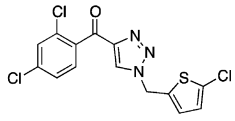
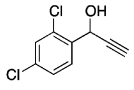
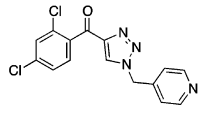
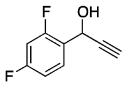
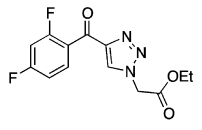
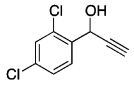
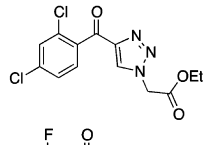
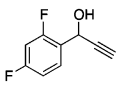
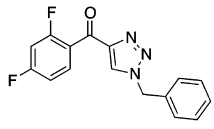
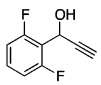
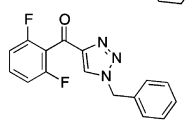
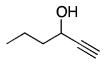
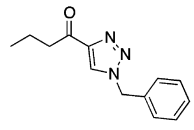
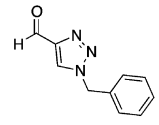
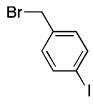
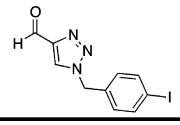
Table 2. Representative 1,2,3-Triazoles Obtained Employing Optimized Conditions

Comp.	*Dipolarophile (1b-f)*	*Halide (8a-e)*	*Product (5)*	*Yield (%)*
5b				**79**
5m				**70**
5n				**68**
5o				**69**
5p				**78**
5q				**61**
5r				**41**
5s				**65**
5t				**70**
5u				**78**
5l				**75**
5v				**86**

alized dendritic catalyst systems).[20] According to the requirements of our reaction setup and inspired by the pioneer Houghten's "tea bag" method,[21] an experimental protocol was designed by confining both polymer-supported reagents in mesh bags, enabling the circulation of solvents and reactants, while isolating both polymeric reagents. The practical implementation of the compartmentalization strategy is illustrated in Figure 4.

For a preliminary validation of the tea bag compartmentalization protocol, the required amount of each polymer-supported reagent was encapsulated into polypropylene mesh bags and then placed into a vial containing a DMF solution of the model reactants [1-phenylprop-2-yn-1-ol (**1a**) and benzyl azide (**2a**)]. Subsequently, the reaction mixture was submitted to orbital stirring at room temperature. Under these conditions, the substrates (**1a** and **2a**) would migrate into the membrane

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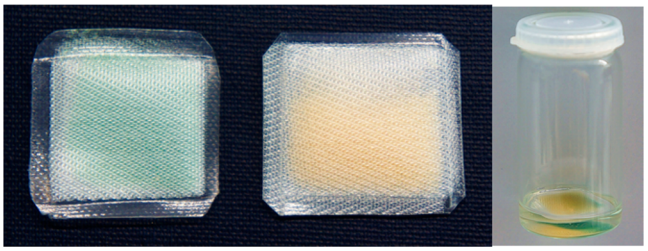

Figure 4. Illustration of the compartmentalization experiments. Polypropylene mesh bag containing PS-TBD/Cu and PS-IBX-amide (left). Both encapsulated reagents enclosed into a vial containing a DMF solution of the reactants (right).

bags, in which they interact with the catalytically active copper species, or the oxidant, and would be converted into the corresponding 1,2,3-triazole or ketone. The success of the designed pathway was confirmed 36 h later, when it was observed that the reactants (**1a** and **2a**) were thoroughly transformed into 4-benzoyl-1-benzyl-1,2,3-triazole (**5a**) with an excellent yield (84%). Notably, a similar experimental design employing ethyl bromoacetate and sodium azide also validated the feasibility of the compartmentalization protocol for the three-component reaction, affording comparable results (e.g., yields and reaction times).

Once the practicability of the tea bag compartmentalization approach was validated, we determined that it effectively enabled the straightforward separation and recycling of both polymer-supported reagents, making it possible to perform the washing and activation (for PS-IBX-amide with oxone) of the polymeric materials in the polypropylene mesh bag. The recycled polymeric materials were employed in new experiments (e.g., synthesis of compounds **5a−c** and **5m−p**) without dramatic yield loss for at least five reaction cycles for PS-TBD and two new experiments for PS-IBX-amide. In addition to its catalytic efficacy and recyclability, the leaching of metal to the reaction media is a key subject to be considered during the development of novel heterogeneous catalytic systems. In an attempt to provide preliminary data on this issue, the copper content of two representative 4-acyl-1,2,3-triazoles (**5a** and **5b**) was determined employing inductively coupled plasma mass spectroscopy (ICP-MS). These experiments evidenced negligible (parts per billion) release of copper to the products (11.2563 ± 0.2141 and 10.2869 ± 0.15587 ppb, respectively), which is in agreement with previous observations.[13]

In summary, we have documented the first example of a reliable copper-catalyzed Huisgen 1,3-dipolar cycloaddition under oxidative conditions. The application of Cohen's "wolf and lamb" principle, combining two polymeric reagents (PS-TBD/Cu and PS-IBX-amide), overcomes the thermodynamic instability of copper(I) species toward oxidation, enabling reliable CuAAC not only under aerobic conditions but also in the presence of a well-known oxidant agent. This polymer-assisted pathway, not feasible under conventional homogeneous conditions, provides a direct assembly of 4-acyl-1-substituted-1,2,3-triazoles contributing to the expansion of the reliability and scope of the Huisgen 1,3-dipolar cycloaddition under previously unexplored conditions.

■ EXPERIMENTAL SECTION

Commercially available starting materials and reagents were purchased and used without further purification from freshly opened containers. Polymer-supported reagents (PS-TBD, 2.6 mmol/g, PS-IBX-amide, 0.5−1.0 mmol/g, PS-DIPEA, 3 mmol/g, Tentagel-TBTA, 0.17 mmol/g) were purchased from commercial sources. Acetylenic carbinols were prepared according to the literature[22] or purchased from commercial sources. Organic extracts were dried with anhydrous Na_2SO_4. The reactions were monitored by TLC, and purified compounds each showed a single spot. Unless stated otherwise, UV light and/or iodine vapor was used for the detection of compounds. The synthesis and purification of all compounds were accomplished using the equipment routinely available in organic chemistry laboratories. Most of the preparative experiments were performed in coated vials on an organic synthesizer with orbital stirring. Purification of isolated products was carried out by column chromatography. Compounds were routinely characterized by spectroscopic and analytical methods. Melting points were determined on a melting point apparatus and are uncorrected. The chemical structures of the obtained compounds were characterized by nuclear magnetic resonance spectroscopy (^{1}H and ^{13}C) and high-resolution mass spectra (HRMS). Unless otherwise quoted, NMR spectra were recorded in $CDCl_3$. Chemical shifts are given as δ values against tetramethylsilane as the internal standard, and J values are given in Hz. Inductively coupled plasma mass spectroscopy (ICP-MS) analysis of compounds **5a** and **5b** was performed on a Varian 820-MS spectrometer (after microwave-assisted digestion of the samples).

Representative Procedure for the Immobilization of Copper Species on Polystyrene-Supported TBD (PS-TBD). To a solution of 18 mg of CuI in 35 mL of MeCN was added 1.0 g of PS-TBD (loading 2.6 mmol/g), and the suspension was vigorously stirred under orbital stirring at room temperature for 24 h. The resulting supported catalyst was filtered through a fritted syringe, washed (DCM, diethyl ether), and dried under vacuum for 8 h at room temperature. Copper loading (0.28%) was determined by wavelength dispersive X-ray fluorescence spectrometry (WD-XRF).[13]

Representative Procedure for the Synthesis of 4-Acyl-1-substituted-1,2,3-triazoles. Method A: A mixture of the acetylenic carbinol (0.189 mmol) and the organic azide (0.189 mmol) in DMF (2 mL) was added to a vial containing a slurry of the polymer-supported reagents [PS-TBD/Cu (0.378 mmol) and PS-IBX-amide (0.567 mmol)] in DMF (3 mL). The reaction mixture was submitted to orbital stirring at room temperature, until reactions reached completion (12−24 h). The polymer-supported catalysts were filtered through a fritted syringe in a 12-channel vacuum manifold and washed with DCM and THF. The filtrate was evaporated to give a residue that afforded the corresponding substituted 1,2,3-triazoles after recrystallization or chromatographic purification.

Representative Procedure for the Three-Component Synthesis of 4-Acyl-1-substituted-1,2,3-triazoles. Method B: A mixture of sodium azide (0.283 mmol), alkyl halide (0.189 mmol), and the corresponding acetylenic carbinol (0.189 mmol) in DMF (2 mL) was added to a vial containing a slurry of the polymer-supported reagents [PS-TBD/Cu (I) (0.567 mmol) and PS-IBX-amide (0.945 mmol)] in DMF (3 mL). The reaction mixture was submitted to orbital stirring at room temperature, until reactions reached completion (18−24 h). The polymer-supported catalysts were filtered through a fritted syringe in a 12-channel vacuum manifold and washed with DCM and THF. The filtrate was evaporated to give a solid or residue that afforded the corresponding substituted 1,2,3-triazoles after recrystallization or chromatographic purification.

Representative Procedure for the Synthesis of 4-Acyl-1-substituted-1,2,3-triazoles. Method C (Click Chemistry in a Tea Bag):[21] A mixture of the acetylenic carbinol (0.189 mmol) and the organic azide (0.189 mmol) in DMF (2 mL) was added to a vial containing the supported reagents encapsulated in polypropylene mesh bags [PS-TBD/Cu(I) (0.378 mmol) and PS-IBX-amide (0.567 mmol)]. The reaction mixture was submitted to orbital stirring at room temperature, until reactions reached completion (24−36 h). The bags were removed, suspended in DCM, and washed with DCM and THF. The filtrate was evaporated to give a solid or residue that afforded the corresponding substituted 1,2,3-triazoles after recrystallization or chromatographic purification.

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(1-Benzyl-1*H*-1,2,3-triazol-4-yl)(phenyl)methanone, 5a: White solid; mp 117−118 °C (lit 115−116 °C);[23] Method A, yield 90% (44 mg); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 8.41 (d, J = 7.0 Hz, 2H), 8.15 (s, 1H), 7.58 (t, J = 7.0 Hz, 1H), 7.48 (t, J = 7.3 Hz, 2H), 7.42−7.38 (m, 3H), 7.34−7.28 (m, 2H), 5.61 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 185.6, 143.9, 136.5, 133.6, 133.2, 130.6, 129.3, 129.2, 128.4, 128.3, 128.2, 54.5; HRESIMS calcd for $C_{16}H_{13}N_3NaO$ (M^+) 286.0951, found 286.0954.

(1-Benzyl-1*H*-1,2,3-triazol-4-yl)(4-chlorophenyl)methanone, 5b: White solid; mp 158−160 °C; Method A, yield 89% (39 mg); Method B, yield 78% (34 mg); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 8.26 (d, J = 8.5 Hz, 2H), 7.99 (s, 1H), 7.33−7.30 (m, 2H), 7.26−7.23 (m, 3H), 7.23−7.14 (m, 2H), 5.44 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 184.1, 148.2, 139.8, 134.7, 133.5, 132.1, 129.4, 129.2, 128.7, 128.4, 128.3, 54.5; HRESIMS calcd for $C_{16}H_{12}ClN_3NaO$ (M^+) 320.0561, found 320.0564.

(1-Benzyl-1*H*-1,2,3-triazol-4-yl)(2-chlorophenyl)methanone, 5c: Yellow solid; mp 80−82 °C; Method A, yield 83% (36 mg); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 8.11 (s, 1H), 7.43−7.41 (m, 2H), 7.37−7.33 (m, 5H), 7.37−7.31 (m, 2H), 5.59 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 186.9, 147.6, 145.0, 137.1, 133.4, 131.8, 130.3, 130.1, 129.2, 129.1, 128.3, 127.4, 126.4, 54.4; HRESIMS calcd for $C_{16}H_{12}ClN_3NaO$ (M^+) 320.0561, found 320.0561.

(1-Benzyl-1*H*-1,2,3-triazol-4-yl)(2,6-dichlorophenyl)-methanone, 5d: White solid; mp 208−210 °C; Method A, yield 87% (35 mg); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 8.10 (s, 1H), 7.43−7.39 (m, 3H), 7.37−7.31 (m, 5H), 5.59 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 185.6, 146.9, 137.2, 133.1, 131.6, 130.9, 129.3, 129.2, 128.4, 127.9, 126.9, 54.5; HRESIMS calcd for $C_{16}H_{11}Cl_2N_3NaO$ (M^+) 354.0171, found 354.0163.

(1-Benzyl-1*H*-1,2,3-triazol-4-yl)(2,4-dichlorophenyl)-methanone, 5e: White solid; mp 163−164 °C; Method B, yield 85% (35 mg); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 8.11 (s, 1H), 7.61 (d, J = 8.2 Hz, 1H), 7.50 (d, J = 1.8 Hz, 1H), 7.50−7.38 (m, 2H), 7.37−7.31 (m, 4H), 5.59 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 185.9, 157.9, 138.9, 135.9, 133.3, 133.2, 131.3, 130.4, 129.4, 129.3, 128.4, 127.5, 126.9, 54.5; HRESIMS calcd for $C_{16}H_{11}Cl_2N_3NaO$ (M^+) 354.0171 found 354.0179.

(1-Benzyl-1*H*-1,2,3-triazol-4-yl)(4-fluorophenyl)methanone, 5f: White solid; mp 145−146 °C (lit. 145−146 °C);[23] Method A, yield 88% (41 mg); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 8.53 (m, 2H), 8.16 (s, 1H), 7.42−7.40 (m, 3H), 7.35−7.32 (m, 2H), 7.18 (d, J = 8.7 Hz, 2H), 5.57 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 183.7, 165.8, 148.19, 133.59, 133.3, 132.6, 129.2, 129.0, 128.3, 128.28, 115.4, 54.3; HRESIMS calcd for $C_{16}H_{12}FN_3NaO$ (M^+) 304.0857, found 304.0861.

(1-Benzyl-1*H*-1,2,3-triazol-4-yl)(2-fluorophenyl)methanone 5g: White solid; mp 101−102 °C; Method A, yield 92% (42 mg); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 8.10 (s, 1H), 7.85−7.80 (m, 1H), 7.56−7.49 (m, 1H), 7.41−7.38 (m, 3H), 7.33−7.28 (m, 2H), 7.23−7.13 (m, 2H), 5.59 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 184.7, 159.4, 148.0, 133.8, 133.5, 131.2, 129.3, 129.2, 128.3, 127.3, 126.1, 124.0, 116.5, 54.5; HRESIMS calcd for $C_{16}H_{12}FN_3NaO$ (M^+) 304.0857, found 304.0855.

(1-Benzyl-1*H*-1,2,3-triazol-4-yl)(3,4,5-trimethoxyphenyl)-methanone, 5h: Yellow solid; mp 104−106 °C; Method A, yield 85% (33 mg); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 8.14 (s, 1H), 7.84 (s, 2H), 7.39−7.37 (m, 3H), 7.33−7.30 (m, 2H), 5.57 (s, 2H), 3.92 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 183.8, 162.4, 152.8, 148.6, 142.8, 133.6, 131.3, 129.1, 128.7, 128.3, 108.0, 60.9, 56.2, 54.4; HRESIMS calcd for $C_{19}H_{19}N_3NaO_4$ (M^+) 376.1268, found 376.1268.

(1-Benzyl-1*H*-1,2,3-triazol-4-yl)(naphthalen-2-yl)methanone, 5i: White solid; mp 158−160 °C; Method A, yield 80% (34 mg); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 8.88 (s, 1H), 8.34−8.21 (m, 2H), 8.05−7.87 (m, 4H), 7.61−7.54 (m, 2H), 7.43−7.34 (m, 4H), 5.63 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 185.3, 148.2, 135.7, 133.7, 133.4, 132.5, 130.1, 129.4, 129.2, 128.6, 128.4, 128.3, 128.1, 127.7, 126.6, 125.5, 54.5; HRESIMS calcd for $C_{20}H_{16}N_3O$ (M + H) 314.1288, found 314.1285.

(1-Benzyl-1*H*-1,2,3-triazol-4-yl)(cyclohexyl)methanone, 5j: Yellow solid; mp 112−114 °C; Method A, yield 92% (44 mg); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.93 (s, 1H), 7.42−7.38 (m, 3H), 7.32−7.27 (m, 2H), 5.55 (s, 2H), 3.59−3.50 (m, 1H), 1.97−1.94 (m, 2H), 1.84−1.70 (m, 3H), 1.55−1.52 (m, 2H), 1.48−1.40 (m, 2H), 1.36−1.22 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 198.5, 133.6, 129.3, 129.1, 128.3, 128.2, 125.7, 54.4, 46.7, 28.6, 25.9, 25.6; HRESIMS calcd for $C_{16}H_{19}N_3NaO$ (M^+) 292.1420, found 292.1423.

1-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)ethanone, 5k: Yellow solid; mp 85−86 °C (lit. 90 °C);[24] Method A, yield 92% (65 mg); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.77 (s, 1H), 7.24−7.12 (m, 5H), 5.39 (s, 2H), 2.51 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 192.8, 133.5, 129.3, 129.1, 128.3, 125.1, 125.0, 54.5, 27.1; HRESIMS calcd for $C_{11}H_{11}N_3NaO$ (M^+) 224.0794, found 224.0800.

1-Benzyl-1*H*-1,2,3-triazole-4-carbaldehyde, 5l: Colorless oil; Method A, yield 79% (64 mg); Method B, yield 75% (61 mg); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 10.07 (s, 1H), 8.01 (s, 1H), 7.37−7.35 (m, 3H), 7.29−7.25 (m, 2H), 5.56 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 184.9, 148.0, 133.3, 129.3, 129.2, 128.3, 125.1, 54.5; HRESIMS calcd for $C_{10}H_9N_3NaO$ (M^+) 210.0638, found 210.0629.

Ethyl 2-[4-(4-Chlorobenzoyl)-1*H*-1,2,3-triazol-1-yl]acetate, 5m: White solid; mp 163−165 °C; Method B, yield 70% (30 mg); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 8.37 (d, J = 8.6 Hz, 2H), 8.35 (s, 1H), 7.43 (d, J = 8.6 Hz, 2H), 5.18 (s, 2H), 4.23 (q, J = 7.1 Hz, 2H), 1.26 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 183.9, 165.5, 148.2, 139.9, 134.6, 132.0, 129.9, 128.7, 62.8, 50.9, 14.04; HRESIMS calcd for $C_{13}H_{12}ClN_3NaO_3$ (M^+) 316.0459, found 316.0471.

(1-((5-Chlorothiophen-2-yl)methyl)-1*H*-1,2,3-triazol-4-yl)-(phenyl)methanone, 5n: White solid; mp 115−116 °C; Method B, yield 68% (38 mg); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 8.43−8.39 (m, 2H), 8.24 (s, 1H), 7.61−7.58 (m, 1H), 7.54−7.48 (m, 2H), 6.96 (d, J = 3.9 Hz, 1H), 6.85 (d, J = 3.9 Hz, 1H), 5.68 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 185.4, 148.2, 136.2, 133.6, 133.3, 132.2, 130.4, 128.3, 128.2, 127.9, 126.3, 48.7; HRESIMS calcd for $C_{14}H_{10}ClN_3NaOS$ (M^+) 326.0125, found 326.0133.

(1-((5-Chlorothiophen-2-yl)methyl)-1*H*-1,2,3-triazol-4-yl) (2,4-dichlorophenyl) methanone, 5o: Yellow solid; mp 115−116 °C; Method B, yield 69% (30 mg); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 8.20 (s, 1H), 7.60 (d, J = 8.2 Hz, 1H), 7.49 (s, 1H), 7.42 (d, J = 8.2 Hz, 1H), 6.96 (d, J = 3.6 Hz, 1H), 6.86 (d, J = 3.6 Hz, 1H), 5.67 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 185.7, 147.6, 137.6, 135.3, 133.2, 133.1, 132.6, 131.3, 130.4, 128.4, 127.1, 126.9, 126.5, 48.9; HRESIMS calcd for $C_{14}H_8Cl_3N_3NaOS$ (M^+) 393.9346, found 393.9351.

(2,4-Dichlorophenyl)(1-((pyridin-4-yl)methyl)-1*H*-1,2,3-triazol-4-yl)metha-none, 5p: Yellow solid; mp 125−126 °C; Method B, yield 78% (32 mg); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 8.66 (d, J = 5.9 Hz, 2H), 8.22 (s, 1H), 7.62 (d, J = 8.2 Hz, 1H), 7.51 (d, J = 1.9 Hz, 1H), 7.38 (d, J = 8.2 Hz, 1H), 7.16 (d, J = 5.9 Hz, 2H), 5.63 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 185.6, 150.7, 147.7, 142.2, 137.6, 135.1, 133.0, 131.2, 130.4, 127.8, 126.9, 122.1, 53.0; HRESIMS calcd for $C_{15}H_{11}Cl_2N_4O$ (M + H) 333.0304, found 333.0310.

Ethyl 2-[4-(2,4-difluorobenzoyl)-1*H*-1,2,3-triazol-1-yl]-acetate, 5q: Yellow solid; mp 170−171 °C; Method B, yield 61% (26 mg); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 8.36 (s, 1H), 7.61 (d, J = 8.3 Hz, 1H), 7.61 (d, J = 8.3 Hz, 1H), 7.49 (d, J = 1.3 Hz, 1H), 5.22 (s, 2H), 1.30 (q, J = 7.3 Hz, 2H), 1.30 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 185.6, 165.4, 147.6, 137.6, 135.4, 133.1, 131.3, 130.4, 129.1, 126.9, 62,8, 51.0, 14.0; HRESIMS calcd for $C_{13}H_{11}F_2N_3NaO_3$ (M^+) 318.0661, found 318.0660.

Ethyl-2-[4-(2,4-dichlorobenzoyl-1*H*-1,2,3-triazol-1-yl]-acetate, 5r: Yellow solid; mp 164−166 °C; Method B, yield 41% (16 mg); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 8.35 (s, 1H), 7.99−7.93 (m, 1H), 6.99−6.96 (m, 1H), 6.93−6.88 (m, 1H), 5.22 (s, 2H), 4.29 (q, J = 7.3 Hz, 2H), 1.30 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 183.5, 165.4, 133.3, 131.3, 130.4, 129.0, 126.9, 111.4, 105.2, 104.9, 62.8, 50.9, 14.0; HRESIMS calcd for $C_{13}H_{11}Cl_2NaN_3O_3$ (M^+) 350.0070, found 350.0069.

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(1-Benzyl-1*H*-1,2,3-triazol-4-yl)(2,4-difluorophenyl)-methanone, 5s: White solid; mp 118−120 °C; Method B, yield 65% (28 mg); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 8.09 (s, 1H), 7.96−7.90 (m, 1H), 7.40−7.36 (m, 3H), 7.31−7.23 (m, 2H), 6.99−6.94 (m, 1H), 6.91−6.86 (m, 1H), 5.57 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 183.3, 166.6, 147.9, 133.4, 133.3, 133.1, 129.3, 129.2, 128.3, 128.0, 122.6, 111.6, 105.1, 54.5; HRESIMS calcd for $C_{16}H_{11}F_2N_3NaO$ (M^+) 322.0762, found 322.0765.

(1-Benzyl-1*H*-1,2,3-triazol-4-yl)(2,6-difluorophenyl)-methanone, 5t: Yellow solid; mp 92−94 °C; Method B, yield 70% (31 mg); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 8.15 (s, 1H), 7.50−7.40 (m, 4H), 7.33−7.30 (m, 2H), 7.02−6.96 (t, J = 8.0 Hz, 2H), 5.59 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 188.1, 133.3, 132.6, 132.5, 132.4, 129.4, 129.3, 128.4, 126.7, 112.0, 111.8, 54.6; HRESIMS calcd for $C_{16}H_{11}F_2N_3NaO$ (M^+) 322.0762, found 322.0765.

1-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)butan-1-one, 5u: White solid; mp 72−74 °C; Method B, yield 78% (6 mg); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.77 (s, 1H), 7.23−7.19 (m, 3H), 7.14−7.09 (m, 2H), 5.38 (s, 2H), 2.91 (t, J = 7.4 Hz, 2H), 1.63−1.54 (m, 2H), 0.81 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 195.2, 148.1, 133.5, 129.1, 129.0, 128.2, 125.1, 54.3, 41.2 17.2, 13.6; HRESIMS calcd for $C_{13}H_{15}N_3NaO$ (M^+) 252.1107, found 252.1114.

1-(4-Iodobenzyl)-1*H*-1,2,3-triazole-4-carbaldehyde, 5v: White solid; mp 120−121 °C; Method B, yield 86% (11 mg); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 10.10 (s, 1H), 8.01 (s, 1H), 7.72 (d, J = 6.6 Hz, 2H), 7.03 (d, J = 6.6 Hz, 2H), 5.52 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 184.8, 148.1, 138.5, 133.0, 130.0, 125.0, 95.1, 53.9; HRESIMS calcd for $C_{10}H_8N_3NaIO$ (M^+) 335.9604, found 335.9614.

■ ASSOCIATED CONTENT

Supporting Information

Copies of (^{1}H and ^{13}C) NMR spectra and HRMS for all compounds described. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Hein, J. E.; Fokin, V. V. *Chem. Soc. Rev.* **2010**, *39*, 1302. (b) Medal, M.; Tornøe, C. W. *Chem. Rev.* **2008**, *108*, 2952. (c) Worrell, B. T.; Malik, J. A.; Fokin, V. V. *Science* **2013**, *340*, 457.

(2) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004.

(3) For representative examples, see: (a) Kolb, H. C.; Sharpless, K. B. *Drug Discovery Today* **2003**, *8*, 1128. (b) Sharpless, K. B.; Manetsch, R. *Expert Opin. Drug Discovery* **2006**, *1*, 525. (c) Tron, G. C.; Pirali, T.; Billington, R. A.; Canonico, P. L.; Sorba, G.; Genazzani, A. A. *Med. Res. Rev.* **2008**, *28*, 278. (d) Nandivada, H.; Jiang, X. W.; Lahann, J. *Adv. Mater.* **2007**, *19*, 2197. (e) Fournier, D.; Hoogenboom, R.; Schubert, U. *Chem. Soc. Rev.* **2007**, *36*, 1369. (f) Yan, R.; Sander, K.; Galante, E.; Rajkumar, V.; Badar, A.; Robson, M.; El-Emir, E.; Lythgoe, M. F.; Pedley, R. B.; Arstad, E. *J. Am. Chem. Soc.* **2013**, *135*, 703. (g) Ke, C.; Smaldone, R. A.; Kikuchi, T.; Li, H.; Davis, A. P.; Stoddart, J. F. *Angew. Chem., Int. Ed.* **2013**, *52*, 381. (h) Budin, I.; Devaraj, N. K. *J. Am. Chem. Soc.* **2012**, *134*, 751.

(4) Tornøe, C. W.; Christensen, C.; Medal, M. *J. Org. Chem.* **2002**, *67*, 3057.

(5) Rostovtset, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596.

(6) For representative examples, see: (a) Chan, T. R.; Hilgraf, R.; Sharpless, K. B.; Fokin, V. V. *Org. Lett.* **2004**, *6*, 2853. (b) Rodionov, V. O.; Presolski, S. I.; Diaz, D. D.; Fokin, V. V.; Finn, M. G. *J. Am. Chem. Soc.* **2007**, *129*, 12705. (c) Tanaka, K.; Kageyama, C.; Fukase, K. *Tetrahedron Lett.* **2007**, *48*, 6475. (d) Xu, W. M.; Huang, X.; Tang, E. *J. Comb. Chem.* **2005**, *7*, 726. (e) Bodine, K. D.; Gin, D. Y.; Gin, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 1638. (f) Reck, F.; Zhou, F.; Girardot, M.; Kern, G.; Eyermann, C. J.; Hales, N. J.; Ramsay, R. R.; Gravestock, M. B. *J. Med. Chem.* **2005**, *48*, 499. (g) Rodionov, V. O.; Presolski, S. I.; Gardinier, S.; Lim, Y. H.; Finn, M. G. *J. Am. Chem. Soc.* **2007**, *129*, 12696.

(7) (a) Girard, C.; Onen, E.; Aufort, M.; Beauviére, S.; Samson, E.; Herscovici, J. *Org. Lett.* **2006**, *8*, 1689. (b) Smith, C. D.; Baxendale, I. R.; Lanners, S.; Hayward, J. J.; Smith, S. C.; Ley, S. V. *Org. Biomol. Chem.* **2007**, *5*, 1559. (c) Sirion, U.; Bae, Y. J.; Lee, B. S.; Chi, D. Y. *Synlett* **2008**, 2326. (d) Chan, T. R.; Fokin, V. V. *QSAR Comb. Sci.* **2007**, *26*, 1274. (e) Ozkal, E.; Özçubukçu, S.; Jimeno, C.; Pericàs, M. A. *Catal. Sci. Technol.* **2012**, *2*, 195.

(8) (a) Caliendo, G.; Fiorino, F.; Perissutti, E.; Severino, B.; Scolaro, D.; Gessi, S.; Cattabriga, E.; Borea, P. A.; Santagada, V. *Eur. J. Pharm. Sci.* **2002**, *16*, 15. (b) Calderone, V.; Giorgi, I.; Livi, O.; Martinotti, E.; Mantuano, E.; Martelli, A.; Nardi, A. *Eur. J. Med. Chem.* **2005**, *40*, 521. (c) Blass, B. E.; Coburn, K.; Lee, W.; Fairweather, N.; Fluxe, A.; Wu, S.; Janusz, J. M.; Murawsky, M.; Fadayel, G. M.; Fang, B.; Hare, M.; Ridgeway, J.; White, R.; Jackson, C.; Djandjighian, L.; Hedges, R.; Wireko, F. C.; Ritter, A. L. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4629. (d) Pardin, C.; Roy, I.; Lubell, W. D.; Keillor, J. W. *Chem. Biol. Drug Des.* **2008**, *72*, 189.

(9) Cohen, B. J.; Kraus, M. A.; Patchornik, A. *J. Am. Chem. Soc.* **1981**, *103*, 7620.

(10) (a) Flynn, D. L.; Devraj, R. V.; Parlow, J. J. Polymer-Assisted Solution-Phase Methods for Chemical Library Synthesis. In *Solid-Phase Organic Synthesis*; Burgess, K., Ed.; John Wiley: New York, 2000; pp 149−194. (b) Ley, S. V.; Baxendale, I. R.; Bream, R. N.; Jackson, P. S.; Leach, A. G.; Longbottom, D. A.; Nesi, M.; Scott, J. S.; Storer, R. I.; Taylor, S. J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3815.

(11) For representative examples, see: (a) Chassaing, S.; Kumarraja, M.; Souna-Sido, A. S.; Pale, P.; Sommer, J. *Org. Lett.* **2007**, *9*, 883. (b) Miao, T.; Wang, L. *Synthesis* **2008**, 363. (c) Park, I. S.; Kwon, M. S.; Kim, Y.; Lee, J. S.; Park, J. *Org. Lett.* **2008**, *10*, 497. (d) Kantam, M. L.; Jaya, V. S.; Sreedhar, B.; Rao, M. M.; Choudary, B. M. *J. Mol. Catal. A: Chem.* **2006**, *256*, 273. (e) Sharghi, H.; Khalifeh, R.; Doroodmand, M. M. *Adv. Synth. Catal.* **2009**, *351*, 207. (f) Lipshutz, B. H.; Taft, B. R. *Angew. Chem., Int. Ed.* **2006**, *45*, 8235.

(12) Angell, Y.; Burgess, K. *Angew Chem., Int. Ed.* **2007**, *46*, 3649.

(13) Coelho, A.; Diz, P.; Caamaño, O.; Sotelo, E. *Adv. Synth. Catal.* **2010**, *352*, 1179.

(14) (a) Chung, W. J.; Ki, D. K.; Lee, Y. S. *Tetrahedron Lett.* **2003**, *44*, 9251. (b) Barontini, M.; Bernini, R.; Crisante, F.; Fabrizi, G. *Tetrahedron* **2010**, *66*, 6047. (c) Satam, V.; Harad, A.; Rajule, R.; Pati, H. *Tetrahedron* **2010**, *66*, 7659. (d) Frigerio, M.; Santagostino, M.; Sputore, S. *J. Org. Chem.* **1999**, *64*, 4537.

(15) (a) Zhdankin, V. V.; Koposov, A. Y.; Netzel, B. C.; Yashin, N. V.; Ferguson, M. J.; Rempel, B. P.; Tykwinski, R. R. *Angew. Chem., Int. Ed.* **2003**, *42*, 2194. (b) Lecarpentier, P.; Crosignani, S.; Linclau, B. *Mol. Diversity* **2005**, *9*, 341. (c) Jang, H. S.; Chung, W. J.; Lee, Y.-S. *Tetrahedron Lett.* **2007**, *48*, 3731.

(16) (a) Bastide, J.; Henri-Rousseau, O. Cycloadditons and Cyclizations Involving Triple Bonds. In *The Chemistry of the Carbon—Carbon Triple Bond*; Patai, S., Ed.; Interscience Publishers: London, 1978; pp 447−522. (b) Huisgen, R. 1,3-Dipolar Cycloadditions—Introduction, Survey, Mechanism. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984; pp 1−176.

(c) Palacios, F.; Renata, A. M.; Pagalday, J. *Heterocycles* **1994**, *38*, 95. (d) Katritzky, A. R.; Zhang, Y.; Singh, S. K.; Steel, P. J. *ARKIVOC* **2003**, *xv*, 47.
(17) (a) Kacprzack, K. *Synlett* **2005**, 943. (b) Feldman, A. K.; Colasson, B.; Fokin, V. V. *Org. Lett.* **2004**, *6*, 3897. (c) Yadav, J. S.; Reddy, B. V. S.; Reddy, G. M.; Chary, D. N. *Tetrahedron Lett.* **2007**, *48*, 8773. (d) Appukkuttan, P.; Dehaen, W.; Fokin, V. V.; Van der Eycken, E. *Org. Lett.* **2004**, *6*, 4223.
(18) Moorthy, J. N.; Singhal, N.; Senapati, K. *Tetrahedron Lett.* **2006**, *47*, 1757.
(19) (a) Anastas, P. T.; Kirchhoff, M. M. *Acc. Chem. Res.* **2002**, *35*, 686. (b) Anastas, P.; Eghbali, N. *Chem. Soc. Rev.* **2010**, *39*, 301.
(20) Gaab, M.; Bellemin-Laponnaz, S.; Gade, L. H. *Chem.—Eur. J.* **2009**, *15*, 5450.
(21) Houghten, R. A. *Proc. Natl. Acad. Sci.* **1985**, *82*, 5131.
(22) Buzas, A.; Gagosz, F. *J. Am. Chem. Soc. U.S.A.* **2006**, *128*, 12614.
(23) (a) Hwang, S.; Bae, H.; Kim, S.; Kim, S. *Tetrahedron* **2012**, *68*, 1460. (b) Chassaing, S.; Kumarraja, M.; Sido, A. S. S.; Pale, P.; Sommer, J. *Org. Lett.* **2007**, *9*, 883.
(24) (a) Cuevas, F.; Oliva, A. I.; Pericas, M. A. *Synlett* **2010**, 1873. (b) Roque, D. R.; Neill, J. L.; Antoon, J. W.; Stevens, E. P. *Synthesis* **2005**, *15*, 2497.