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Heterogeneously Catalyzed Synthesis of Imidazolones via Cycloisomerizations of Propargylic Ureas Using Ag and Au/Al SBA-15 Systems

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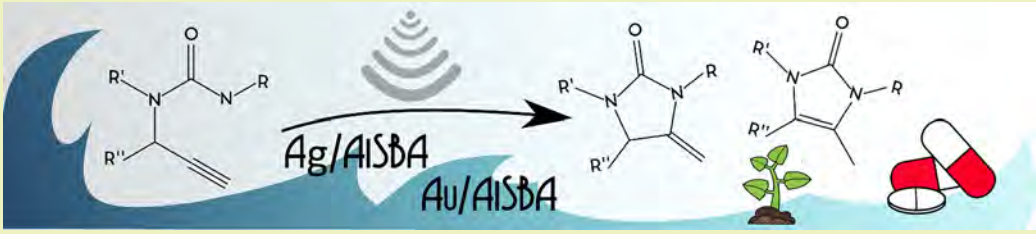
Supporting Information



ABSTRACT: The synthesis of imidazolones through the cycloisomerization of ureas, specifically propargylureas, has gained attention due to the large availability of starting materials. However, this type of synthesis normally requires the utilization of strong bases, such as NaOH, expensive homogeneous metal catalysts, such as Ag-, Au-, and Ru-based systems, or toxic and hazardous chemicals. Herein, a study of different synthetic routes for the preparation of imidazolones through the cycloisomerization of propargylic ureas under fast, mild, and environmentally friendly conditions with heterogeneous catalysis was undertaken. First, the synthesis were carried out under mild conditions using toluene and acetonitrile as solvents. Silver and gold nanoparticles supported on AlSBA-15 were used as heterogeneous catalysts. The catalysts were prepared by mechanochemical and microwave-assisted techniques. Sequentially, a range of solvents was replaced by the greener ethanol. Finally, all obtained results were combined in order to carry out the reaction using only water as solvent and promoter of the reaction. Aiming to expedite the procedure, the synthesis were carried out under conventional and microwave irradiation.

KEYWORDS: *Heterogeneous catalysis, Microwave chemistry, Isomerization, Mesoporous materials, Amides*

INTRODUCTION

Imidazolones are well-known compounds widely used in industry for the preparation of different chemicals, agrochemicals, and pharmaceuticals. Indeed, due to the existence of tautomeric forms, they can easily interact with biopolymers and receptors present in living systems, which accounts for the different biological activities.[1] Some substituted imidazolones were found to be herbicides, insecticidal, antifungal, anti-inflammatory, and antitumor agents, while others showed cardiotonic, antioxidant, vasodilator, and memory-enhancing properties.[2−5] For example, in 2008 Congiu et al. reported imidazole-2-one derivatives as active antitumoral against human cancer cells.[6] More recently, some other imidazolone derivatives were demonstrated to show high hypertensive activity by molecular modeling approaches.[7] Imidazolones have been also proved to be novel ligands for the synthesis of catalytically active complexes with transition metals. Ong and co-workers reported the hydroamination of aminoalkenes with zirconium complexes supported on imidazolones.[8]

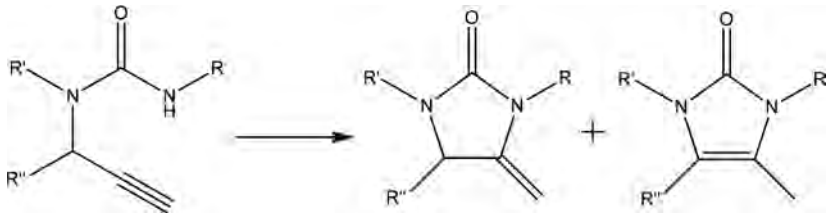
As a result, the preparation of substituted imidazolones is gaining more attention day by day. The most studied methods for the preparation of imidazolones include the synthesis from acyloins and ureas;[4] the intramolecular cyclization of ureidoacetals, ureidoxazinanes, and ureido ketones;[9] or the transformations of imidazole derivatives such as imidazolidinediones or imidazole oxides.[10] During recent years, the synthesis of substitued imidazolones from ureas, specifically from propargylureas, as illustrated in Scheme 1, have gained more attention due to the large availability of the starting materials propargylureas and isocynates.[11] In fact, diverse types of propargylamines can be synthesized in one-pot reactions through A-3 coupling of alkynes, amines, and aldheydes, which are starting material of low economic impact. However, the cycloisomerization of propargylic ureas normally requires the

Received: January 11, 2019
Revised: February 5, 2019
Published: February 8, 2019

ACS Publications © XXXX American Chemical Society

DOI: 10.1021/acssuschemeng.9b00198
ACS Sustainable Chem. Eng. XXXX, XXX, XXX−XXX

Scheme 1. General Scheme of Cycloisomerization of Propargylic Urea



utilization of strong bases, such as KOH or NaOH, or the use of highly toxic, hazardous, and expensive chemicals, limiting the applicability in terms of safety, waste/byproducts production, and environmental impact.[12,13] The challenge of developing sustainable and low-toxicity paths for the efficient cycloisomerization of proparygylureas is therefore a captivating topic.

In some previous works we have synthesized several substituted imidazolones starting from propargylic ureas, operating in toluene, and employing silver and gold homogeneous catalysts, avoiding the use of any strong bases and highly toxic chemicals.[14,15] The homogeneous catalytic conditions were selected, as they offer better selectivity and high reactivity, avoiding mass transfer limitations, which decrease the overall time of reaction. However, the utilization of homogeneous catalysts entails some inherent disadvantages, including metal contamination in the final product and the high cost of production due to the impossible recovery of the precious metals.[16,17] In addition, the US Department of Health and Human Services Food and Drug Administration classified toluene as a Class 2 solvent and its utilization should be limited in the pharmaceutical industry.[18]

Herein, in order to switch the reaction to greener conditions, different sustainable, environmentally friendly, low-toxicity and efficient paths for the catalyzed cycloisomerization of propargylic ureas were investigated. Initially, the study of the reaction was accomplished in toluene and acetonitrile, substituting gold and silver homogeneous catalysts with heterogeneous systems based on gold and silver nanoparticles supported on AlSBA-15. In general, metal nanoparticles supported on solids allow the exploitation of nanocatalysis, at the boundary between homogeneous and heterogeneous catalysis, with the simplified recovery of the material.[17,19] In the last years, different mesoporous materials have been studied as supports for the stabilization of gold and silver nanoparticles, and mesoporous silica materials emerged due to the abundance of Si−OH bonds on the surface, which can stabilize metal nanoparticles.[20−22] Specifically, SBA-15 emerged for its outstanding characteristics featuring high surface areas, chemical and hydrothermal stability, and possibilities for functionalization.[23] To the best of our knowledge, no report on similar works was found in the literature. The catalyst was prepared through environmentally friendly and highly innovative paths, including solventless ball-milling techniques and fast microwave-assisted synthesis. Triphenylphosphine was used as a mild additive to increase the reaction yield without any leaching effects. Sequentially, the solvents were substitute with ethanol, which is classified as a Class 3 solvent by the US FDA (less toxic and of lower risk to human health).[18] Finally, a new methodology for the cycloisomerization of propargylic ureas using only water as solvent and synthesis promoter was developed. In order to sensibly accelerate all the reactions, the synthesis were carried out under conventional and microwave heating. In fact, microwave heating offers the possibility to perform experiments in an extremely effective, safe, rapid, and highly reproducible way.[24,25] The results indicated that heterogeneous catalyst in toluene promoted most N-cyclization reactions, while ethanol favored the cyclization of propargylic ureas characterized by more electron-withdrawing groups. Finally, water-mediated reactions favored the cyclization of propargylic ureas containing electron-donor compounds in the structure.

■ MATERIALS AND METHODS

Materials. Pluronic P123 (PEG−PPG−PEG), hydrochloric acid (HCl, 37 wt %), aluminum isopropoxide {$Al[OCH(CH_3)_2]_3$, ≥98%}, tetraethyl orthosilicate [TEOS, $Si(OC_2H_5)_4$, 98%], silver nitrate ($AgNO_3$, ≥99.0%), gold bromide ($AuBr_3$, 99.9%), ethanol (CH_3CH_2OH, 99.8%), acetonitrile (CH_3CN, 99.8%), toluene (C_7H_8, 99.8%), triphenylphosphine [$(C_6H_5)_3P$, 99%], chloroform-*d* ($CDCl_3$, 99.96 atom % D), chloro(triphenylphosphine)gold(I) {$[(C_6H_5)_3P]AuCl$, ≥99.9%}, silver trifluoromethanesulfonate (CF_3SO_3Ag, ≥98.0%), 1,4-diazabicyclo[2.2.2]octane (DABCO, $C_6H_{12}N_2$, ≥99%), 4-(dimethylamino)pyridine (DMAP, $C_7H_{10}N_2$, ≥99%), triethylamine [$(C_2H_5)_3N$, ≥99.5%], and *N*-methylpropargylamine ($HC{\equiv}CCH_2NHCH_3$, 95%) were purchased from Sigma-Aldrich Inc. (St. Louis, MO). All reagents were used without any further purification.

General Procedure for the Synthesis of the Catalysts. AlSBA-15 was synthesized according to a procedure reported in a previous work.[26] Briefly, 20 g of Pluronic P123 was dissolved with stirring in 750 mL of a 1.5 pH solution of distilled water and HCl at room temperature (rt). After the complete dissolution of P123 (1 h), 2.10 g of aluminum isopropoxide was slowly added. Finally, 45 mL of TEOS was added drop-by-drop. The mixture was stirred at 35 °C for 24 h and hydrothermally treated for 24 h at 100 °C. The precipitated white solid was filtrated and dried at rt for 12 h. The template was removed by calcination under N_2 flux at 600 °C for 8 h.

Silver nanoparticles were supported on the so-produced AlSBA-15 by a ball-milling technique developed in our laboratories.[27] In order to obtain 2 wt % metal charge, 0.16 g of $AgNO_3$ (0.9 mmol) was added to 5 g of AlSBA-15 in a 125 mL ball-milling bowl equipped with 18 5-mm ϕ stainless steel balls. Sequentially, the powders were grounded in a Retsch PM-100 planetary ball mill (350 rpm, 10 min). The resulting material was calcined at 450 °C for 4 h under synthetic air flux. The same procedure was applied for the production of 2 wt % gold nanoparticles supported on AlSBA-15, using 0.226 g of $AuBr_3$ (0.5 mmol) mixed with 5 g of AlSBA-15. The supported nanocatalysts produced by ball-milling were denoted BM-2%Au@AlSBA-15 and BM-2%Ag@AlSBA-15.

Alternatively, silver and gold nanoparticles were supported on AlSBA-15 though a microwave-assisted methodology.[28] Briefly, 0.2 g of AlSBA-15 was mixed together with 0.0063 g of $AgNO_3$ (0.04 mmol) in 2 mL of ethanol in a 10 mL Pyrex microwave (MW) vial sealed with the proper cap. The mixture was stirred at 700 rpm for 15 min prior to MW heating. Subsequently, the vial was placed in a CEM microwave reactor and heated at 150 °C for 3 min. The rapid heating led to the quick precipitation of metallic silver well-distributed over AlSBA-15. Finally, the mixture was filtered and washed with ethanol

DOI: 10.1021/acssuschemeng.9b00198
ACS Sustainable Chem. Eng. XXXX, XXX, XXX−XXX

(10 mL). The filtrated solid was recovered and dried overnight at 100 °C. Similarly, gold nanoparticles were prepared using 0.009 g of $AuBr_3$ (0.02 mmol) and 0.2 g of AlSBA-15. The supported nanocatalysts produced by microwave-assisted techniques were denoted MW-2% Au@AlSBA-15 and MW-2%Ag@AlSBA-15, respectively.

General Procedure for Catalyzed Cycloisomerization of Propargylic Ureas. To accomplish the cycloisomerization reaction, the selected propargylic urea was mixed with the appropriate solvent (dry in the case of toluene, acetonitrile, and ethanol) in a 10 mL screw cap vial or 10 mL Pyrex microwave vial. The reaction vial was charged with the different catalysts and sealed with a proper cap. The reaction mixture was stirred at 800 rpm for 10 min prior to reaction. The reaction was carried out in a preheated oil bath or in a CEM microwave reactor. After completion, the reaction mixture was filtered through a micropore filter (Chromafil 0-20/25MS, PTFE) and the filter was washed with EtOH (3 × 1 mL).

Characterization of Product. All products were analyzed by ^{1}H NMR and ^{13}C NMR and can be found in our previous reports.[14,15]

■ RESULTS AND DISCUSSION

Heterogeneous Catalyzed Reactions in Toluene and Acetonitrile. The first studies were carried out in order to switch the catalyzed cycloisomerization of propargylureas from homogeneous to heterogeneous conditions. Gold and silver nanoparticles supported on AlSBA-15 (2% metal load), which showed good activity in previous work for the synthesis of spiroindolenines, were selected as catalysts.[28] The catalysts were prepared by both mehanochemical methods and microwave-assisted synthesis. On the one hand, mechanochemistry emerged as a promising solventless technology were the kinetic energy is transferred to the milled material, achieving the breaking of chemical bonds and/or creating new surfaces by fractures.[29] In recent years, this method has allowed the simple, clean, versatile, and highly reproducible preparation of advanced materials, such as MOFs, supported nanometals, and metal oxides, for diverse applications in catalysis or related advanced technologies (e.g., electrochemistry).[30−32] The preparation of the catalysts via mechanochemistry involved two simple steps, namely, grinding of AlSBA-15 with the metal precursors and sequential calcination at high temperatures under different atmospheres in order to generate the metal (oxide) nanoparticles strongly attached on the surface of AlSBA-15.[27] On the other hand, microwave techniques show several advantages, including the reduction of reaction time, the possibility to obtain higher yields, different selectivities, and the potential to accomplish reactions/chemistries that do not take place under conventional heating conditions.[33,34] Furthermore, microwave-assisted methods emerged to provide promising synthetic processes without suffering thermal gradient effects, leading to an important advancement in the synthesis of nanomaterials.[35] In the present work, the catalysts were prepared by a unique, easy step where a homogeneous mixture of the metal precursors and AlSBA-15 in ethanol were quickly heated under microwave irradiation. This rapid heating allowed the fast precipitation of the metal precursor, which were reduced by ethanol, forming the nanoparticles on the SBA surface.[28] Mesoporous silica SBA-15 was selected as the supporting material for gold and silver nanoparticles because of the abundance of Si−OH bonds on the surface, which can stabilize nanoparticles.[36] In addition, SBA-15 features unique properties, including large surface areas (up to 1000 m^2/g), controllably thick walls, small pore sizes (4−30 nm), and high thermal and mechanical stability.[37] Lastly, aluminum can be easily inserted into the structure of SBA-15, forming AlSBA-15 with enhanced Lewis acidic, ion-exchanging, and catalytic properties.[38] The employed catalysts were fully characterized in previous reports. Specifically, XRD, SEM, TEM, XPS, surface area analysis, and thermal stability analysis can be found in the literature.[28] As an example, Figure 1 depicts a TEM image of BM-2%Ag@AlSBA-15 in which silver nanoparticles can be observed inside and outside the channels of AlSBA-15.

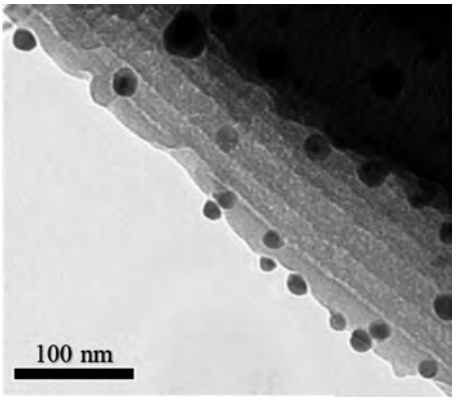


Figure 1. TEM of BM-2%Ag@AlSBA-15. Reprinted with permission from ref 28. Copyright 2016 American Chemical Society.

Initially, the experiments examining the cycloisomerization of propargylic urea were carried out using terminal propargylic urea **1** synthesized by tosyl isocyanate and *N*-methylpropargylamine (Table 1). Ball-mill-synthesized catalysts BM-2%Ag@AlSBA-15 and BM-2%Au@AlSBA-15 were first employed. The proposed general reaction mechanism is illustrated in Scheme 2.

The first aim consisted of the determination of the selectivities and the comparison of these results with those reported using homogeneous catalysts. The cycloisomerization of propargylic ureas derived from tosyl isocyanate was selected

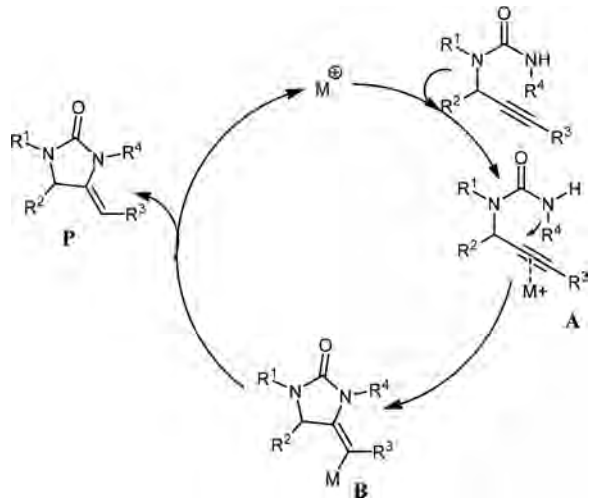
Table 1. Optimization of the Reaction Illustrated in Scheme 3[a]

entry	cat. (g)	solvent	T (°C)	t (h)	% yield (**a**/**b**)[f]
1[b]	Au (0.018)	toluene	40	3	47/20
2[b]	Au (0.035)	toluene	40	3	78/20
3[b]	Au (0.035)	toluene	40	2	70/20
4[b]	Au (0.035)	toluene	40	1	20/0
5[b]	Au (0.035)	toluene	80	1	60/36
6[b]	Au (0.035)	ACN	40	0.5	17/0
7[b]	Au (0.035)	ACN	40	1	22/0
8[c]	Ag (0.006)	toluene	40	1	85/0
9[c]	Ag (0.008)	toluene	40	1	96/0
10[c]	**Ag (0.010)**	**toluene**	**40**	**1**	**97/0**
11[c]	Ag (0.019)	toluene	40	2	97/0
12[c]	Ag (0.019)	toluene	80	1	98/0
13[c]	Ag (0.010)	ACN	40	2	87/0
14[c]	Ag (0.010)	ACN	40	1	80
15[d]	AgOTf (0.002)	ACN	80	4	66
16[e]	$AuPPh_3Cl$ (2)	$CDCl_3$	50	22	40/6
17	no cat.	ACN	80	8	–

[a]All reactions were run with **1** (72 μmol, 0.5 mL solvent) in a screw-cap vial. Bold text highlights the best conditions. [b]BM-2%Au@Al-SBA15. [c]BM-2%Ag@Al-SBA15. [d]AgOTf. [e]$AuPPh_3Cl$. [f]Reaction yield.

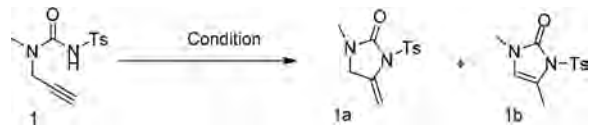
DOI: 10.1021/acssuschemeng.9b00198
ACS Sustainable Chem. Eng. XXXX, XXX, XXX−XXX

Scheme 2. Plausible Mechanism for Formation of 2-Imidazole



as a model reaction, as illustrated in Scheme 3. As shown in Table 1, the reaction was first run with 0.018 g of BM-2%Au@

Scheme 3. Reaction Scheme for the Cycloisomerization of Propargylic Ureas Derived from Tosyl Isocyanate



Al-SBA15 in toluene, obtaining a 47% yield of imidazolidin-2-one **1a** with 20% of migrated double bond product imidazol-2-one **1b** (Table 1, entry 1). The result was close to that previous reported, in which the synthesis of imidazolidin-2-one was successfully promoted by PPh_3AuCl (Table 1, entry 16) in homogeneous conditions.[14] Furthermore, increasing the amount of BM-2%AuAlSBA-15 employed improved the formation of **1a** (Table 1, entry 2).

The decrease of the reaction time resulted in a decrease of the yield with more selectivity to the formation of imidazolidin-2-one (Table 1, entries 3 and 4). This can be explained in terms of kinetic vs thermodynamic stability: kinetically favorable product **1a** was dominating over thermodynamically stable **1b** in short reaction times. The use of ACN as an alternative solvent was not as effective as compared to toluene (Table 1, entries 6 and 7). Sequentially, BM-2%Au@AlSBA-15 was replaced by BM-2%Ag@AlSBA-15 (Table 1, entries 8−14), a cheaper catalyst. Interestingly, a smaller amount of BM-2%Ag@AlSBA-15 was needed to obtained higher yields and selectivity, as compared to gold catalyst (Table 1, entries 8−10). Indeed, 0.01 g of catalyst and 1 h of reaction time were found to be the best conditions to obtain a 97% yield of imidazolidin-2-one **1a** with 0% production of migrated[39] double bond imidazol-2-one **1b** (Table 1, entry 10 compared with 11). The above results showed the higher metallic character of Ag@AlSBA-15 over Au@AlSBA-15. In fact, XPS measurement of Au@AlSBA-15 showed the existence of some Au^{3+} (band at 85.7 and 89.4 eV) species with mostly Au(0), while XPS measurement of Ag@AlSBA-15 exhibited mainly metallic silver, not oxidic.[28] The switch to acetonitrile (ACN) provided good selectivity and excellent yields of **1a** (Table 1, entries 13 and 14). However, silver mirror was noticed inside the NMR tube, demonstrating the leaching of silver with acetonitrile.[40] As a consequence, ACN was considered inappropriate for the reaction. Positively, no silver mirror was observed in the NMR tube using toluene.

Sequentially, on the basis of the optimized conditions of using 0.01 g of BM-2%Ag@AlSBA-15 in toluene, the reaction was attempted using phenyl isocyanate (compound **2** in Scheme 4). As shown in Table 2, the high reaction yields and

Scheme 4. Cycloisomerization of Propargylic Ureas Derived from Phenyl Isocyanate

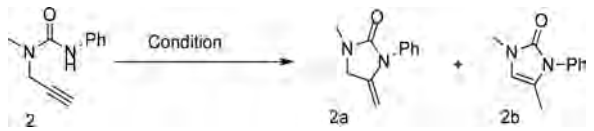


Table 2. Optimization of the Reaction Illustrated in Scheme 4[a]

entry	additive (equiv)	pK_a	T (°C)	t (h)	% yield (**a**/**b**)[b]
1			40	1	0
2			40	3	0
3			40	17	0/17
4			80	17	0/41
5	PPh_3 (1)	7.6[c]	40	3	0/70
6	PPh_3 (0.5)		80	3	0/86
7	PPh_3 (0.5)		80	2.5	0/86
8	DABCO (0.5)	8.2[c]	80	3	0/10
9	DMAP (0.5)		80	3	10/0
10	Et_3N (0.5)	10.7[d]	80	3	0/0

[a]All reactions were run with **2** (72 μmol, 0.5 mL toluene) in a screw-cap vial and BM-2%Ag@Al-SBA15 (0.01 g). [b]Reaction yield was determined by the NMR integration method. [c]Basicity measurement in acetonitrile. [d]Determined in water for deprotonation of conjugate acid.

selectivities obtained with propargylic ureas **1** (Table 1) were never observed, despite increasing the reaction time up to 17 h and the temperature up to 80 °C (Table 2, entries 1−4).

Aiming to increase the reaction yield, some additives were tested. On the basis of previous results, the effect of triphenylphosphine was investigated in combination with the new heterogeneous conditions.[14] Using 1 equiv of triphenylphosphine and operating at 40 °C, a major selectivity for imidazol-2-one was observed (Table 2, entry 5). This trial was repeated up to 10 times by reusing the same catalyst, without noting any decrease of conversion. As triphenylphosphine is a well-known ligand for gold and silver, the possible leaching of BM-2%Ag@AlSBA-15 was evaluated by the hot filtration test after every cycle. To execute this test, the catalyst was removed from the reaction mixture after 30 min of ongoing stirring under the investigated reaction conditions (35% conversion). Fresh triphenylphosphine was subsequently introduced to avoid any loss and the reaction was continued for other 6 h. No appreciable conversion by NMR was observed, in good agreement with an identical Ag loading in the catalyst before/after removal from the reaction mixture. These findings were a good indication about the heterogeneous nature of the reaction (please see the Supporting Information for additional details of leaching tests). The utilization of triphenylphosphine was subsequently tested at 80 °C with lowered reaction time. The

DOI: 10.1021/acssuschemeng.9b00198
ACS Sustainable Chem. Eng. XXXX, XXX, XXX−XXX

best condition led to the synthesis of product **2b** with 87% yield operating at 80 °C for 2.5 h (Table 2, entry 7). In order to gain more insights, other Lewis bases were tested as additive (Table 2, entries 8−10). However, no improvement of the reaction yield was observed. These results may point to a unique and efficient electron-donating effect of the phosphorus of triphenylphosphine, which upon coordination to Ag nanoparticles led to Ag species with an improved "metallic" character correlated to an improved reactivity for the investigated chemistry. This electron-donating effect is well-documented in the literature for homogeneous catalysts and metals but first approached here as a stabilizing effect for heterogeneous catalysts.[41]

With the new optimized conditions, the reaction was successively run using other substitued propargylic ureas (compound **3** in Scheme 5), as shown in Table 3. The

Scheme 5. General Scheme for Cycloisomerization of Substituted Propargylic Ureas

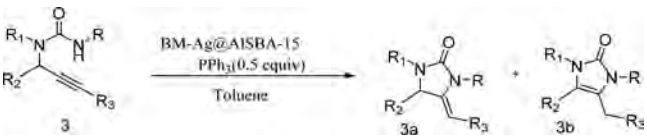


Table 3. Optimization of the Reaction Illustrated in Scheme 5[a]

entry	R	R_1	R_2	R_3	T (°C)	t (h)	% yield (**a**/**b**)[a]
1	p-$NO_2C_6H_5$	Me	H	H	40	1	0/90
2	Bn	Me	H	H	40	6	0/10
3	Bn	Me	H	H	80	6	0/22
4	p-Tol	Me	H	H	80	3	0/73
5	Ph	Bn	Pr	Ph	80	3	0/14
6[b]	Ph	Bn	Pr	Ph	80	4	0/56

[a]All reactions were run with **3** (72 μmol, 0.5 mL toluene) in a screw-cap vial using BM-2%Ag@AlSBA15 (0.02 g). Bn = Benzyl group. [b]Reaction yield was determined by the NMR integration method. [c]Catalyst = 0.04 g, 1 mL of toluene.

reaction was remarkably more efficient with nitrophenyl isocyanate derived ureas as compared to aryl-substituted ureas (Table 3, entries 1−3). The observed low activity may be due to the free rotation of the benzyl group, which can be responsible for steric hindrance.[15] The reaction with non-terminal alkynes under the same optimized condition, resulted in less than 20% conversion. This was expected due to the steric hindering substituent on the triple bond.[42] Sequentially, catalyst loading and reaction time were increased, resulting in 56% yield (Table 3, entry 6).

Due to the high load of the catalysts, these last reaction conditions (Table 3, entry 6) were selected for the comparison of nanocatalysts synthesized by ball-milling and microwave-assisted techniques (Scheme 6 and Table 4).

Gold nanocatalsyts were found to be almost inactive for the reaction (Table 4, entries 3 and 4). Considering silver catalysts, the ball-mill-synthesized one was more active than MW-2% Ag@AlSBA-15. Despite this lowest activity, it has to be highlighted that the microwave-assisted synthesis was much more favorable compared to the synthesis of nanocatalysts prepared by ball-milling. In fact, BM catalysts needed longer time of preparation, resulting from the sum of the 10 min of

Scheme 6. Cycloisomerization of Substituted Propargylic Ureas

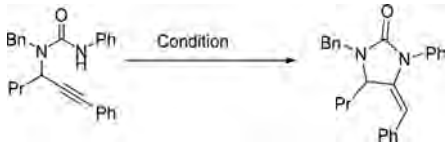


Table 4. Cycloisomerization of Propargylic Urea Comparing BM- and MW-2%Ag@AlSBA-15 and BM- and MW-2%Au@AlSBA15, as Well as Microwave Heating vs Conventional Heating[a]

entry	cat.	% yield[b]
1	BM-2%Ag@AlSBA-15	56
2	MW-2%Ag@AlSBA-15	35
3	BM-2%Au@AlSBA-15	<5
4	MW-2%Au@AlSBA-15	<5

[a]All reactions were run with **1** (72 μmol, 1 mL toluene) in a screw-cap vial. [b]Reaction yield was determined by the NMR integration method. Catalyst = BM/MW-2%Ag@AlSBA-15 (0.04 g), BM/MW-2%Au@AlSBA-15 (0.07 g).

ball-milling and the several hours of muffle treatment for the calcination. Instead, nanocatalysts prepared by microwave-assisted techniques were prepared through one easy reduction step of 5 min irradiation in the microwave reactor. However, in order to obtain the higher yields, the ensuing trials were carried out using BM-2%Ag@AlSBA-15.

Switching to Ethanol. In order to accomplish the reaction in greener conditions, the synthesis was switched from toluene to ethanol, which is classified as a Class 3 solvent by the US FDA.[18] Following the same logical evolution accomplished in the first part of the research, the reactions were initially carried out without any additive, operating under conventional heating conditions, using propargyl urea **5** synthesized by tosyl isocyanate and N-methylpropargylamine (Scheme 7 and Table 5).

Scheme 7. Cycloisomerization of Propargylic Ureas Derived from Tosyl Isocynate in EtOH

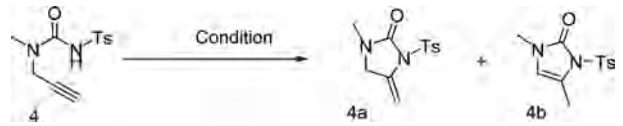


Table 5. Optimization of the Reaction Illustrated in Scheme 7[a]

entry	cat. (g)	T (°C)	t (h)	% yield (**a**/**b**)[d]
1[b]	Au (0.018)	80	14	27/32
2[b]	Au (0.035)	80	14	44/32
3[c]	Ag (0.008)	40	1	97/0
4[c]	Ag (0.006)	40	0.5	93/0
5[c]	Ag (0.004)	40	0.5	80/0
6[c]	Ag (0.006)	40	0.16	78/0

[a]All reactions were run with **4** (72 μmol, 0.5 mL ethanol) in a screw-cap vial. [b]BM-2%Au@Al-SBA15 [c]BM-2%Ag@Al-SBA15. [d]Reaction yield was determined by the NMR-integration method.

DOI: 10.1021/acssuschemeng.9b00198
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The best results were observed using 2 wt % BM-Ag@AlSBA-15 catalysts and operating at 40 °C for 30 min. (Table 5, entry 4), finding the same results observed in toluene (Table 1, entry 10). In order to evaluate the effect of triphenylphosphine in ethanol (Scheme 8), different trials were carried out. As summarized in Table 6, no cyclization occurred when triphenylphosphine was added.[43,44]

Scheme 8. Effect of Polar Solvent EtOH on Cycloisomerization of Propargylic Ureas Derived from Phenyl Isocynate with PPh_3 as an Additive

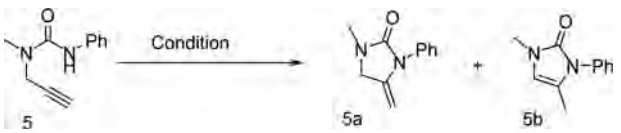


Table 6. Optimization of the Reaction Illustrated in Scheme 8[a]

entry	R	T (°C)	t (h)	% yield (**a**/**b**)
1		40	6	–
2	PPh_3(0.5 equiv)	40	3	–
3	PPh_3(0.5 equiv)	80	3	–

[a]All reactions were run with **5** (72 μmol, 0.5 mL solvent) in a screw-cap vial with BM-2%Ag@Al-SBA15 (0.01 mg).

Developing the Conditions for Water-Mediated Reaction. All obtained results were combined aiming to carry out the reaction in water. As AlSBA-15 is unstable in water, all the reactions were run in a microwave reactor using only H_2O as solvent and promoter of the reaction. As reported by Mohan et al.,[45] water can act as a mediator for the construction of different heterocycles. The possible mechanism is shown in Scheme 9.

As summarized in Table 7, different trails have been carried out, varying reaction time, temperature, and structure of propargylic ureas (Scheme 10). The best results were obtained operating at 130 °C for 20 min. The outcomes clearly showed that water was favoring the cyclization of propargylic ureas containing electron-donor compounds. As shown in Table 7 (entry 4), the best conditions allowed the preparation of substituted imizadolones in 72% yield with 20 min reaction time.

Scheme 9. Possible Mechanism for Water-Mediated Formation of 2-Imidazole

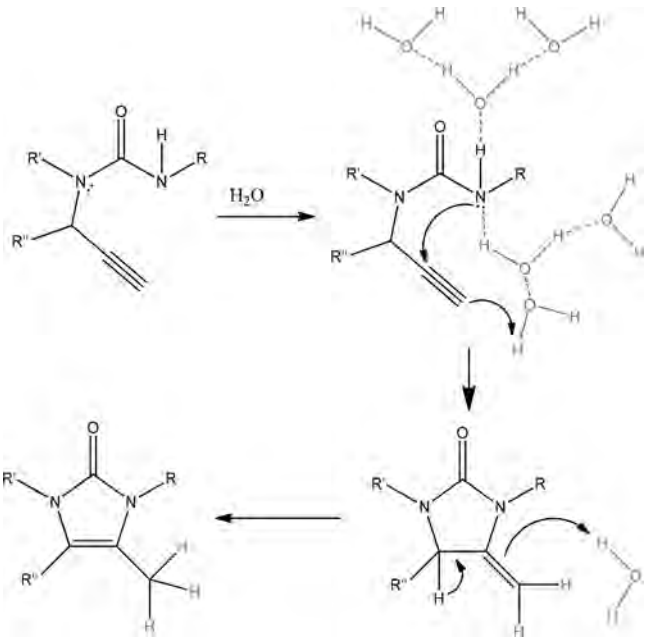
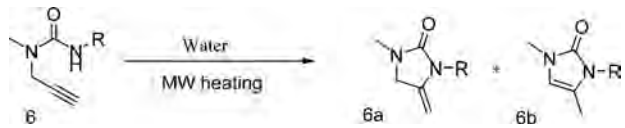


Table 7. Optimization of the Reaction Illustrated in Scheme 10[a]

entry	R	T (°C)	t (h)	% yield (**a**/**b**)
1	Ph	80	20	–
2	Ph	100	20	0/10
3	Ph	120	20	0/50
4	Ph	130	20	0/72
5	Ph	130	5	0/8
6	Ph	130	10	0/30
7	p-FC_6H_4	130	20	0/66
8	Bn	130	20	0/3
9	p-$NO_2C_6H_4$	130	20	0/68

[a]All reactions were run with **6** (72 μmol, 0.5 mL water) in a screw-cap vial.

Scheme 10. Cycloisomerization of Different Propargylic Ureas in Water under Microwave Irradiation



CONCLUSIONS

In conclusion, the environmentally friendly paths for the cycloisomerization of propargylic ureas were explored. The syntheses were carried out in toluene, acetonitrile, ethanol, and water, using gold and silver heterogeneous catalysts produced by innovative ball-milling and microwave-assisted techniques. Several scopes were studied, highlighting the reaction mechanism in the selected different paths, where heterogeneous catalyst in toluene promoted N-cyclization reactions, ethanol favored the cyclization of propargylic ureas characterized by more-electron-withdrawing groups and water-mediated reactions favored the cyclization of propargylic ureas containing electron-donor compounds in the structure. In contrast to previous studies, the new developed paths offer the possibility to accomplish the cycloisomerization reaction in greener solvents using recoverable heterogeneous catalysts and avoiding the utilization of any strong base. In addition, all the reactions were carried out under conventional and microwave heating, emphasizing the possibility of using a microwave technique to reduce the reaction time.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acssuschemeng.9b00198.

General information regarding laboratory procedures, leaching determination by a hot-filtration experiment, reusability of catalyst, and synthesis of starting materials (PDF)

DOI: 10.1021/acssuschemeng.9b00198
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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This project has received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No. 721290. This publication reflects only the author's view, exempting the Community from any liability. Project website: http://cosmic-etn.eu/. M.J.M-B thanks MINECO for the award of a postdoctoral JdC contract (FJCI-2016-29014). The publication has been prepared with support from RUDN University program 5-100.

REFERENCES

(1) Contreras, J. G.; Madariaga, S. T. Intramolecular proton transfer in tautomeric 2-imidazolone and 2-thioimidazolone. *J. Phys. Org. Chem.* **2003**, *16* (1), 47−52.

(2) Wu, C. H.; Hung, M. S.; Song, J. S.; Yeh, T. K.; Chou, M. C.; Chu, C. M.; Jan, J. J.; Hsieh, M. T.; Tseng, S. L.; Chang, C. P.; Hsieh, W. P.; Lin, Y.; Yeh, Y. N.; Chung, W. L.; Kuo, C. W.; Lin, C. Y.; Shy, H. S.; Chao, Y. S.; Shia, K. S. Discovery of 2- 5-(4-Chloro-phenyl)-1-(2,4-dichloro-phenyl)-4-ethyl-1H-pyrazol-3-yl - 1,5,5-trimethyl-1,5-dihydro-imidazol-4-thione (BPR-890) via an Active Metabolite. A Novel, Potent and Selective Cannabinoid-1 Receptor Inverse Agonist with High Antiobesity Efficacy in DIO Mice. *J. Med. Chem.* **2009**, *52* (14), 4496−4510.

(3) Narasimhan, B.; Sharma, D.; Kumar, P. Biological importance of imidazole nucleus in the new millennium. *Med. Chem. Res.* **2011**, *20* (8), 1119−1140.

(4) Antonova, M. M.; Baranov, V. V.; Kravchenko, A. N. Methods for the synthesis of 1-substituted 1H-imidazol-2(3H)-ones. *Chem. Heterocycl. Compd.* **2015**, *51* (5), 395−420.

(5) Wani, M. Y.; Ahmad, A.; Shiekh, R. A.; Al-Ghamdi, K. J.; Sobral, A. Imidazole clubbed 1,3,4-oxadiazole derivatives as potential antifungal agents. *Bioorg. Med. Chem.* **2015**, *23* (15), 4172−4180.

(6) Congiu, C.; Cocco, M. T.; Onnis, V. Design, synthesis, and in vitro antitumor activity of new 1,4-diarylimidazole-2-ones and their 2-thione analogues. *Bioorg. Med. Chem. Lett.* **2008**, *18* (3), 989−993.

(7) Aksoydan, B.; Kantarcioglu, I.; Erol, I.; Salmas, R. E.; Durdagi, S. Structure-Based Design of hERG-Neutral Antihypertensive Oxazalone and Imidazolone Derivatives. *J. Mol. Graphics Modell.* **2018**, *79*, 103−117.

(8) Hu, Y. C.; Liang, C. F.; Tsai, J. H.; Yap, G. P. A.; Chang, Y. T.; Ong, T. G. Zirconium Complexes Supported by Imidazolones: Synthesis, Characterization, and Application of Precatalysts for the Hydroamination of Aminoalkenes. *Organometallics* **2010**, *29* (15), 3357−3361.

(9) Cheng, J. F.; Kaiho, C.; Chen, M.; Arrhenius, T.; Nadzan, A. A traceless solid-phase synthesis of 2-imidazolones. *Tetrahedron Lett.* **2002**, *43* (26), 4571−4573.

(10) Dandepally, S. R.; Elgoummadi, R.; Williams, A. L. Schwartz reagent mediated synthesis of thiazolones and imidazolones from thiazolidine-2,4-diones and imidazolidine-2,4-diones. *Tetrahedron Lett.* **2013**, *54* (8), 925−928.

(11) Lauder, K.; Toscani, A.; Scalacci, N.; Castagnolo, D. Synthesis and Reactivity of Propargylamines in Organic Chemistry. *Chem. Rev.* **2017**, *117* (24), 14091−14200.

(12) Wen, J. J.; Zhu, Y.; Zhan, Z. P. The Synthesis of Aromatic Heterocycles from Propargylic Compounds. *Asian J. Org. Chem.* **2012**, *1* (2), 108−129.

(13) Huguenot, F.; Delalande, C.; Vidal, M. Metal-free 5-exo-dig cyclization of propargyl urea using TBAF. *Tetrahedron Lett.* **2014**, *55*, 4632−4635.

(14) Pereshivko, O. P.; Peshkov, V. A.; Jacobs, J.; Van Meervelt, L.; Van der Eycken, E. V. Cationic Gold- and Silver-Catalyzed Cycloisomerizations of Propargylic Ureas: A Selective Entry to Oxazolidin-2-imines and Imidazolidin-2-ones. *Adv. Synt. Catal.* **2013**, *355* (4), 781−789.

(15) Peshkov, V. A.; Pereshivko, O. P.; Sharma, S.; Meganathan, T.; Parmar, V. S.; Ermolat'ev, D. S.; Van der Eycken, E. V. Tetrasubstituted 2-Imidazolones via Ag(I)-Catalyzed Cycloisomerization of Propargylic Ureas. *J. Org. Chem.* **2011**, *76* (14), 5867−5872.

(16) Shylesh, S.; Schunemann, V.; Thiel, W. R. Magnetically Separable Nanocatalysts: Bridges between Homogeneous and Heterogeneous Catalysis. *Angew. Chem., Int. Ed.* **2010**, *49* (20), 3428−3459.

(17) Astruc, D.; Lu, F.; Aranzaes, J. R. Nanoparticles as recyclable catalysts: The frontier between homogeneous and heterogeneous catalysis. *Angew. Chem., Int. Ed.* **2005**, *44* (48), 7852−7872.

(18) https://www.fda.gov/.

(19) Gawande, M. B.; Branco, P. S.; Varma, R. S. Nano-magnetite (Fe_3O_4) as a support for recyclable catalysts in the development of sustainable methodologies. *Chem. Soc. Rev.* **2013**, *42* (8), 3371−3393.

(20) Abis, L.; Armelao, L.; Belli Dell'Amico, D. B.; Calderazzo, F.; Garbassi, F.; Merigo, A.; Quadrelli, E. A. Gold molecular precursors and gold-silica interactions. *J. Chem. Soc. Dalton* **2001**, *18*, 2704−2709.

(21) Gawande, M. B.; Monga, Y.; Zboril, R.; Sharma, R. K. Silica-decorated magnetic nanocomposites for catalytic applications. *Coord. Chem. Rev.* **2015**, *288*, 118−143.

(22) Deng, X. H.; Chen, K.; Tuysuz, H. Protocol for the Nanocasting Method: Preparation of Ordered Mesoporous Metal Oxides. *Chem. Mater.* **2017**, *29* (1), 40−52.

(23) Vinu, A.; Murugesan, V.; Bohlmann, W.; Hartmann, M. An optimized procedure for the synthesis of AISBA-15 with large pore diameter and high aluminum content. *J. Phys. Chem. B* **2004**, *108* (31), 11496−11505.

(24) Kappe, C. O.; Pieber, B.; Dallinger, D. Microwave Effects in Organic Synthesis: Myth or Reality? *Angew. Chem., Int. Ed.* **2013**, *52* (4), 1088−1094.

(25) Gawande, M. B.; Shelke, S. N.; Zboril, R.; Varma, R. S. Microwave-Assisted Chemistry: Synthetic Applications for Rapid Assembly of Nanomaterials and Organics. *Acc. Chem. Res.* **2014**, *47* (4), 1338−1348.

(26) Pineda, A.; Balu, A. M.; Campelo, J. M.; Romero, A. A.; Carmona, D.; Balas, F.; Santamaria, J.; Luque, R. A Dry Milling Approach for the Synthesis of Highly Active Nanoparticles Supported on Porous Materials. *ChemSusChem* **2011**, *4* (11), 1561−1565.

(27) Campelo, J. M.; Conesa, T. D.; Gracia, M. J.; Jurado, M. J.; Luque, R.; Marinas, J. M.; Romero, A. A. Microwave facile preparation of highly active and dispersed SBA-12 supported metal nanoparticles. *Green Chem.* **2008**, *10* (8), 853−858.

(28) Schroder, F.; Sharma, U. K.; Mertens, M.; Devred, F.; Debecker, D. P.; Luque, R.; Van der Eycken, E. V. Silver-Nanoparticle-Catalyzed Dearomatization of Indoles toward 3-Spiroindolenines via a 5-exo-dig Spirocyclization. *ACS Catal.* **2016**, *6* (12), 8156−8161.

(29) James, S. L.; Adams, C. J.; Bolm, C.; Braga, D.; Collier, P.; Friscic, T.; Grepioni, F.; Harris, K. D. M.; Hyett, G.; Jones, W.; Krebs, A.; Mack, J.; Maini, L.; Orpen, A. G.; Parkin, I. P.; Shearouse, W. C.; Steed, J. W.; Waddell, D. C. Mechanochemistry: opportunities for new and cleaner synthesis. *Chem. Soc. Rev.* **2012**, *41* (1), 413−447.

DOI: 10.1021/acssuschemeng.9b00198
ACS Sustainable Chem. Eng. XXXX, XXX, XXX−XXX

(30) Matoga, D.; Oszajca, M.; Molenda, M. Ground to conduct: mechanochemical synthesis of a metal-organic framework with high proton conductivity. *Chem. Commun.* **2015**, *51* (36), 7637−7640.
(31) Paseta, L.; Potier, G.; Sorribas, S.; Coronas, J. Solventless Synthesis of MOFs at High Pressure. *ACS Sustainable Chem. Eng.* **2016**, *4* (7), 3780−3785.
(32) Muralidharan, N.; Brock, C. N.; Cohn, A. P.; Schauben, D.; Carter, R. E.; Oakes, L.; Walker, D. G.; Pint, C. L. Tunable Mechanochemistry of Lithium Battery Electrodes. *ACS Nano* **2017**, *11* (6), 6243−6251.
(33) Horikoshi, S.; Serpone, N. *Microwaves in Nanoparticle Synthesis: Fundamentals and Applications*; Wiley-VCH, 2013.
(34) Mirzaei, A.; Neri, G. Microwave-assisted synthesis of metal oxide nanostructures for gas sensing application: A review. *Sens. Actuators, B* **2016**, *237*, 749−775.
(35) Panda, A. B.; Glaspell, G.; El-Shall, M. S. Microwave Synthesis of Highly Aligned Ultra Narrow Semiconductor Rodsand Wires. *J. Am. Chem. Soc.* **2006**, *128*, 2790−2791.
(36) Rajabi, F.; Fayyaz, F.; Luque, R. Cytosine-functionalized SBA-15 mesoporous nanomaterials: Synthesis, characterization and catalytic applications. *Microporous Mesoporous Mater.* **2017**, *253*, 64−70.
(37) Zhao, D. Y.; Feng, J. L.; Huo, Q. S.; Melosh, N.; Fredrickson, G. H.; Chmelka, B. F.; Stucky, G. D. Triblock copolymer syntheses of mesoporous silica with periodic 50 to 300 angstrom pores. *Science* **1998**, *279* (5350), 548−552.
(38) Han, Y.; Xiao, F. S.; Wu, S.; Sun, Y. Y.; Meng, X. J.; Li, D. S.; Lin, S.; Deng, F.; Ai, X. J. A novel method for incorporation of heteroatoms into the framework of ordered mesoporous silica materials synthesized in strong acidic media. *J. Phys. Chem. B* **2001**, *105* (33), 7963−7966.
(39) Akin, S. T.; Liu, X.; Duncan, M. A. Laser synthesis and spectroscopy of acetonitrile/silver nanoparticles. *Chem. Phys. Lett.* **2015**, *640*, 161−164.
(40) Manahan, S. E.; Iwamoto, R. T. Complexes of copper(I) and silver(I) with acetonitrile in water lower alcohols acetone and nitroethane. *J. Electroanal. Chem. Interfacial Electrochem.* **1967**, *14* (2), 213−217.
(41) Zhou, Z.; He, C.; Yang, L.; Wang, Y. F.; Liu, T.; Duan, C. Y. Alkyne Activation by a Porous Silver Coordination Polymer for Heterogeneous Catalysis of Carbon Dioxide Cycloaddition. *ACS Catal.* **2017**, *7* (3), 2248−2256.
(42) Schroder, F.; Ojeda, M.; Erdmann, N.; Jacobs, J.; Luque, R.; Noel, T.; Van Meervelt, L.; Van der Eycken, J.; Van der Eycken, E. V. Supported gold nanoparticles as efficient and reusable heterogeneous catalyst for cycloisomerization reactions. *Green Chem.* **2015**, *17* (6), 3314−3318.
(43) Bantreil, X.; Bourderioux, A.; Mateo, P.; Hagerman, C. E.; Selkti, M.; Brachet, E.; Belmont, P. Phosphine-Triggered Selectivity Switch in Silver-Catalyzed o-Alkynylbenzohydroxamic Acid Cyclo-isomerizations. *Org. Lett.* **2016**, *18* (19), 4814−4817.
(44) Parker, E.; Leconte, N.; Godet, T.; Belmont, P. Silver-catalyzed furoquinolines synthesis: from nitrogen effects to the use of silver imidazolate polymer as a new and robust silver catalyst. *Chem. Commun.* **2011**, *47* (1), 343−345.
(45) Mohan, D. C.; Rao, S. N.; Adimurthy, S. Synthesis of Imidazo 1,2-a pyridines: "Water-Mediated" Hydroamination and Silver-Catalyzed Aminooxygenation. *J. Org. Chem.* **2013**, *78* (3), 1266−1272.

DOI: 10.1021/acssuschemeng.9b00198
ACS Sustainable Chem. Eng. XXXX, XXX, XXX−XXX