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Divergent Syntheses of (Z)-3-Alkylideneisobenzofuran-1(3H)ones and 1H-Isochromen-1-ones by Copper-Catalyzed Cycloisomerization of 2-Alkynylbenzoic Acids in Ionic Liquids

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Divergent Syntheses of (Z)-3-Alkylideneisobenzofuran-1(3H)-ones and 1H-Isochromen-1-ones by Copper-Catalyzed Cycloisomerization of 2-Alkynylbenzoic Acids in Ionic Liquids Raffaella Mancuso,^{*,†} Christian S. Pomelli,[‡] Piera Chiappetta,[†] Katia F. Gioia,[†] Asif Maner,[†] Nadia Marino,^{\$} Lucia Veltri,[†] Cinzia Chiappe,[‡] and Bartolo Gabriele^{*,†} + Laboratory of Industrial and Synthetic Organic Chemistry (LISOC), Department of Chemistry and Chemical Technologies, University of Calabria, Via Pietro Bucci 12/C, 87036 Arcavacata di Rende (CS), Italy [‡] Department of Pharmacy, University of Pisa, Via Bonanno 33, 56126 Pisa, Italy ^{\$} Department of Chemistry and Chemical Technologies, University of Calabria, Via Pietro Bucci 14/C, 87036 Arcavacata di Rende (CS), Italy raffaella.mancuso@unical.it; bartolo.gabriele@unical.it CuCl₂ (5 mol %) CuCl₂ (5 mol %) OH Mor_{1 2}N(CN)₂ 100 °C, 3 h 100 °C, 3 h (R = alkyl, alkenyl) (R = H, aryl)(70-82%)(base free - solvent recyclable)

(80-84%)

Abstract

The cycloisomerization of readily available 2-alkynylbenzoic acids **1** in ionic liquids (ILs) as recyclable reaction media has been studied under the catalytic action of CuCl₂. With substrates bearing an aryl group on the triple bond, a mixture of (*Z*)-3-alkylideneisobenzofuran-1(3*H*)-ones (from 5-*exo-dig* cyclization) and 1*H*-isochromen-1-ones (from 6-*endo-dig* cyclization) was observed in 1-ethyl-3-methylimidazolium ethyl sulfate (EmimEtSO₄), while the reaction turned out to be selective toward the formation of the isobenzofuranone only using *N*-ethyl-*N*-methylmorpholinium dicyanamide [Mor_{1,2}N(CN)₂], as the solvent. The 5-membered product was also obtained selectively when the substrate bearing a terminal triple bond was employed, either in EmimEtSO₄ or Mor_{1,2}N(CN)₂. On the other hand, 2-alkynylbenzoic acids bearing an alkyl or an alkenyl group on the triple bond selectively led, in EmimEtSO₄, to 1*H*-isochromen-1-ones, while the formation of a regioisomeric mixture was observed in Mor_{1,2}N(CN)₂. In any case, the solvent/catalyst system could be easily recycled after extraction of the product from the reaction mixture with diethyl ether. DFT calculations have been carried out to clarify the reaction outcome depending on reaction conditions, and the structures of two representative products, that are, (*Z*)-3-benzylideneisobenzofuran-1(3*H*)-one and (*Z*)-3-(4-methylphenylmethylidene)isobenzofuran-1(3*H*)-one, have been confirmed by X-ray diffraction analysis.

Introduction

Cycloisomerization of 2-alkynylbenzoic acids¹⁻³ is a convenient method for the direct and atom-economical synthesis of important heterocyclic derivatives, with important biological activities.^{4,5} Depending on the substitution pattern of the substrate and reaction conditions, the process may lead to either 3-alkylideneisobenzofuran-1(3*H*)-ones (from 5-*exo-dig* cyclization) or 1*H*-isochromen-1-ones (from 6-*endo-dig* cyclization) (Scheme 1).



Scheme 1. Cycloisomerization of 2-alkynylbenzoic acids leading to either 3-alkylideneisobenzofuran-1(3*H*)ones (from 5-*exo-dig* mode, path *a*) or 1*H*-isochromen-1-ones (from 6-*endo-dig* mode, path *b*).

Although different catalysts have been proposed for promoting this reaction, including acid,¹ basic,^{1a,2} and transition-metal catalysts,³ to the best of our knowledge the use of copper-based catalytic systems has not been reported so far. Moreover, the process has been previously reported to occur in conventional volatile organic solvents,¹⁻³ while the use of non-conventional solvents, such as ionic liquids (ILs), has not been investigated. In this paper, we wish to fill this gap, by reporting on the cycloisomerization of 2-alkynylbenzoic acids under the catalytic action of CuCl₂ as very simple catalyst and using ILs as safer unconventional solvents.⁶

Results and Discussion

Copper–Catalyzed Divergent Syntheses of (Z)-3-Alkylideneisobenzofuran-1(3H)-ones 2 and 1H-Isochromen-1-ones 3 by Copper-Catalyzed Cycloisomerization of 2-Alkynylbenzoic Acids 1 in Ionic Liquids, and Recycling Experiments

We firstly tested 2-alkynylbenzoic aids bearing an aryl group on the triple bond. 2-(2-Phenylethynyl)benzoic acid **1a** was initially allowed to react in 1-ethyl-3-methylimidazolium ethyl sulfate (EmimEtSO₄) (substrate concentration = 0.2 mmol / mL of solvent) in the presence of 5 mol % of CuCl₂. After 3 h at 100 °C, a mixture of (Z)-3-benzylideneisobenzofuran-1(3H)-one 2a and 3-phenyl-1H-isochromen-1-one 3a was obtained, with a total yield of 88% (2a/3a ratio ca. 0.6; Table 1, entry 1). The process took place also in the absence of catalyst, even though with significantly less satisfactory results (total yield 48%, Table 1, entry 2). These results confirmed the possibility to perform the cycloisomerization of a 2-alkynylbenzoic acid in an ionic liquid as the solvent, using CuCl₂ as simple and inexpensive catalyst. To assess the influence of the solvent the reaction outcome, several ILs were then tested. In 1-butyl-3-methylimidazolium on trifluoromethanesulfonate (BmimOTf), 1-ethyl-3-methylimidazolium tosylate (EmimOTs), and 1,3dimethylimidazolium dimethyl phosphate (Mmim(MeO)₂PO₂), again a mixture of 2a and 3a was obtained, 3a being still formed preferentially (entries 3-5). On the other hand, in 3-butyl-1-methylimidazolium dicyanamide [BmimN(CN)₂], N-(cyanopropyl)-N-methyl pyrrolidinium triflimide [C₃CNmpyr)(NTf)₂], and Nethyl-N-methylmorpholinium dicyanamide [Mor_{1,2}N(CN)₂], the process turned out to be completely selective toward the formation of the 5-membered product 2a (Table 1, entries 6-8), whose structure was confirmed by X-ray diffraction analysis (see the Supporting information for details). In particular, the highest yield (70%) was obtained in Mor_{1.2}N(CN)₂, as shown in Table 1 (entry 8). Under these latter conditions, we then tested the recyclability of the catalyst/solvent system, by extracting the product from the reaction mixture with diethyl ether and adding fresh substrate to the ionic liquid residue, still containing the catalyst dissolved in it. As shown in Table 1, entry 8, the CuCl₂/Mor_{1.2}N(CN)₂ system could be successfully recycled up to 5 times, without appreciable loss of activity. It is worth noting that the same reaction, carried out in the absence of CuCl₂, led to **2a** in a significantly lower yield (35%, Table 1, entry 9).

Under the same conditions as those reported in Table 1, entry 8, other 2-alkynylbenzoic acids, bearing a tolyl (**1b**) or a 3-thienyl (**1c**) substituent, behaved similarly, with selective formation of the corresponding (*Z*)-3-alkylideneisobenzofuran-1(3*H*)-ones **2b** and **2c** in good yields and excellent recyclability of the solvent/catalyst system (Table 1, entries 10 and 11, respectively). The structure of (*Z*)-3-(4-

 methylphenylmethylidene)isobenzofuran-1(3*H*)-one **2b** was also confirmed by X-ray diffraction analysis (see the Supporting information for details). Isobenzofuranone derivative **2d** was also selectively obtained starting from 2-ethynylbenzoic acid **1d**, bearing a terminal triple bond, in $Mor_{1,2}N(CN)_2$ (Table 1, entry 12) as well as in EmimEtSO₄ (Table 1, entry 13).

The behavior of substrates substituted with an alkyl group on the triple bond was quite different from that observed with those bearing an aryl group. The reaction of 2-(hex-1-ynyl)benzoic acid **1e**, carried out in Mor_{1,2}N(CN)₂ under the same conditions as those of Table 1, entry 8, led to the formation of a mixture of the corresponding 5-membered and 6-membered cycloisomerization products (**2e** and **3e**, respectively) (Table 2, entry 14). However, the process turned out to be selective toward the formation of the isochromenone derivative **3e** when it was conducted in EmimEtSO₄, with a high product yield and an excellent catalyst/solvent recyclability (Table 1, entry 15). The same reaction, carried out in the absence of catalyst, also selectively led to the 6-membered product **3e**, even though in a significant lower yield (Table 1, entry 16). Under the optimized conditions of entry 15 (Table 1), other substrates bearing a phenethyl (**1f**, Table 1, entry 17), an alkenyl group such as 1-cyclohexenyl (**1g**, Table 1, entry 18), or even a sterically demanding alky group such as *tert*-butyl (**1h**, Table 1, entry 19) behaved similarly, leading to the corresponding isochromenones **3f-h** in a selective manner and in high yields (80-84%).





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^{*a*} Unless otherwise noted, all reactions were carried out under nitrogen at 100 °C for 3 h with a substrate concentration of 0.2 mmol of **1** per mL of ionic liquid, in the presence of 5 mol % of CuCl₂. ^{*b*} Determined by GLC. ^{*c*} Based on starting **1**. ^{*d*} The reaction was carried out in the absence of CuCl₂. ^{*e*} The yields in the next catalyst/solvent recycles (see text for details) were 71, 70, 70, 70%. ^{*f*} The yields in the next catalyst/solvent recycles (see text for details) were 71, 70, 70, 70%. ^{*f*} The yields in the next catalyst/solvent recycles (see text for details) were 69, 70, 69, 69%. ^{*g*} The yields in the next catalyst/solvent recycles were 71, 70, 71, 71%. ^{*h*} Traces of regioisomeric 1*H*-isochromen-1-one were observed by GLC-MS analysis. ^{*i*} The yields in the next catalyst/solvent recycles were 82, 84, 84, 85%. ^{*i*} Substrate conversion was 86%, by GLC. ^{*k*} The yields in the next catalyst/solvent recycles were 80, 82, 83, 82%. ^{*i*} The yields in the next catalyst/solvent recycles were 80, 77, 79, 80%. ^{*m*} The yields in the next catalyst/solvent recycles were 80, 81, 81, 83%.

Reaction mechanism and DFT Calculations

As previously evidenced, the IL nature – and more in particular the anion structure- strongly affects the product selectivity. This effect is not surprising considering the peculiar solvent properties of ionic liquids, which are mainly related to the ability of IL components (cation and/or anion) to give specific interactions with substrate, transition states and intermediates. In this case, moreover, the IL can interact also with the catalytic system, both at the stage of dissolved salt or after interaction with the triple bond. According to other CuCl₂-catalyzed cyclization processes of functionalized alkynes,⁷ formation of products **2** and **3** should occur through an *anti* 5-*exo-dig* (path *a*), or 6-*endo-dig* (path *b*), nucleophilic attack of the carboxylate

group to the triple bond coordinated to CuCl₂, followed by protonolysis (Scheme 2). As shown in Scheme 2, the *anti* attack is in perfect agreement with the (*Z*) stereochemistry observed in the 3-alkylideneisobenzofuran-1(3*H*)-ones **2**, as confirmed by the X-ray diffraction analysis of products **2a** and **2b** (see the Experimental Section for details).



Scheme 2. Divergent CuCl₂-catalyzed cycloisomerization of 2-alkynylbenzoic acids **1** leading to either 3alkylideneisobenzofuran-1(3*H*)-ones **2** or 1*H*-isochromen-1-ones **3**, occurring through *anti* 5-*exo-dig* (path *a*) or 6-*endo-dig* (path *b*), respectively, nucleophilic attack of the carboxylate group to the triple bond coordinated to CuCl₂, followed by protonolysis.

The relationship between the deprotonation of the carboxylic group and the regiochemical output of the cyclization of 2-alkynylbenzoic acids, performed under acidic or basic conditions in conventional organic solvents, was previously investigated by Uchiyama and coworkers.^{1a} In the present reaction, the IL anion could determine the regiochemical behavior of the reaction affecting 1) the complexation shell of Cu(II) center; 2) acting as a base so favoring the proton removal from the carboxylic group. It is noteworthy that most of the selected ILs are characterized by relatively strong hydrogen bonding acceptor anions. The Kamlet-Taft β parameters ranges indeed from 0.5 to 1, in the order TfO⁻ < N(CN)₂⁻ ≤ EtSO₄⁻ < (MeO)₂PO₂⁻,

the sole exception being represented by Tf_2N^{-} (β around 0.25).⁸ This parameter, however, appears unable to determine the product distribution: ILs with anions having similar β values give a completely different product distribution (runs 1,6) whereas ILs having anions with different β values give the same product (runs 6,7). Nonetheless, BmimN(CN)₂ and (C₃CNmpyr)(NTf)₂ present also a completely different water affinity, the first one is hydrophilic the second hydrophobic: the observed similar product distribution strongly suggests that also this parament is not relevant. In a similar manner, polarizability, π^* , and hydrogen bond acidity, α , are unable to explain the observed reaction behavior.⁹

Thus, to rationalize the effect of the nature of the IL on the regioselectivity of the process we decided to carry out DFT calculations, which have been proven to be useful to describe the behavior of similar reactions.^{7a} In particular, we decided to focalize our attention on two IL anions, $N(CN)_2^-$ and $EtSO_4^-$, taking into account the following aspects:

1. anion can coordinate the Cu(II) center. Since the catalytic role of Cu(II) is the activation of the triple bond via a η^2 coordination, two anions are necessary to saturate the metal atom coordination sphere. With respect to the previously investigated iodocyclization reaction, where copper is replaced by a positively charged iodine atom,⁹ here there is a higher structural rigidity, due to the coordination of a d^9 center instead of the formation of two partial halogen-carbon bonds and a higher steric hindrance (two anions are coordinate to the copper center whereas the iodonium ion forms a far less rigid ionic pair with a counteranion). Since CuCl₂ has been used as catalyst, and this small anion can be strongly coordinated to the metal center, two subcases have been considered:

1.1. chloride ion is still coordinated to copper atom;

1.2. chloride ion is replaced by the IL anion $[N(CN)_2]$ or $EtSO_4$ in our specific cases]

- 2. Furthermore, since the anion could act as base in the proton removal from the carboxylic group also in this case, we have considered two possible situations:
 - 2.1. The anion acting as base is also involved in the coordination of the copper center. Given the geometry and possible conformations of the 2-alkynylbenzoic acid molecule, this possibility is reasonable. Therefore, chloride, N(CN)₂⁻ and EtSO₄⁻ have been considered obtaining an electrical neutral model system consisting of a 2-alkynylbenzoic acid molecule and two anions (Figure 1a). In this scenario, the coordinated anion practically "fishes" the carboxylic group proton. We refer to this mechanism as "internal mechanism";
 - 2.2. The anion acting as base is different from those coordinating the copper center. In this role, we have considered only $N(CN)_2^-$ and $EtSO_4^-$ since the probability that the chloride ion, present in catalytic quantities, replaces the solvent anions is negligible. For steric reasons, the anion acting as a base should approach the carboxylic group from the opposite side with respect the acetylenic moiety. This model system presents three anions and an unitary negative charge. We refer to this mechanism as "external mechanism".

These two mechanisms have been previously considered for substrates characterized by the presence of an amidic group instead of carboxylic one.^{7a} In the case of amides, the external mechanism presented always lower energy barriers than the internal one. However, considering the structural difference and the different reactivity of carboxylic and amidic groups, we have checked both mechanisms. For all the above outlined possibilities, the two paths that lead to five or six ring products have been considered for the 2alkynylbenzoic acid with R = Ph (**1a**). For some external mechanisms, moreover, the case of R = H (**1d**) has been taken into account. The most relevant results are shown in Table 2.

3

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Five-membered product Six-membered product R Anion 1 Anion 2 $\Delta G_{R \to TS}$ $\Delta G_{P \to TS}$ $\Delta G_{R \to P}$ $\Delta G_{R \rightarrow TS} \quad \Delta G_{P \rightarrow TS} \quad \Delta G_{R \rightarrow P}$ Ph Cl⁻ 130.30 73.00 57.30 149.35 129.76 19.59 121.57 187.52 -65.96 407.56 527.53 -119.98 $N(CN)_2^$ none $EtSO_4$ 248.69 93.39 155.30 173.38 143.73 29.95 Cl^{-} 128.27 -104.78 $N(CN)_2$ 19.64 103.31 -83.67 23.49 Cl^{-} -52.90 -152.46 $EtSO_4$ $N(CN)_2^{-1}$ $N(CN)_2^{-1}$ 2.60 132.76 -130.1728.10 181.37 -153.27 $EtSO_4^-$ 13.54 63.25 -48.71 226.77 EtSO₄⁻ 77.78 -148.99Н 447.17 N(CN)₂ 6.65 145.07 -138.43 618.29 N(CN)₂ -171.12 $EtSO_4^ EtSO_4^-$ 67.60 182.45 -114.86 386.51 619.90 -233.39

Table 2: Some energetic values related to the reaction paths. Energies in KJ/mol.

Except for the case where the Cu(II) is still coordinated to chloride and the external ion is EtSO₄⁻, all the reaction paths present barriers. In the above-mentioned case, instead, the reaction path is monotone with the energies of the products lower than the energies of the reactants. It is to note that the energy of six member ring product is always lower than one of the five member ring: this pathway favors the formation of compounds **3**. All the internal paths present transition states with barrier values higher than those characterizing the external mechanisms (of course, when this latter present a barrier). Thus, the internal mechanism is never energetically favored (as in the case of amides). Probably, this kind of structure forces the carboxylic group to be considerably rotated with respect the central aromatic ring and the leaving

proton is forced to migrate toward the metal center, a situation which is not electrostatically favored. In any case, this geometry, as it is evident from Figure 1a, would promote the formation of **2**: the carboxylic group is oriented in a way that facilitates the closing of a five-membered ring. Since we can consider that this kind of mechanism is not relevant for the reaction, given its high barriers, we can pass to discuss in more detail the external paths.



Figure 1: (a) Starting structure related to internal mechanism: when the proton migrates toward the anion, it also approaches the metal ion. This is not energetically favorable. (b) Six-membered ring product ensuing from the external mechanism with the $EtSO_4^-$ anion: it is evident the steric hindrance and the deformation of the lactone ring. (c) The same structure as (b), but with chlorine coordinated to Cu(II): the sterical hindering disappears. (d) The same structure of (b) with R = H: also in this case, there is no sterical hindering.

In all the paths with a barrier, the energetic profile leads to a preference for the five-membered ring compound, while the six-membered one is consistently the most stable from the energetic point of view. This scenario is like the one reported in our previous paper about amides cyclization.^{7a} The experimental data show that, when the solvent anion is $EtSO_4^-$ and R = Ph, both five and six membered ring products are formed, whereas when R = H the five-membered isomer is the only product formed; moreover, in all cases, the five-membered product is preferred where the anion is $N(CN)_2^-$. A possible rationalization of these results can be found analyzing the different situations from the point of view of steric hindrance, considering that:

- 1. In the activated reactant, the catalytic center Cu(II) is coordinated by the acetylenic mojety via a η^2 coordination. The other two coordination sites can be occupied by the original catalyst anion (chlorine) or by the ionic liquid anion (EtSO₄⁻ or N(CN)₂⁻). The steric hindrance of chloride and of the flat N(CN)₂⁻ anion is relatively small, while that of EtSO₄⁻, organized about a tetrahedral phosphorous atom, is comparatively large.
- The R group of the substrate is nearby the metallic center. When R = Ph, its size can exert steric interactions, thus affecting the reaction path.

These steric effects are more relevant in the case of the path that leads to the six-membered product, where the double bond is part of the ring. The structures reported in Figure 1b-d show that, when the Cu(II) center is coordinated to $EtSO_4^-$, there is an appreciable deformation of the ring (Figure 1b) that disappears when copper is coordinated to the smaller chloride, Figure 1c, or hydrogen replaces the phenyl ring, Figure 1d. In ILs, metal salts dissolution generally occurs through the formation of metal anionic complexes, in our case of the type [CuCl_nA_m]^{x-} where A is the IL anion.¹⁰ The large concentration of A⁻ with respect to chlorine can lead to a replacement of chloride by A⁻, although it is well-known that is not easy to remove a chloride ligand from copper.¹⁰ However, some of the Cu(II) ligands must be removed to allow the formation of the η^2 bond with the reactant. As evidenced, in the presence of a hindered R group on triple

bond, the size of the anion coordinated to the metal center can induce a significant deformation of the starting structure. In the examined cases, this condition is verified only when the anion is EtSO₄⁻ and the R group is phenyl. In this case, probably also favored by the relatively low coordinating ability of this anion, the reaction prevalently occurs through a starting complex having chloride as metal ligand, i.*e.* through the monotone pathway bearing preferentially to **3**. At variance, in the case of N(CN)₂⁻ based ILs the strong complexing ability of this anion can facilitate the displacement of chloride, giving a starting complex with dicyanamide ligands at copper center and the external mechanism leads to **2**, having this pathway a lower barrier than that bearing to **3**. These considerations, which are valid for any sterically hindered group (including also *tert*-butyl or cyclohexyl) can qualitatively explain the regioselectivity of the investigated reaction in ILs. A more quantitative analysis would require an evaluation of the relative quantities of these different complexes, which depend also on factors that our simplified model does not take in account, such as cation anion interaction, ions and molecules diffusion in the ionic liquid environment, kinetic of ligand exchange, etc.

Conclusions

We have shown that it is possible to efficiently carry out the cycloisomerization of readily available 2alkynylbenzoic acids using an ionic liquid as the reaction medium in the presence of CuCl₂ as a simple and inexpensive catalyst. Although in principle two different cyclization pathways can be followed, leading to either (*Z*)-3-alkylideneisobenzofuran-1(3*H*)-ones (from 5-*exo-dig* mode) or 1*H*-isochromen-1-ones (from 6*endo-dig* mode), we have found that substrates bearing an aryl group on the triple bond or a terminal triple bond can be selectively converted into the isobenzofuranone derivatives, using *N*-ethyl-*N*methylmorpholinium dicyanamide [Mor_{1,2}N(CN)₂] as the solvent. On the other hand, and in a complementary manner, substrates substituted with an alkyl or an alkenyl group on the triple bond selectively led to isochromenones when the reaction was carried out in 1-ethyl-3-methylimidazolium ethyl

sulfate (EmimEtSO₄). In all cases, products were obtained in good to high yields and with excellent recyclability of the catalyst/ionic liquid system. The DFT calculations show that the selectivity is related to the sterical interactions between the anion and the 2-alkynylbenzoic acid substrate.

Experimental Section

General Experimental Methods. Solvent and chemicals were reagent grade and were used without further purification. All reactions were analyzed by TLC on silica gel 60 F254 and by GLC using capillary columns with polymethylsilicone + 5% phenylsilicone as the stationary phase. Column chromatography was performed on silica gel 60 (70-230 mesh). Evaporation refers to the removal of solvent under reduced pressure. Melting points are uncorrected. ¹H NMR and ¹³C(¹H)NMR spectra were recorded at 25 °C on a 300 Spectrometer in CDCl₃ with Me₄Si as internal standard. Chemical shifts (δ) and coupling constants (J) are given in ppm and in Hz, respectively. IR spectra were taken with an FT-IR spectrometer. Mass spectra were obtained using a GC-MS apparatus at 70 eV ionization voltage (normal resolution) and by electrospray ionization mass spectrometry (ESI-MS) (high resolution). The LC-MS was operated in the positive ion mode. Water and acetonitrile were of HPLC/MS grade. Formic acid was of analytical quality. A reversed-phase C18 column with a C18 security guard column (4mm×3mm) was used. The flow-rate was 0.4 mL/min and the column temperature was set to 30°C. The eluents were formic acid-water (0.1:99.9, v/v) (phase A) and formic acid-acetonitrile (0.1:99.9, v/v) (phase B). The following gradient was employed: 0-10 min, linear gradient from 5% to 95% B; 10-15 min, washing and reconditioning of the column to 5% B. Injection volume was 10 mL. The eluate was monitored through MS TIC. Mass spectra were obtained on a UHD accurate-mass Q-TOF spectrometer equipped with a Dual AJS ESI source working in positive mode. N_2 was employed as desolvation gas at 300°C and a flow rate of 8 L/min. The nebulizer was set to 45 psig. The Sheat gas temperature was set at 400°C and a flow of 12 L/min. A potential of 3.5 kV was used on the

capillary for positive ion mode. The fragmentor was set to 175 V. MS spectra were recorded in the 150–1000 m/z range.

Computational Details. All calculation has been performed at B3LYP/def-sv[p] level using the Terachem package¹¹ version 1.5k. Grimme's dispersion correction has been included.¹² A GPU workstation with four GeForce GTX Titanium Z has been used for all calculations.

Preparation of ILs. The ILs EmimEtSO_4 ,⁸ BmimN(CN)_2 ,⁸ $\text{Mor}_{1,2}\text{N(CN)}_2$,⁸ $\text{Mmim(MeO)}_2\text{PO}_2$,¹³ BmimOTf,¹⁴ EmimOTs,¹⁴ and (C₃CNmpyr)(NTf)₂¹⁴ were prepared according to literature procedures.

Preparation of Substrates. 2-Alkynylbenzoic acids **1a-e** and **1g-h** were prepared by Sonogashira coupling between the corresponding methyl 2-iodobenzoates (commercially available) and terminal alkynes followed by hydrolysis, as we already reported.⁸ Substrates **1f** was prepared in a similar way, according to the procedure given below.

Sonogashira Coupling Between Methyl 2-Iodobenzoates and But-3-ynylbenzene to Give Methyl 2-(4-Phenylbut-1-ynyl)benzoate. The method of Kundu¹⁵ was adapted. A solution of methyl 2-iodobenzoate (4.0 mmol; 1.05 g), $PdCl_2(PPh_3)_2$ (99.2 mg, 0.14 mmol), Cul (61.0 mg, 0.32 mmol) and Et_3N (1.9 mL) in anhydrous DMF (10 mL) was allowed to stir under nitrogen for 1 h. The but-3-ynylbenzene, 625 mg (4.8 mmol), was then added under nitrogen, and the resulting mixture was heated at 85 °C (oil bath) for 15 h. After cooling, CH_2Cl_2 (100 mL) was added, and the mixture washed with water (3 × 100 mL). After drying over Na_2SO_4 , the solvent was evaporated, and the residue purified by column chromatography on silica gel using hexane-AcOEt from 99:1 to 95:5 as eluent.

Methyl 2-(4-Phenylbut-1-ynyl)benzoate. Yield: 856 mg, starting from 1.05 g of methyl 2-iodobenzoate (81%). Yellow oil. IR (film): v = 2228 (w), 1733 (s), 1252 (m), 1083 (m), 757 (m), 698 (m) cm⁻¹; ¹H NMR (300 MHz, CDCl₃): $\delta = 7.88$ (d, J = 7.8, 1 H), 7.50-7.46 (m, 1 H), 7.39 (td, J = 7.4, 1.4, 1 H), 7.35-7.16 (m, 6 H), 3.86 (s, 3 H), 2.96 (t, J = 7.5, 2 H), 2.76 (t, J = 7.5, 2 H); ¹³C{¹H}NMR (75 MHz, CDCl₃): $\delta = 166.8, 140.7, 134.2, 131.8, 131.5, 130.1, 128.5, 128.4, 127.3, 126.3, 124.3, 95.0, 79.9, 52.0, 35.0, 22.0; GC-MS: <math>m/z = 264$ (22)

 $[M^{+}]$, 263 (56), 249 (35), 231 (69), 143 (35), 91 (100). The spectroscopic data were in good agreement with those reported.¹⁶

Hydrolysis of Methyl 2-(4-Phenylbut-1-ynyl)benzoate to Give 2-(4-Phenylbut-1-ynyl)benzoic acid 1f. The method of Kundu¹⁵ was adapted. A stirred solution of methyl 2-(4-phenylbut-1-ynyl)benzoate (2.5 mmol; 661 mg) and 1 N NaOH (14.0 mL) in THF (3.0 mL) was heated at 50 °C for 12 h. After cooling to room temperature, the mixture was washed with Et₂O (3 × 15 mL), further cooled with the aid of an ice bath, and neutralized with 1 N HCl. The resulting mixture was extracted at room temperature with CH₂Cl₂ (3 × 50 mL), and the collected organic layers dried over Na₂SO₄. Filtration and evaporation of the solvent afforded crude 2-(4-phenylbut-1-ynyl)benzoic acid. The product **1f** was further purified by crystallization with Et₂O/hexane. *2-(4-Phenylbut-1-ynyl)benzoic acid* (**1f**). Yield: 513 mg, starting from 661 mg of methyl 2-(4-phenylbut-1ynyl)benzoate (82%). White solid, mp = 54-56°C, IR (KBr): v = 2220 (w), 1704 (s), 1303 (m), 933 (m), 758 (s) cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ = 10.95 (s, br, 1 H), 8.04 (d, *J* = 7.9, 1 H), 7.54-7.41 (m, 2 H), 7.38-7.15 (m, 6 H), 2.95 (t, *J* = 7.4, 2 H), 2.75 (t, *J* = 7.4, 2 H); ¹³C{¹H}NMR (75 MHz, CDCl₃): δ =171.5, 140.6, 134.4, 132.4, 131.1, 130.6, 128.5, 128.4, 127.4, 126.3, 124.8, 96.3, 79.8, 34.8, 22.0; HRMS-ESI [(M+H)⁺]: *m/z* calcd for (C₁₇H₁₅O₂): 251.1072; found, 250.1070.

General Procedure for the Recyclable Copper-Catalyzed Cycloisomerization of of 2-Alkynylbenzoic Acids in Ionic Liquids (Table 2). To a solution of 1 (0.4 mmol) (1a, 90.0 mg; 1b, 95.0 mg; 1c, 91.5 mg; 1d, 59.0 mg; 1e, 81.5 mg; 1f, 100.5 mg; 1g, 91.5 mg; 1h, 81.0 mg) in EmimEtSO₄ or MorfN(CN)₂ (2 mL) were added CuCl₂ (2.7 mg, 2.0×10^{-2} mmol) under nitrogen in a Schlenk flask. The mixture was allowed to stir at 100 °C for 3 h. After cooling, the product was extracted with diethyl ether (6 × 5 mL), and the residue (still containing the catalyst dissolved in the IL) was used as such for the next recycle (see below). The collected ethereal phases were concentrated. After evaporation of the solvent, the products 2a-d and 3e-3h were purified by column chromatography on silica gel using 98 : 2 hexane–AcOEt as the eluent. Mixtures 2a+3a and 2e+3e were collected by column chromatography on silica gel using 9 : 1 hexane–AcOEt as the eluent.

Recycling Procedure. To the residue obtained as described above, still containing the catalyst dissolved in the ionic liquid, was added a solution of fresh **1** (0.4 mmol) in Et₂O (3 mL). Et₂O was removed under vacuum, and then the same procedure described above was followed.

Mixture of (Z)-3-Benzylidene-3H-isobenzofuran-1-one (2a) + 3-Phenylisochromen-1-one (3a). Total yield: 79.1 mg, starting from 90.0 mg of **1a** (88%; **2a** / **3a** = 0.60, determined by GLC and ¹H NMR; Table 1, entry 1). IR (KBr): v = 1752 (s), 1717 (m), 1473 (w), 1072 (m), 983 (m) cm⁻¹; ¹H NMR (300 MHz, CDCl₃): $\delta = 8.30$ (d, J = 9.0, 1 H, **3a**), 7.95-7.90 (m, 1 H, **2a**), 7.90-7.82 [m, 2 H (**2a**) + 2 H (**3a**)], 7.78-7.66 [m, 2 H (**2a**) + 1 H (**3a**)], 7.57-7.52 (m, 1 H, **2a**), 7.52-7.37 [m, 2 H (**2a**) + 5 H (**3a**)], 7.37-7.30 (m, 1 H, **2a**), 6.95 (s, br, 1 H, **3a**), 6.42 (s, 1 H, **2a**); ¹³C{¹H}NMR (75 MHz, CDCl₃): $\delta = 167.1$ (**2a**), 162.3 (**3a**), 153.6 (**3a**), 144.6 (**2a**), 140.6 (**2a**), 137.5 (**3a**), 134.9 (**3a**), 134.5 (**2a**), 133.1 (**2a**), 132.0 (**3a**), 130.1 (**2a**), 130.0 (**3a**), 129.8 (**2a**), 129.7 (**3a**), 128.83 (**3a**), 128.77 (**2a**), 128.4 (**2a**), 128.2 (**3a**), 126.0 (**3a**), 125.6 (**2a**), 125.2 (**3a**), 123.4 (**2a**), 120.5 (**3a**), 119.8 (**2a**), 107.1 (**2a**), 101.8 (**3a**); GC-MS: **2a**: m/z = 222 (M⁺) (100), 194 (15), 165 (58), 139 (5); **3a**: m/z = 222 (M⁺) (100), 194 (63), 165 (61), 105 (24). The spectroscopic data for **2a** and **3a** were in good agreement with those reported.¹⁶

(*Z*)-3-Benzylidene-3H-isobenzofuran-1-one (**2a**). Yield: 62.5 mg, starting from 90.0 mg of **1a** (70%; Table 1, entry 8). White solid, mp = 80-83 °C. IR (KBr): v = 1774 (s), 1473 (m), 1085 (m), 978 (s), 764 (s) cm⁻¹; ¹H NMR (300 MHz, CDCl₃): $\delta = 7.93$ (dt, J = 7.7, 0.9, 1 H), 7.88-7.82 (m, 2 H), 7.80-7.73 (m, 1 H), 7.73-7.68 (m, 1 H), 7.58-7.51 (m, 1 H), 7.46-7.37 (m, 2 H), 7.36-7.28 (m, 1 H), 6.42 (s, 1 H); ¹³C{¹H}NMR (75 MHz, CDCl₃): $\delta = 167.1, 144.6, 140.6, 134.5, 133.1, 130.2, 129.8, 128.8, 128.4, 125.6, 123.5, 119.8, 107.1; GC-MS: <math>m/z = 222$ (M⁺) (100), 194 (14), 165 (41), 139 (3). The spectroscopic data were in good agreement with those reported.¹⁷

(*Z*)-3-(4-Methyl-benzylidene)-3H-isobenzofuran-1-one (**2b**). Yield: 67.0 mg, starting from 95.0 mg of **1b** (71%; Table 1, entry 10). White solid, mp = 109-111 °C. IR (KBr): v = 1780 (s), 1472 (m), 1077 (m), 972 (m), 760 (m) cm⁻¹; ¹H NMR (300 MHz, CDCl₃): $\delta = 7.92$ (d, J = 7.7, 1 H), 7.79-7.67 (m, 4 H), 7.52 (t, J = 7.2, 1 H), 7.28-7.17 (m, 2 H), 6.40 (s, 1 H), 2.38 (s, 3 H); ¹³C{¹H}NMR (75 MHz, CDCl₃): $\delta = 167.2, 144.0, 140.7, 138.7,$ 134.4, 130.3, 130.1, 129.5, 125.5, 123.3, 119.7, 107.2, 21.4; GC-MS: m/z = 236 (M⁺) (100), 218 (6), 193 (13), 178 (13), 165 (32). The spectroscopic data were in good agreement with those reported.¹⁷

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(*Z*)-3-*Thiophen-3-ylmethylene-3H-isobenzofuran-1-one* (**2***c*). Yield: 64.0 mg, starting from 91.5 mg of **1***c* (70%; Table 1, entry 11). White solid, mp = 54.1-55.1 °C. IR (KBr): v = 1775 (s), 1474 (w), 1078 (m), 982 (m), 689 (m) cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ = 7.92-7.86 (m, 1 H), 7.74-7.66 (m, 3 H), 7.60-7.55 (m, 1 H), 7.55-7.47 (m, 1 H), 7.33 (dist dd, *J* = 5.0, 3.0, 1 H), 6.49 (s, 1 H); ¹³C{¹H}NMR (75 MHz, CDCl₃): δ = 166.9, 143.6, 140.2, 134.4, 134.2, 129.5, 128.8, 126.7, 125.9, 125.5, 123.5, 119.6, 101.5; GC-MS: *m/z* = 228 (M⁺) (100), 200 (9), 171 (58), 127 (8). The spectroscopic data were in good agreement with those reported.¹⁸

(*Z*)-3-Methylene-3H-isobenzofuran-1-one (**2d**). Yield: 50.5 mg, starting from 59.0 mg of **1d** (86%; Table 1, entry 13). White solid, mp = 50-51 °C. IR (KBr): v = 1779 (s), 1469 (m), 1288 (m), 759 (m), 691 (w) cm⁻¹; ¹H NMR (300 MHz, CD₃CN): $\delta = 7.89$ (d, J = 7.7, 1 H), 7.73 (d, J = 4.0, 2 H), 7.63-7.53 (m, 1 H), 5.24 (s, br, 2 H); ¹³C{¹H}NMR (75 MHz, CD₃CN): $\delta = 166.9$, 151.8, 139.0, 134.5, 130.5, 125.2, 125.0, 120.7, 91.3; GC-MS: m/z = 146 (M⁺) (100), 118 (21), 104 (58), 76 (66). The spectroscopic data were in good agreement with those reported.¹⁹

3-Butylisochromen-1-one (*3e*). Yield: 68.0 mg, starting from 81.5 mg of **1e** (84%; Table 1, entry 15). White solid, mp = 30-32 °C. IR (KBr): v = 1718 (s), 1656 (m), 1481 (w), 1138 (w) cm⁻¹; ¹H NMR (300 MHz, CDCl₃): $\delta = 8.25$ (dd, J = 8.0, 0.6, 1 H), 7.71-7.62 (m, 1 H), 7.50-7.40 (m, 1 H), 7.33 (d, J = 7.8, 1 H), 6.26 (s, 1 H), 2.53 (t, J = 7.5, 2 H), 1.77-1.63 (m, 2 H), 1.48-1.34 (m, 2 H), 1.00-0.90 (m, 3 H); ¹³C{¹H}NMR (75 MHz, CDCl₃): $\delta = 163.1, 158.3, 137.6, 134.7, 129.5, 127.5, 125.0, 120.1, 102.9, 33.2, 29.0, 22.1, 13.8; GC-MS: <math>m/z$ =202 (M⁺) (27), 160 (26), 131 (15), 118 (100). The spectroscopic data were in good agreement with those reported.²⁰

3-Phenethylisochromen-1-one (*3f*). Yield: 80.4 mg, starting from 100.5 mg of **1f** (80%; Table 1, entry 17). White solid, mp = 32-34 °C. IR (KBr): v = 1728 (s), 1654 (m), 1481 (w), 1161 (w), 1074 (m) cm⁻¹; ¹H NMR (300 MHz, CDCl₃): $\delta = 8.26$ (d, J = 8.0, 1 H), 7.72-7.62 (m, 1 H), 7.50-7.41 (m, 1 H), 7.37-7.16 (m, 6 H), 6.22 (s, 1 H), 3.10-2.97 (m, 2 H), 2.90-2.87 (m, 2 H); ¹³C{¹H}NMR (75 MHz, CDCl₃): $\delta = 163.0, 156.9, 140.3, 137.4, 134.8, 129.6, 128.6, 128.4, 127.7, 126.3, 125.1, 120.2, 103.5, 35.5, 33.2; GC-MS: <math>m/z = 250$ (M⁺) (27), 159 (3), 131 (7), 91 (100). The spectroscopic data agreed with those reported.²⁰

3-Cyclohex-1-enylisochromen-1-one (*3g*) Yield: 76.3 mg, starting from 91.5 mg of **1g** (84%; Table 1, entry 18). White solid, mp = 80-82 °C. IR (KBr): v = 1715 (s), 1640 (m), 1621 (m), 1482 (w), 1221 (w), 1076 (m)

cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ = 8.24 (d, *J* = 7.6, 1 H), 7.65 (t, *J* = 7.6, 1 H), 7.47-7.34 (m, 2 H), 6.82 (s, br, 1 H), 6.37 (s, 1 H), 2.35-2.20 (m, 4 H), 1.85-1.73 (m, 2 H), 1.73-1.62 (m, 2 H); ¹³C{¹H}NMR (75 MHz, CDCl₃): δ = 162.4, 154.4, 137.9, 134.6, 130.1, 129.5, 127.6, 125.8, 120.6, 100.1, 25.6, 24.1, 22.3, 21.8; GC-MS: *m/z* = 226 (M⁺) (100), 211 (13), 183 (16), 141 (15), 89 (47). The spectroscopic data were in good agreement with those reported.²¹

3-tert-Butylisochromen-1-one (*3h*). Yield: 66.7 mg, starting from 81.0 mg of **1h** (82%; Table 1, entry 19). White solid, mp = 63-64 °C. IR (KBr): v = 1735 (s), 1648 (m), 1340 (w), 1086 (m) cm⁻¹; ¹H NMR (300 MHz, CDCl₃): $\delta = 8.26$ (d, J = 8.0, 1 H), 7.67 (td, J = 7.6, 0.9, 1 H), 7.44 (t, J = 7.6, 1 H), 7.38 (dist d, J = 7.9, 1 H), 6.31 (s, 1 H), 1.33 (s, 9 H); ¹³C{¹H}NMR (75 MHz, CDCl₃): $\delta = 165.1, 163.0, 137.7, 134.6, 129.4, 127.6, 125.5, 120.1, 99.7, 35.6, 28.0; GC-MS: <math>m/z = 202$ (M⁺) (63), 187 (100), 169 (18), 160 (60), 145 (47), 131 (32), 89 (60). The spectroscopic data were in good agreement with those reported.^{16,22}

Supporting Information. X-ray data for compounds **2a** and **2b**, Tables of absolute energies, optimized structures, copy of HRMS spectrum for compound **1f**, and copies of ¹H NMR and ¹³C{¹H}NMR spectra.

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References

(1) (a) Uchiyama, M.; Ozawa, H.; Takuma, K.; Matsumoto, Y.; Yonehara, M.; Hiroya, K.; Sakamoto, T. Regiocontrolled Intramolecular Cyclizations of Carboxylic Acids to Carbon–Carbon Triple Bonds Promoted by Acid or Base Catalyst. *Org. Lett.* **2006**, *8*, 5517-5520. (b) Zhang, X.; Hou, W.; Zhang-Negrerie, D.; Zhao, K.; Du, Y. Hypervalent Iodine-Mediated Intramolecular *trans*-Aminocarboxylation and Oxoaminocarboxylation

of Alkynes: Divergent Cascade Annulations of Isocoumarins under Metal-Free Conditions. Org. Lett. 2015, 17, 5252-5255.

(2) (a) Kanazawa, C.; Terada, M. Organic-Base-Catalyzed Synthesis of Phthalides via Highly Regioselective Intramolecular Cyclization Reaction. *Tetrahedron Lett.* **2007**, *48*, 933-935. (b) Terada, M.; Kanazawa, C.; Yamanaka, M. Theoretical Studies of 5-exo Selective Intramolecular Cyclization of *o*-Alkynylbenzoic Acid Catalyzed by Organic Base. *Heterocycles* **2007**, *74*, 819-825.

(3) For recent examples, see: (a) Umeda, R.; Yoshikawa, S.; Yamashita, K.; Nishiyama, Y. Synthesis of Isocoumarins: Rhenium Complex-Catalyzed Cyclization of 2-Ethynylbenzoic Acids. *Heterocycles* **2015**, *91*, 2172-2179. (b) Doherty, S.; Knight, J. G.; Perry, D. O.; Ward, N. A. B.; Bittner, D. M.; McFarlane, W.; Wills, C.; Probert, M. R. Triaryl-Like MONO-, BIS-, and TRISKITPHOS Phosphines: Synthesis, Solution NMR Studies, and a Comparison in Gold-Catalyzed Carbon–Heteroatom Bond Forming 5-*exo*-dig and 6-*endo*-dig Cyclizations. *Organometallics* **2016**, *35*, 1265-1278. (c) Conde, N.; SanMartin, R.; Herrero, M. T.; Domínguez, E. Palladium NNC Pincer Complex as an Efficient Catalyst for the Cycloisomerization of Alkynoic Acids. *Adv. Synth. Catal.* **2016**, *358*, 3283–3292.

(4) For very recent examples of bioactive 3-(alkylidene)isobenzofuran-1(3*H*)-one derivatives, see: (a) Su, Y.-J.; Huang, S.-Y.; Ni, Y.-H.; Liao, K.-F.; Chiu, S.-C. Anti-Tumor and Radiosensitization Effects of *N*-Butylidenephthalide on Human Breast Cancer Cells. *Molecules* **2018**, *23*, art. no. 240. (b) Giap, T. H.; Dung, N. A.; Thoa, H. T.; Dang, N. H.; Dat, N. T.; Hang, N. T. M.; Cuong, P. V.; Hung, N. V.; Minh, C. V.; Mishchenko, N. P.; Fedoreev, S. A.; Thanh, L. N. Phthalides and Other Metabolites from Roots of *Ligusticum wallichii*. *Chem. Nat. Compds.* **2018**, *54*, 34–37. (c) Yen, S.-Y.; Chuang, H.-M.; Lin, S.-Z.; Chiou, T.-W.; Harn, H.-J. *n*-Butylidenephthalide Regulated Tumor Stem Cell Genes EZH2/AXL and Reduced Its Migration and Invasion in Glioblastoma. *Int. J. Mol. Sci.* **2017**, *18*, art. no. 372.

(5) For very recent examples of bioactive 1*H*-isochromen-1-one derivatives, see: (a) Chen, Y.; Liu, Z.; Liu, H.; Pan, Y.; Li, J.; Liu, L.; She, Z. Dichloroisocoumarins with Potential Anti-Inflammatory Activity from the Mangrove Endophytic Fungus *Ascomycota* sp. CYSK-4. *Mar. Drugs* **2018**, *16*, art. no. 54. (b) Casnati, A.;

Maggi, R.; Maestri, G.; Della Ca', N.; Motti, E. Pd-Catalyzed/Iodide-Promoted α-Arylation of Ketones for the Regioselective Synthesis of Isocoumarins. *J. Org. Chem.* **2017**, *82*, 8296–8303. (c) Hussain, H.; Green, I. R. A Patent Review of Two Fruitful Decades (1997-2016) of Isocoumarin Research. *Expert Opin. Ther. Patents* **2017**, *27*, 1267-1275.

(6) For some very recent reviews on the use of ILs in organic synthesis, see: (a) Bodachivskyi, I.; Kuzhiumparambil, U.; Williams, D. B. G. Acid-Catalyzed Conversion of Carbohydrates into Value-Added Small Molecules in Aqueous Media and Ionic Liquids. *ChemSusChem* **2018**, *11*, 642-660. (b) Kaur, N. Perspectives of Ionic Liquids Applications for the Synthesis of Five- and Six-Membered *O,N*-Heterocycles. *Synth. Commun.* **2018**, *48*, 473-495. (c) Itoh, T. The Beneficial Sinergy of MW Irradiation and Ionic Liquids in Catalysis of Organic Reactions. *Chem. Rev.* **2017**, *117*, 10567-10607.

(7) For recent examples from our laboratories, see: (a) Mancuso, R.; Pomelli, C. S.; Raut, D. S.; Marino, N.; Giofrè, S. V.; Romeo, R.; Sartini, S.; Chiappe, C.; Gabriele, B. Copper-Catalyzed Recyclable Synthesis of (*Z*)-3-Alkylideneisoindolinones by Cycloisomerization of 2-Alkynylbenzamides in Ionic Liquids. *ChemistrySelect* **2017**, *2*, 894-899. (b) Gabriele, B.; Veltri, L.; Plastina, P.; Mancuso, R.; Vetere, M. V.; Maltese, V. Copper-Catalyzed Synthesis of Substituted Furans and Pyrroles by Heterocyclodehydration and Tandem Heterocyclodehydration–Hydration of 3 Yne-1,2-diols and 1 Amino-3-yn-2-ol Derivatives. *J. Org. Chem.* **2013**, *78*, 4919-4928. (c) Gabriele, B.; Mancuso, R.; Lupinacci, E.; Spina, R.; Salerno, G.; Veltri, L.; Dibenedetto, A. Recyclable Catalytic Synthesis of Substituted Quinolines: Copper-Catalyzed Heterocyclization of 1-(2-Aminoaryl)-2-yn-1-ols in Ionic Liquids. *Tetrahedron* **2009**, *65*, 8507-8512. (d) Gabriele, B.; Mancuso, R.; Salerno, G.; Ruffolo, G.; Plastina, P. Novel and Convenient Synthesis of Substituted Quinolines by Copper- or Palladium-Catalyzed Cyclodehydration of 1-(2-Aminoaryl)-2-yn-1-ols. *J. Org. Chem.* **2007**, *72*, 6873-6877.

(8) Mancuso, R.; Pomelli, C. S.; Malafronte, F.; Maner, A.; Marino, N.; Chiappe, C.; Gabriele, B. Divergent Syntheses of Iodinated Isobenzofuranones and Isochromenones by Iodolactonization of 2-Alkynylbenzoic Acids in Ionic Liquids. *Org. Biomol. Chem.* **2017**, *15*, 4831-4841.

(9) (a) Chiappe, C.; Pomelli, C. S.; Rajamani S. Influence of Structural Variations in Cationic and Anionic Moieties on the Polarity of Ionic Liquids. *J. Phys. Chem. B* 2011, *115*, 9653–9661. (b) Jessop ,P. G.; Jessop, D. A.; Fu, D.; Phan L. Solvatochromic Parameters for Solvents of Interest in Green Chemistry. *Green Chem.* 2012, *14*, 1245–1259. (c) Ab Rani, M. A.; Brant, A.; Crowhurst, L.; Dolan, A.; Lui, M.; Hassan, N. H., Hallett, J. P.; Hunt, P. A.; Niedermeyer, H.; Perez-Arlandis, J. M.; Schrems, M., Welton, T.; Wildinga, R. Understanding the Polarity of Ionic Liquids. *Phys. Chem. Chem. Phys.* 2011, *13*, 16831-16840.

(10) Boudesocque, S.; Mohamadou, A.; Dupont, L.; Martinez, A. ; Déchamps, I. Use of Dicyanamide Ionic Liquids for Extraction of Metal Ions. *RSC Adv.* **2016**, *6*, 107894-107904.

(11) (a) Ufimtsev S.; Martínez, T. J. Quantum Chemistry on Graphical Processing Units. 3. Analytical Energy Gradients, Geometry Optimization, and First Principles Molecular Dynamics. *J. Chem. Theor. Comp.* 2009, *5*, 2619-2628. (b) Titov, A. V.; Ufimtsev, Luehr, N.; S; Martínez, T. J. Generating Efficient Quantum Chemistry Codes for Novel Architectures. *J. Chem. Theor. Comp.* 2013, *9*, 213-221.

(12) Grimme, S; Antony, J.; Ehrlich, S; Krieg, H. A Consistent and Accurate *ab initio* Parametrization of Density Functional Dispersion Correction (DFT-D) for the 94 Elements H-Pu. *J. Chem. Phys.* **2010**, *132*, article No. 154104.

(13) Chiappe, C.; Margari, P.; Mezzetta, A.; Pomelli, C. S.; Koutsoumpos, S.; Papamichael, M.; Giannios, P.; Moutzouris, K. Temperature Effects on the Viscosity and the Wavelength-Dependent Refractive Index of Imidazolium-Based Ionic Liquids with a Phosphorus-Containing Anion. *PhysChemChemPhys* **2017**, *19*, 8201-8209.

(14) Chiappe, C.; Pomelli, C. S.; Rajamani, S. Influence of Structural Variations in Cationic and Anionic Moieties on the Polarity of Ionic Liquids. *J. Phys Chem. B* **2011**, *115*, 9653-9661.

(15) Kundu, N. G.; Khan, M. W. Palladium-Catalysed Heteroannulation with Terminal Alkynes: a Highly Regio- and Stereoselective Synthesis of (*Z*)-3-Aryl(alkyl)idene Isoindolin-1-ones. *Tetrahedron* **2000**, *56*, 4777-4792.

(16) Padwa, A.; Chiacchio, U.; Fairfax, D. J.; Kassir, J. M.; Litrico, A.; Semones, M. A.; Xu, S. L. A Comparative Study of the Decomposition of *o*-Alkynyl-Substituted Aryl Diazo Ketones. Synthesis of Polysubstituted Beta-Naphthols via Arylketene Intermediates. *J. Org. Chem.* **1993**, *58*, 6429-6437.

(17) Fei, X.-D.; Ge, Z.-Y.; Tang, T.; Zhu, Y.-M.; Ji, S.-J. Palladium-Catalyzed Synthesis of Isocoumarins and Phthalides via *tert*-Butyl Isocyanide Insertion. *J. Org. Chem.* **2012**, *77*, 10321-10328.

(18) Lácová, M.; Chovancová, J.; Veverková, E.; Toma, S. Microwaves Assisted Gabriel Synthesis of Phthalides. *Tetrahedron* **1996**, *52*, 14995-15006.

(19) Shao, C.; Lu, A.; Wang, A.; Zhou, B.; Guan, X.; Zhang, Y. Oxalic Acid as the *in situ* Carbon Monoxide Generator in Palladium-Catalyzed Hydroxycarbonylation of Arylhalides. *Org. Biomol. Chem.* **2017**, *15*, 5033-5040.

(20) Zhang, M.; Zhang, H.-J.; Han, T.; Ruan, W.; Wen, T.-B. Rh(III)-Catalyzed Oxidative Coupling of Benzoic Acids with Geminal-Substituted Vinyl Acetates: Synthesis of 3-Substituted Isocoumarins. *J. Org. Chem.* , *80*, 620-627.

(21) (a) Liao, H.-Y.; Cheng, C.-H. Synthesis of Isocoumarins from *o*-lodobenzoic Acid and Terminal Acetylenes Mediated by Palladium Complexes and Zinc Chloride. *J. Org. Chem.* **1995**, *60*, 3711-3716. (b) Yoo, W.-J.; Nguyen, T. V. Q.; Kobayashi, S. Synthesis of Isocoumarins through Three-Component Couplings of Arynes, Terminal Alkynes, and Carbon Dioxide Catalyzed by an NHC–Copper Complex. *Angew. Chem. Int. Ed.* **2014**, *53*, 10213-10217.

(22) Ogawa, Y.; Maruno, M.; Wakamatsu, T. Silver Catalyzed Cyclization of Alkynoic Acids: Efficient Synthesis of 3-Alkylidenephthalides, γ-Alkylidenebutenolides, and γ-Alkylidenebutyrolactones. *Heterocycles* **1995**, *41*, 2587-2599.