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Authors: Fabiola Curti, Matteo Tiecco, Valentina Pirovano, Raimondo Germani, Alessandro Caselli, Elisabetta Rossi, and Giorgio Abbiati

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FULL PAPER

p-TSA-Based DESs as "Active Green Solvents" for Microwave Enhanced Cyclization of 2-Alkynyl-(hetero)-arylcarboxylates: an Alternative Access to 6-Substituted 3,4-Fused 2-Pyranones

Fabiola Curti,[a] Matteo Tiecco,[b] Valentina Pirovano,[a] Raimondo Germani,[c] Alessandro Caselli,[d] Elisabetta Rossi[a] and Giorgio Abbiati*[a]

Abstract: In this paper, we describe the use of *p*-TSA based Deep Eutectic Solvents (DESs) as alternative environmental-friendly "active" solvents for the microwave-mediated synthesis of 6-substituted 3,4-fused 2-pyranones, and in particular isocoumarins, starting from 2-alkynyl-(hetero)arylcarboxylates. When the alkyne terminus bears a neutral or an electron-donating group (EDG), the reactions are fast, clean and highly regioselective, to give the 6-*endo-dig* cyclization products in good to excellent yields. For substrates bearing an electron-withdrawing group (EWG) on the alkyne end, the regioselectivity can be tuned by adding a small amount of silver(I) triflate as co-catalyst. DES was demonstrated to be reusable without loss of efficiency in terms of reaction yields. Based on experimental evidences and previous findings, two competitive mechanisms working simultaneously are proposed to explain the outcomes and the regioselectivity issues.

Introduction

In the area of sustainability, the development of green alternative solvents for chemical transformation is a topic of growing interest in both the research community and the chemical industry, [1] due to the increasing awareness about the impact of common organic solvents on water and air pollution, energy consumption, and climate change. Water,[2] fluorinated solvents,[3] supercritical carbon dioxide[4] and biomass derived solvents (e.g., limonene, [5] glycerol, [6] 2-methyloxolane[7]) have been proposed as possible alternatives to conventional organic solvents, displaying positive and negative points, and confirming the statement of Roger Sheldon: "*the best solvent is (still, Ed.) no-solvent*". [8] In this context, the deep eutectic solvents[9] (DESs) represent a family of media suitable for organic synthesis, [10] characterized by quite low melting points, low vapor pressures and chemical-physical properties similar to the close relatives and more extensively studied ionic liquids[11] (ILs). However, with respect to ILs, DESs are less expensive, more biodegradable, and less-or-non toxic. [12] DESs are typically prepared by blending quaternary onium salts (ammonium[13] or phosphonium[14]) with hydroxylated compounds able to act as hydrogen bonds donors, such as alcohols, phenols, polyols, carbohydrates, but also carboxylic acids[15] and sulfonic acids.[16] The strong interaction between the hydrogen-bond donor and the hydrogen-bond acceptor, namely the anion of the quaternary salt, is responsible for the reduction of the melting point of the eutectic mixture.[9] As well highlighted in a couple of recent reviews,[17] in the last decade the use of DESs as alternative media for organic transformations has been far explored, due to their particular features and to their "greenness", mainly related to a very low or absent volatility, a low flammability and interesting reuse and recycling capabilities. Depending on the nature of reaction studied, DESs can act as simple innocent polar solvents, as reagents, or as catalysts.[17] In this context, very recently we prepared some optically active DESs that disclosed a promising active role as chiral organocatalysts.[18] DESs have been used as reagents in additions reactions and in the synthesis of nitrogen containing heterocycles; as catalysts for redox transformations, esterifications, cyclisations and multicomponent processes; as innocent polar solvents in alkylations, condensations, organometallic transformation and also bioorganic reactions.[17] However, there are only sporadic reports on cyclization or cycloisomerisation reactions involving an addition of an oxygen/nitrogen nucleophile on a triple bond in DESs, and in the few cases reported an additional metal catalysts is ever required. For example, Garcia-Alvarez and co-workers studied the Au(I) catalyzed cycloisomerisation of γ-alkynoic acids,[19] γ-alkynoic amides[20] and (*Z*)-2-en-4-yn-1-ols[21] in *ChCl/U* (choline chloride/urea) or *ChCl/Gly* (choline chloride/glycerol) eutectic mixtures to give the corresponding five-membered heterocycles. Recently, an analogous study on γ-alkynoic acid derivatives has been performed under PdO-Fe_3O_4 catalysis in water and *ChCl/U* DES. [22] A similar Pd catalyzed approach in *ChCl/Gly* DES, starting from 1-mercapto-3-yn-2-ols

[a] Dr Fabiola Curti, Dr Valentina Pirovano, Prof Elisabetta Rossi, Prof Giorgio Abbiati
Dipartimento di Scienze Farmaceutiche, Sezione di Chimica Generale e Organica "Alessandro Marchesini"
Università degli Studi di Milano
Via Venezian 21 – 20133 Milano – Italy
e-mail: giorgio.abbiati@unimi.it
https://orcid.org/0000-0002-2502-4127
[b] Dr Matteo Tiecco
Dipartimento di Farmacia
Università di Chieti-Pescara "G. D'Annunzio"
Via dei Vestini 31 – 66100 Chieti – Italy
[c] Prof Raimondo Germani
Dipartimento di Chimica, Biologia e Biotecnologie
Università di Perugia
Via Elce di Sotto 8 – 06123 Perugia – Italy
[d] Prof Alessandro Caselli
Dipartimento di Chimica
Università degli Studi di Milano
Via Golgi 19 – 20133 Milano – Italy

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to give the corresponding thiophene derivatives, has been recently reported by Mancuso, Gabriele and co-workers.[23] Also some MCRs of terminal alkynes, aldehydes and (hydroxyl)amines for the synthesis of five-membered heterocycles in DESs have been documented, catalyzed by $CuFeO_2$ nanoparticles or NCS/NaOH.[24] Nevertheless, to the best of our knowledge, no examples have been already reported regarding the synthesis of 2-pyranone scaffold in DESs.

2-Pyranone is the unsaturated lactone moiety of different important fused heterocycles, above all isocoumarins. Substituted isocoumarins [25] are a class of molecules that display a number of different biological activities.[26] In particular, 3-substituted isocoumarins represent the most plentiful class of naturally occurring isocoumarins. The cyclization of 2-alkynyl benzoic acids or esters represents an interesting strategy for the construction of the isocoumarin nucleus. Different approaches have been reported, involving Brønsted acid catalysis,[27] the presence of additional electrophile[28] and LA/TM catalysis.[29] Moreover, some approach to isocoumarins by domino coupling/annulation sequences starting from *o*-halobenzoic acid/esters and terminal alkynes[30] or by CH bond-activation/annulation sequence starting from benzoic acids and internal alkynes[31] have been described.

For many years, we have been interested in the study of new valuable approaches for the synthesis of oxygen containing heterocycles starting from alkyne derivatives.[32] In this context, we recently reported a AgOTf/*p*-TSA co-catalyzed synthesis of 3,4-fused 2-pyranones, mainly isocoumarins, starting from 2-alkynyl-(hetero)arylcarboxylates characterized by mild reaction conditions, high yields and selectivity, low catalysts loading.[33] In particular we fine-tuned the composition of the catalytic system and we found that the optimal ratio between the silver salt and the acidic catalyst with respect to starting material was 1 mol% and 30 mol%, respectively.

Well aware that an acidic environment is determinant for a successful cyclization of 2-alkynyl-(hetero)arylcarboxylates,[33] we were intrigued to explore the possibility to carry out our approach by using acidic DESs as active, alternative and environmental-friendly media. Our venture was well-grounded, so we report here our findings.

Results and Discussion

Methyl 2-(*p*-tolylethynyl)benzoate **1a** was chosen as model substrate to screen among different DESs and to optimize the reaction conditions (Table 1). We tried the reaction in six DESs characterized by the presence of different acidic partner: glycolic acid (pKa = 3.8)/trimethylglycine (*Gly/TMG*);[15b] (+)-mandelic acid (pKa = 3.9)/trimethylglycine (*Man/TMG*);[15b] benzoic acid (pK_a = 4.2)/trimethylglycine (*Benz/TMG*);[15b] 2-chlorobenzoic acid(pK_a = 2.9)/trimethylglycine (*2-Cl-Benz/TMG*);[15b] phenylacetic acid (pK_a = 4.3)/octadecyldimethylamine-*N*-oxide (*PhAA/AO-18*);[15c] *p*-toluensulfonic acid (pK_a = -1.3) monohydrate/benzyl-trimethylammonium mesylate (*PTSA/BTMAMes*).[16b] Based on our previous findings,[33] the reactions were performed in the presence of a catalytic amount of silver triflate (1 mol%) and by heating the reaction mixture at 60 °C by traditional conductive heat transfer (Table 1, entries 1-6). The progress of the reactions was monitored by TLC analysis. Only the reaction in the DES with the strong *p*-TSA · H_2O as acidic component gave after 22 h the desired product **2a** in very good yield (Table 1, entry 6), whereas DESs with weaker acidic partners completely failed, and the starting materials were quantitatively recovered (Table 1, entries 1-5). Therefore, under the same reaction conditions we explored the behavior of three other *p*-TSA monohydrate-based DESs characterized by the presence of different ammonium salts partners,[16b] i.e. octyltrimethylammonium mesylate (*PTSA/OctMes*), cyclohexyltrimethylammonium mesylate (*PTSA/CyMes*), and cyclohexylammonium tosylate (*PTSA/CyTos*), (Table 1, entries 7-9). *PTSA/OctMes* and *PTSA/CyTos* gave a results comparable to *PTSA/BTMAMes* (Table 1, compare entry 6 with entries 7 and 9), while the reactions in *PTSA/CyMes* seemed to be slower (Table 1, entry 8).

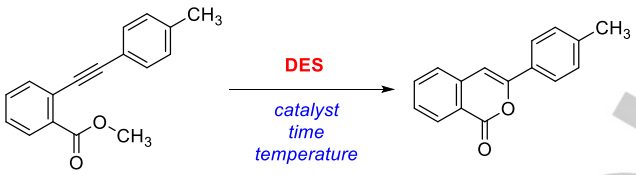
In some tries of this screening, we estimated the reaction yields by comparison of diagnostic signals of reagents and products, directly on the ^{1}H NMR spectra of crudes (obtained after a typical water/ethyl acetate work-up), because these spectra are very clean and no signals arising from possible by-products or DESs residues were observed (for an example see Supporting Info). Based on these preliminary results we selected *PTSA/BTMAMes* as media of choice to develop our investigation, because it is characterized by the lower melting point in the series (0 °C),[16b] a not excessive viscosity (75 η at 80 °C)[16b] and a fairly broad operating temperature range (about 0-100°C).

Then we tried an experiment without the silver catalyst and we were pleased to observe that he reaction worked, and gave the desired product only in slightly lower yield (Table 1, entry 10). This trend was confirmed comparing the results of the analogous reactions with and without 10 mol% of the silver catalyst in another “active” DES, i.e. *PTSA/OctMes* (Table 1, entries 11 and 12), were we also verified that an excess of metal catalyst did not produce any advantage (Table 1, compare entries 11 and 7).

Therefore, taking into account our previous findings,[33] we concluded that in the presence of a *p*-TSA based DES as acidic “active” reaction media in our model reaction, the contribution of the silver catalyst in alkyne activation is rather limited; and it has a logical explanation, taking into account that in *p*-TSA based DES, the amount of the acid is considerably higher than its content in optimized reaction conditions previously reported (i.e. 30 mol%).[33]

However, the reactions still appeared quite slow, thus to boost them we raised the reaction temperature to 90 °C under dielectric heating,[34] evaluating the optimal reaction time in four trials (Table 1, entries 13-16). Higher yields were obtained after 1 h of microwave heating (Table 1, entry 14). As a control experiment, we performed the reaction at the same temperature under conventional heating (oil bath), but comparable results in terms of reaction yield were obtained only in a six-fold longer time (Table 1, entry 17).

Table 1. Optimization of the reaction conditions.



1a **2a**

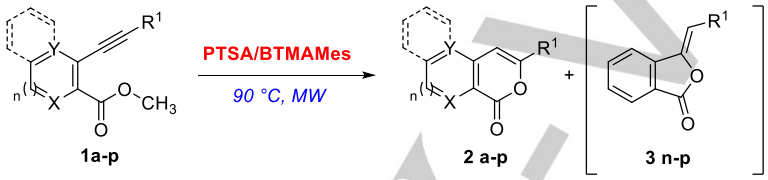
Entry	DES	Catalyst *(mol%)*	*Energy source*	*T* [°C]	*t* [h]	2a yield[a] [%]	1a rec. yield[a] [%]
1	Gly/TMG	AgOTf (1)	oil bath	60°	24	-	Quant.
2	Man/TMG	AgOTf (1)	oil bath	60°	24	-	Quant.
3	PhAA/AO-18	AgOTf (1)	oil bath	60°	23	-	Quant.
4	Benz/TMG	AgOTf (1)	oil bath	60°	26	-	Quant.
5	2-Cl-Benz/TMG	AgOTf (1)	oil bath	60°	25	-	Quant.
6	PTSA/BTMAMes	AgOTf (1)	oil bath	60°	22	88 (94) [b]	(6) [b]
7	PTSA-OctMes	AgOTf (1)	oil bath	60°	22	87 (96) [b]	(4) [b]
8	PTSA-CyMes	AgOTf (1)	oil bath	60°	29	(59) [b]	(41) [b]
9	PTSA-CyTos	AgOTf (1)	oil bath	60°	24	(87) [b]	(13) [b]
10	PTSA/BTMAMes	-	oil bath	60°	24	78	-
11	PTSA-OctMes	AgOTf (10)	oil bath	60°	25	(95) [b]	(5) [b]
12	PTSA-OctMes	-	oil bath	60°	22	(88) [b]	(12) [b]
13	PTSA/BTMAMes	-	MW	90°	2	89	-
14	PTSA/BTMAMes	-	MW	90°	1	93 (97) [b]	(3) [b]
15	PTSA/BTMAMes	-	MW	90°	0.5	87	3
16	PTSA/BTMAMes	-	MW	90°	0.25	(59) [b]	(41) [b]
17	PTSA/BTMAMes	-	oil bath	90°	6	(85) [b]	(15) [b]

[a] Yields of pure isolated product. [b] Yields estimated by comparison of characteristic signals on ^{1}H NMR spectra of clean reaction crude.

With the optimal reaction conditions in hands (Table 1, entry 14), we explored scope and limitations of the approach. We selected some methyl 2-alkynyl-(hetero)arylcarboxylate derivatives with different steric and electronic properties (**1a-p**), easily prepared by Sonogashira-Hagihara cross-coupling[35] reactions starting from methyl 2-halo-(hetero)arylcarboxylates and suitable terminal acetylenes. The results of the MW-mediated cyclization reactions of γ-alkynyl carboxylates **1a-p** in *PTSA/BTMAMes* are presented in Table 2. Overall, the approach worked very well and gave the desired isocoumarin products in good to excellent yields. As yet observed in the model reaction, the crudes displayed very clean NMR spectra after standard work-up, and a quick flash column chromatography over a short silica gel pad is enough to obtain the pure final products. The approach well tolerates the presence of electron-rich aryl groups on alkyne terminus (Table 2, entries 1-9) also if sterically hindered (Table 2, entry 3). Unprotected hydroxy and dimethylamino groups on phenyl ring are well tolerated and do not affect the reaction course (Table 2, entries 4 and 5). Also electron-rich heterocycles, such as thiophene, are allowed, giving the corresponding cyclization product in excellent yield (Table 2, entry 6). Upon modification of the core of the carboxylate moiety, 2-naphthalene carboxylate and heterocyclic carboxylates (i.e. methyl 3-(arylethynyl)thiophene-2-carboxylate and methyl 2-(arylethynyl)nicotinate), gave satisfactory results (Table 2, entries 7-9). Very good reaction yields were also obtained reacting 2-alkynylbenzoates characterized by linear or cyclic aliphatic substitution on the alkyne end (Table 2, entries 10-13), even if sterically demanding (Table 2, entry 13). Otherwise, when the alkyne terminus bears an electron-withdrawing moiety, some problems in terms of regioselectivity and reaction times were encountered (Table 2, entries 14-22). In the presence of a weak EWG (I- and M+) such as chlorine, the reaction became three times slower and a small amount of the isomeric 3-arylideneisobenzofuran-1-one **3n** was isolated beside the isocoumarin **2n**, (ratio **2n** : **3n** = 5.7 : 1), even though the overall reaction yield remained quantitative (Table 2, entry 14). Conversely, strong inductive EWG such as trifluoromethyl seriously affect the regioselectivity, and a 1.2 : 1 mixture of 6-*endo-dig* (**2o**) and 5-*exo-dig* (**3o**) cyclization products was obtained (Table 2, entry 15). Interestingly, we observe that in

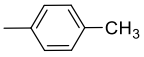
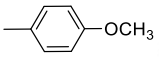
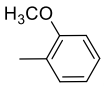
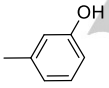
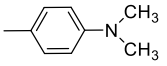
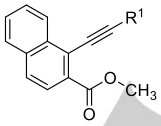
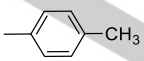
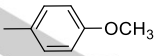
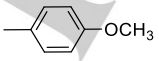
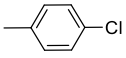
cases like these, the addition of silver triflate is surprisingly able to affect the regioselectivity in favor of the isocoumarin regioisomer **2o** (Table 2, entries 16 and 17). A fourfold improvement in the regioselectivity of cyclization of **1o** was obtained by addition of 20 mol% of silver triflate (ratio **2o** : **3o** = 4.8 : 1, Table 2, entry 17). Further increase of the amount of the catalyst did not give better result (Table 2, entry 18). A comparable, but more exasperated, behavior was observed in the reaction of alkyne **1p** characterized by the presence of a pyridine group linked to the alkyne end (Table 2, entry 19-22). In the absence of silver, even under a prolonged reaction time, the reaction gave poor results in terms of both yields and selectivity (Table 2, entries 19 and 20). The addition of 1 mol% of silver triflate shows a glimmer of improvement in both yields and selectivity (Table 2, entry 21). We forced the reaction raising the amount of metal catalyst to 35 mol%, and after 3h of dielectric heating at 90 °C we observed an improvement in the overall reaction yield (83%) beside only a modest increase of regioselectivity (ratio **2p** : **3p** = 1.9 : 1) (Table 2, entry 22). Despite these last results are rather modest, it is worth to note that in our previous protocol for the synthesis of isocoumarins, the presence of a pyridine ring was not tolerated at all, and both the reactions of substrates **1i** and **1p** were completely unsuccessful.[33]

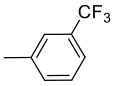
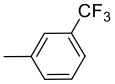
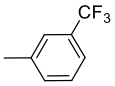
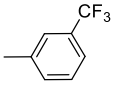
Table 2. Scope and limitations of the approach.



1a-p **2 a-p** **3 n-p**

X = C, S; Y = N; n = 0,1; R^1 = Alk, Ar, Het.

Entry	1	n	X	Y	R^1	Catalyst [mol-%]	*t* [h]	2 yield[a] [%]	3 yield[a] [%]	Overall yield [%]
1	a	1	C	C		-	1	**2a** (93)	-	93
2	b	1	C	C		-	1	**2b** (100)	-	100
3	c	1	C	C		-	1	**2c** (93)	-	93
4	d	1	C	C		-	1	**2d** (74)	-	74
5	e	1	C	C		-	1	**2e** (85)	-	85
6	f	1	C	C		-	1	**2f** (92)		92
7	g					-	5	**2g** (88)	-	88
8	h	0	S	C		-	1	**2h** (87)	-	87
9	i	1	C	N		-	1	**2i** (91)	-	91
10	j	1	C	C		-	1	**2j** (78)	-	78
11	k	1	C	C		-	1	**2k** (80)	-	80
12	l	1	C	C		-	1	**2l** (94)	-	94
13	m	1	C	C		-	1	**2m** (94)	-	94
14	n	1	C	C		-	3	**2n** (85)	**3n** (15)	100

15	**o**	1	C	C		-	3	**2o** (47)	**3o** (38)	85
16	**o**	1	C	C		AgOTf (5)	3	**2o** (56)	**3o** (31)	87
17	**o**	1	C	C		AgOTf (20)	3	**2o** (77)	**3o** (16)	92
18	**o**	1	C	C		AgOTf (30)	3	**2o** (75)	**3o** (17)	93
19	**p**	**p**	1	C		-	3	**2p** (8)	**3p** (38)	46[b]
20	**p**	**p**	1	C		-	6	**2p** (8)	**3p** (42)	50[c]
21	**p**	**p**	1	C		AgOTf (1)	3	**2p** (16)	**3p** (50)	66[d]
22	**p**	**p**	1	C		AgOTf (35)	3	**2p** (54)	**3p** (29)	83[e]

[a] Yields of pure isolated product. [b] 42% starting material recovered. [c] 40% starting material recovered. [d] 27% starting material recovered. [e] 8% starting material recovered.

In order to test the possibility to reuse DESs, a recycling trial was carried out on the model compound **1a** in *PTSA/BTMA-Mes*. The reaction was performed under our optimized MW-enhanced conditions, and after the usual work-up the aqueous layer was evaporated under reduced pressure to recover the DES, then it was reused for a new cycle of the same reaction. This cycle was successfully repeated three times providing the desired product **2a** in very good yields, ranging from 92 to 98% (Figure 1).

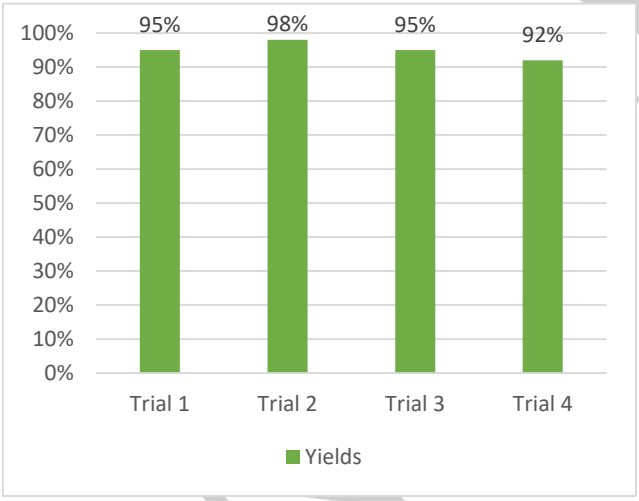


Figure 1. Reuse trials of PTSA/BTMA-Mes in the reaction with substrate 1a under optimized conditions (yields calculated via ^{1}H NMR with CH_2Br_2 as internal standard).

In terms of yields, the results obtained during the recycling stages are high and comparable with that obtained using freshly prepared DES. Nevertheless, at each cycle a little amount of DES was lost due to some difficulties in the quantitative recovery of the medium on a semi-micro laboratory scale.

It is common knowledge that the regioselectivity of such cyclization reactions are a critical issue. A simple remind to Baldwin rules[36] suggests that both *5-exo-dig* and 6-*endo-dig* cyclization modes are allowed. Some years ago, an outstanding study on a simple model substrate revealed that in the absence of metal catalysts or additional electrophiles an alkaline environment promotes the 5-*exo-dig* cyclization mode, whereas the 6-*endo-dig* cyclization mode is favored by acidic conditions.[37] Due to the nature of the DES used as medium, in our reaction conditions the cyclization surely occur in an acid environment, nevertheless we observed in some cases the formation of the five terms cyclization products - but only in the presence of a EWG on alkyne terminus. It has been documented that in this type of cyclization, the 6-*endo-dig* mode is favored by the formation of a benzopyrylium cation intermediate stabilized by resonance.[38] On the other hand, the key reaction is an intramolecular nucleophilic addition of a carbonyl oxygen to a triple bond, thus we envisaged that the presence of groups with particular electronic features on the alkyne can disrupting its electronic arrangement (Figure 2). In particular, a conjugated EWG can affect the electronic density of the alkyne by increasing the positive character (so the electrophilicity) of the α-carbon, thus supporting the competitive nucleophilic attach on this carbon, resulting in the formation of the *5-exo-dig* cyclization product (Figure 2).

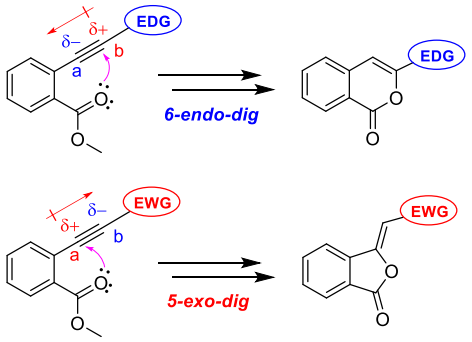


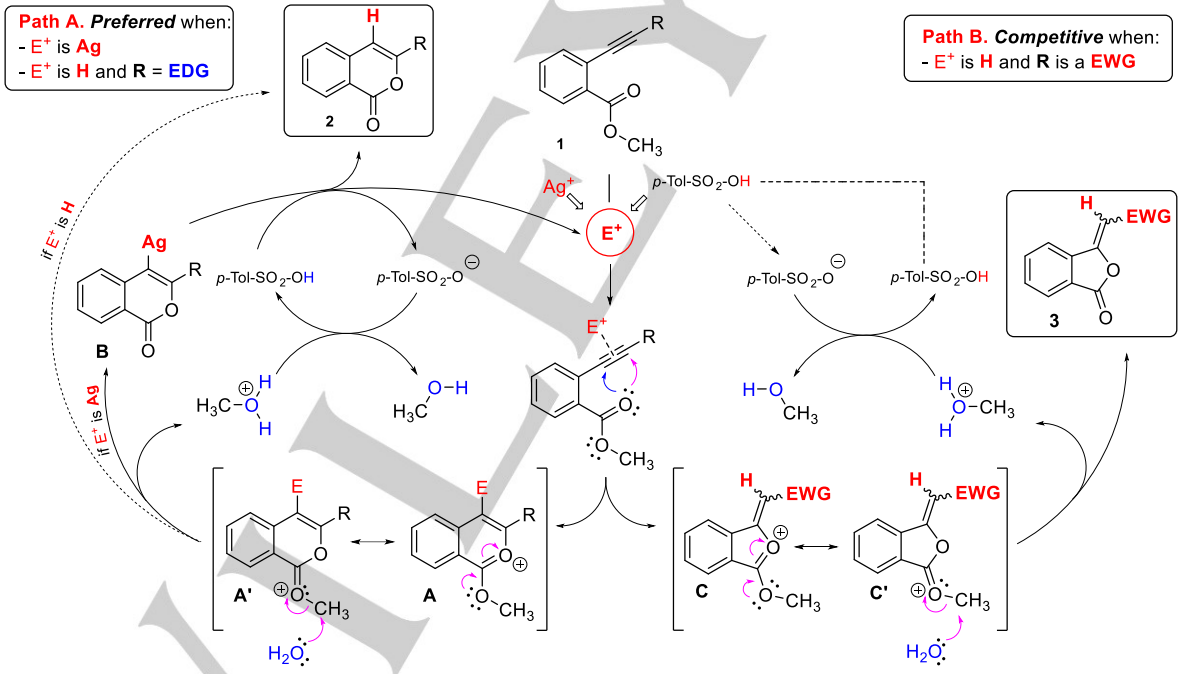
Figure 2.

These observations evidence the reasons why the selectivity of this type of reactions is still a challenging topic. Based on these considerations, the experimental evidences and our previous findings,[33] we envisaged that two competitive reaction mechanisms could be involved in this transformation, as described in Scheme 1. Irrespective to its nature, the role of the electrophile (H^+ or Ag^+) is always the activation of the alkyne.

Alkynes with neutral or electron-donating substituents can be activated by H^+ (or Ag^+, as demonstrated in our recent work) and undergo a selective 6-*endo-dig* intramolecular nucleophilic attack from the carbonyl oxygen with formation of an isochromenylium cation (**A, A'**), stabilized by resonance.[38] Then, the water present in the DESs mixtures (also due to the use of *p*-TSA · H_2O) removes the methyl group from intermediate **A'** to give a molecule of protonated methanol as by-product[39] and an adduct that depends from the nature of the electrophile: when E^+ is H^+ the desired product **2** is directly obtained, whereas when E^+ is Ag^+, the silver σ-complex **B** is obtained as intermediate, and the final product **2** is achieved only after the acid mediated protodemetallation (Scheme 1, path A).

Otherwise, when E^+ is H^+ and the alkyne terminus has an EWG, we suggest a competitive path in which H^+ activates the alkyne and direct binds the more electron-rich position β, whereas the nucleophile attaches the more electron-poor position α, with consequent formation of the regioisomeric 3-arylideneisobenzofuran-1-one **3** (Scheme 1, path B).

The reason why silver cation, irrespective to the electronic nature of alkyne substituents, always prefer to bind the α carbon of the triple bond, so enhancing the selectivity of the cyclization, has not yet been clarified.



Scheme 1. Proposed mechanism.

Conclusions

We reported herein the first example of use of an acidic DES as green "active solvent" for the microwave promoted cyclization of 2-alkynyl-(hetero)arylcarboxylates. The active role of the solvent, due to presence of *p*-TSA and water, is a vital feature for the success of this approach. The reactions proceed in a fast and clean fashion, yielding the cyclization products in good to excellent yields. When the starting alkyne is substituted with a neutral or electron-donating group the reaction yields regioselectively the isocoumarin-type products. Notably, the reactions were successful also in the presence of challenging

moieties such as pyridine, phenols, *N,N*-disubstituted anilines and sterically demanding substituents. On the other hand, in the presence of electron-withdrawing groups on the alkyne end, a certain amount of the regioisomeric isobenzofuranone-type cyclization products are isolated beside the desired isocoumarin-type products. Interestingly the regioselectivity toward the *6-endo-dig* cyclization products can be increased by adding silver triflate as co-catalyst. With the aim to elucidate the outcomes and the regioselectivity questions, two competitive mechanistic paths have been proposed, on the basis of experimental evidences and previous findings. Compared to traditional methodologies for the synthesis of isocoumarins and fused 2-pyranones, the proposed procedure is characterized by a high degree of sustainability and noteworthy advantages from environmental point of view: the use of a non-toxic, not-flammable and non-volatile "active" medium, the cleanness of the reactions in reduced times, the cheapness and reusability of the solvent.

Experimental Section

General experimental details: All the reactions, that involve the use of reagents sensitive to oxygen or hydrolysis, were carried out under inert atmosphere. The glassware was previously dried in an oven at 110 °C and set with cycles of vacuum and nitrogen. Also syringes, used to transfer reagents and solvents, were previously set under nitrogen atmosphere. All chemicals and conventional solvents are commercially available and were used without further purification. The chromatographic column separations were performed by flash technique, using silica gel (pore size 60Å, particle size 230-400 mesh, Merck Grade 9385). For thin-layer chromatography (TLC), Silica on TLC Alu foils with fluorescent indicator (254 nm) was employed and the detection was performed by irradiation with UV light (λ = 254 nm and/or 366 nm). ^{1}H NMR analysis were performed with 300 MHz spectrometers at room temperature. ^{13}C NMR analysis were performed with the same instruments at 75 MHz; APT sequence was used to distinguish the methine and methyl carbon signals from those arising from methylene and quaternary carbon atoms. All ^{13}C NMR spectra were recorded with complete proton decoupling. Low resolution MS spectra were recorded with an electrospray/ion trap instrument, using a syringe pump device to directly inject sample solutions. The values are expressed as mass-charge ratio and the relative intensities of the most significant peaks are shown in brackets. Microwave enhanced reactions were performed with the single-mode microwave synthesizer "Biotage® Initiator Classic".

Synthesis of DESs: DESs were prepared following the procedures reported in our previous papers.[15, 16] In particular the DES selected as solvent of choice for this study, *PTSA/BTMAMes*, was prepared as follow: equimolar amounts of benzyl-trimethylammonium mesylate and *p*-toluenesulfonic acid monohydrate were mixed in a screw-capped vial. The solid mixture was magnetically stirred and heated at 60 °C for 20-60 mins, until a clear colourless liquid was obtained. Than it was used without further purifications.

General procedure for the synthesis of methyl 2-halo(hetero)arylcarboxylates. The proper 2-haloarylcarboxylic acid (1 eq.) was dissolved in methanol. To this stirred reaction mixture, concentrated sulfuric acid (12.4 eq.) was very slowly added dropwise. The reaction mixture was stirred at reflux until no more starting product was detected by TLC analysis. The mixture was cooled to r.t. and concentrated under reduced pressure. The residue was diluted with EtOAc and the organic layer is washed three times with saturated aqueous $NaHCO_3$. The organic phase was dried over Na_2SO_4, filtered and the solvent removed under reduced pressure.

Methyl 2-iodobenzoate. 2-iodobenzoic acid (2.00 g, 8.06 mmol), methanol (40 mL), H_2SO_4 conc. (5.3 mL). Reaction time: 2 h. Colorless oil. Yield: 96 % (2.04 g). **^{1}H-NMR** (300 MHz, $CDCl_3$): δ = 7.99 (d, *J* = 7.9 Hz, 1H, arom.), 7.80 (d, *J* = 7.4 Hz, 1H, arom.), 7.40 (t, *J* = 7.5 Hz, 1H, arom.), 7.15 (t, *J* = 7.4 Hz, 1H, arom.), 3.93 (s, 3H, -OCH_3). Spectral are in good agreement with literature values.[40]

Methyl 3-bromothiophene-2-carboxylate. 3-bromo-2-thiophencarboxylic acid (1.00 g, 4.83 mmol), methanol (24 mL, 122 eq.), H_2SO_4 conc. (3.3 mL). Reaction time: 5.5 h. White solid. Yield: 100 % (2.13 g). **^{1}H-NMR** (300 MHz, $CDCl_3$): δ = 7.47 (d, *J* = 5.2 Hz, 1H, arom.), 7.10 (d, *J* = 5.2 Hz, 1H, arom.), 3.90 (s, 3H, -OCH_3). Spectral are in good agreement with literature values.[33]

Methyl 1-bromo-2-naphthoate. 1-bromo-2-naphtoic acid (1.00 g, 3.98 mmol), methanol (20 mL, 122 eq.) and sulfuric acid (2.6 mL). Reaction time: 5 h. Pale yellow solid. Yield: 98 % (1.30 g). **^{1}H-NMR** (300 MHz, $CDCl_3$): δ = 8.46 (d, *J* = 8.3 Hz, 1H, arom.), 7.84 (dd, *J* = 5.2, 3.6 Hz, 2H, arom.), 7.70–7.55 (m, *J* = 8.3 Hz, 3H, arom.), 4.00 (s, 3H, -OCH_3). Spectral are in good agreement with literature values.[41]

Methyl-2-bromonicotinate was purchased from commercial suppliers and used as received.

Synthesis of ((4-chlorophenyl)ethynyl)trimethylsilane. Under a nitrogen atmosphere, to a stirred solution of 4-chloro-iodobenzene (1 g, 4.19 mmol) in anhydrous TEA (17 mL), trimethylsilylacetylene (49.4 mg, 5.03 mmol) and *trans*-dichlorobis-(triphenylphosphine)palladium(II) (59 mg, 0.08 mmol) were added. The reaction was stirred at r.t. for 10 min, then CuI (8 mg, 0.04 mmol) was added. The reaction mixture was stirred at 50 °C until no more starting product was detected by TLC analysis (16 h). The reaction mixture was filtered on celite and the solvent was removed at reduced pressure. The crude material was purified by flash chromatography over silica gel (eluent: hexane) to yield the desired product (822 mg) as an orange oil. Yield: 94 %. **^{1}H-NMR** (300 MHz, $CDCl_3$): δ = 7.39 (d, *J* = 8.4 Hz, 2H, arom.), 7.27 (d, *J* = 8.4 Hz, 2H, arom.), 0.24 (s, 9H, -$Si(CH_3)_3$). Spectral data are in good agreement with literature values.[42]

Synthesis of 1-chloro-4-ethynylbenzene. ((4-chlorophenyl)ethynyl)-trimethylsilane (818 mg, 3.91 mmol) was dissolved in methanol (24 mL), and to the stirred solution solid K_2CO_3 (1.08 g, 7.83 mmol) was added. The reaction mixture was stirred at r.t. until no more starting material was detected by TLC analysis (1 h). The reaction mixture was then concentrated under reduced pressure. The residue was diluted with water and extracted with EtOAc for three times. The reunited organic layers were dried over Na_2SO_4, filtered and the solvent removed at reduced pressure, yielding the desired product (534 mg) as white solid. Yield: 72 %. **^{1}H-NMR** (300 MHz, $CDCl_3$): δ = 7.45–7.39 (m, 2H, arom.), 7.34–7.27 (m, 2H, arom.), 3.11 (s, 1H, -CH- sp). Spectral data are in good agreement with literature values.[43]

General procedure for the synthesis of methyl 2-alkynyl(hetero)arylcarboxylates (**1a-p**). ***Method A.*** Under a nitrogen atmosphere, to a stirred solution of the proper methyl-2-haloarylcarboxylate (1 eq.) in anhydrous TEA (≈ 0.25 M), the appropriate alkyne (1.2 eq.) and *trans*-dichlorobis-(triphenylphosphine)palladium(II) (2 mol%) was added. The reaction was stirred at r.t. for 15 min, then CuI (1 mol%) was added. The suspension was stirred at 50°C until no more

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starting product was detected by TLC analysis. The reaction mixture was filtered on celite and the solvent was removed under reduced pressure. Crude material was purified by flash column chromatography over silica gel. ***Method B.*** Under a nitrogen atmosphere, to a stirred solution of the proper methyl-2-haloarylcarboxylate (1 eq.) in anhydrous DMF (≈ 0.25 M) the appropriate alkyne (1.2 eq.), *trans*-dichlorobis-(triphenylphosphine)palladium(II) (2 mol%) and K_2CO_3 (5 eq.) were added. The reaction was stirred at r.t. for 15 min, then CuI (1 mol%) was added. The reaction mixture was stirred at 50°C until no more starting product was detected by TLC analysis. The suspension was diluted with water and extracted for three times with EtOAc. The organic layer was dried on Na_2SO_4 and then evaporated under reduced pressure. The crude material was purified by flash column chromatography over silica gel.

Methyl 2-(*p*-tolylethynyl)benzoate (1a). Method A. Methyl-2-iodobenzoate (300 mg, 1.14 mmol) in anhydrous TEA (4.5 mL), 1-ethynyl-4-methylbenzene (160 mg, 1.37 mmol), *trans*-dichlorobis-(triphenylphosphine)palladium(II) (16 mg, 0.02 mmol) and CuI (2.18 mg, 0.01 mmol). Reaction time: 1.5 h. Eluent for chromatography: hexane/EtOAc 9:1. Colorless oil. Yield: 285 mg (100 %). **^{1}H-NMR** (300 MHz, $CDCl_3$): δ = 7.97 (dd, *J* = 7.8, 1.4 Hz, 1H, arom.), 7.64 (dd, *J* = 7.8, 1.3 Hz, 1H, arom.), 7.49 (dd, *J* = 12.0, 4.7 Hz, 3H, arom.), 7.37 (td, *J* = 7.6, 1.4 Hz, 1H, arom.), 7.17 (d, *J* = 7.8 Hz, 2H, arom.), 3.96 (s, 3H, -OCH_3), 2.38 (s, 3H, -CH_3). Spectral data are in good agreement with literature values.[44]

Methyl 2-((4-methoxyphenyl)ethynyl)benzoate (1b). Method A. Methyl-2-iodobenzoate (200 mg, 0.76 mmol) in anhydrous TEA (3 mL), alkyne 1-ethynyl-4-methoxybenzene (120 mg, 0.91 mmol), *trans*-dichlorobis-(triphenylphosphine)palladium(II) (10.7 mg, 0.01 mmol) and CuI (1.45 mg, 0.007 mmol). Reaction time: 3 h. Eluent for chromatography: hexane/EtOAc 9:1. Colorless oil. Yield: 240 mg (99 %).**^{1}H-NMR** (300 MHz, $CDCl_3$): δ = 7.96 (d, *J* = 7.8 Hz, 1H, arom.), 7.62 (d, *J* = 7.7 Hz, 1H, arom.), 7.49 (dd, *J* = 16.3, 8.1 Hz, 3H, arom.), 7.35 (t, *J* = 7.6 Hz, 1H, arom.), 6.89 (d, *J* = 8.5 Hz, 2H, arom.), 3.96 (s, 3H, -$COOCH_3$), 3.83 (s, 3H, -OCH_3). Spectral data are in good agreement with literature values.[45]

Methyl 2-((2-methoxyphenyl)ethynyl)benzoate (1c). Method A. Methyl-2-iodobenzoate (150 mg, 0.57 mmol) in anhydrous TEA (2.5 mL), 1-ethynyl-2-methoxybenzene (90.4 mg, 0.68 mmol), *trans*-dichlorobis-(triphenylphosphine)palladium(II) (8 mg, 0.01 mmol) and CuI (1 mg, 0.005 mmol). Reaction time: 2.5 h. Eluent for chromatography: hexane/EtOAc 9:1. Yellow oil. Yield: 150 mg (99 %). **^{1}H-NMR** (300 MHz, $CDCl_3$): δ = 7.97 (dd, *J* = 7.8, 1.3 Hz, 1H, arom.), 7.68 (dd, *J* = 7.8, 1.2 Hz, 1H, arom.), 7.55 (dd, *J* = 7.6, 1.7 Hz, 1H, arom.), 7.48 (td, *J* = 7.6, 1.4 Hz, 1H, arom.), 7.41–7.27 (m, 2H, arom.), 6.95 (td, *J* = 16.3, 4.8 Hz, 2H, arom.), 3.97 (s, 3H, -$COOCH_3$), 3.93 (s, 3H, -OCH_3). Spectral data are in good agreement with literature values.[46]

Methyl 2-((2-hydroxyphenyl)ethynyl)benzoate (1d). Method A. Methyl-2-iodobenzoate (200 mg, 0.76 mmol) in anhydrous TEA (3 mL), 3-ethynylphenol (107.5 mg, 0.91 mmol), *trans*-dichlorobis-(triphenylphosphine)palladium(II) (10.71 mg, 0.01 mmol) and CuI (1.45 mg, 0.007 mmol). Reaction time: 1 h. Eluent for chromatography: hexane/EtOAc 3:1. Orange solid. Yield: 186 mg (97 %). **^{1}H-NMR** (300 MHz, $CDCl_3$): δ = 7.97 (dd, *J* = 7.9, 0.6 Hz, 1H, arom.), 7.64 (d, *J* = 7.7 Hz, 1H, arom.), 7.49 (td, *J* = 7.3, 0.9 Hz, 1H, arom.), 7.44–7.34 (m, 1H, arom.), 7.21 (t, *J* = 7.8 Hz, 1H, arom.), 7.14 (d, *J* = 7.6 Hz, 1H, arom.), 7.05 (s, 1H, arom.), 6.84 (dd, *J* = 7.9, 2.5 Hz, 1H, arom.), 5.25 (s, 1H, -OH), 3.96 (s, 3H, -OCH_3). Spectral data are in good agreement with literature values.[33]

Methyl 2-((4-(dimethylamino)phenyl)ethynyl)benzoate (1e). Method B. Methyl-2-iodobenzoate (200 mg, 0.76 mmol) in anhydrous DMF (3 mL), alkyne *N,N*-dimethyl-4-(prop-1-yn-1-yl)aniline (133 mg, 0.91 mmol), *trans*-dichlorobis-(triphenylphosphine)palladium(II) (10.71 mg, 0.0152 mmol), K_2CO_3 (497 mg, 3.81 mmol) and CuI (1.45 mg, 0.007 mmol). Reaction time: 4 h. Eluent for chromatography: hexane/EtOAc 9:1. Yellow oil. Yield: 208 mg (98 %). **^{1}H-NMR** (300 MHz, $CDCl_3$): δ = 7.94 (dd, *J* = 7.9, 1.1 Hz, 1H, arom.), 7.60 (dd, *J* = 6.4, 2.4 Hz, 1H, arom.), 7.49–7.42 (m, 3H, arom.), 7.31 (td, *J* = 7.7, 1.3 Hz, 1H, arom.), 6.67 (d, *J* = 8.9 Hz, 2H, arom.), 3.97 (s, 3H, -OCH_3), 3.00 (s, 6H, -$N(CH_3)_2$). Spectral data are in good agreement with literature values.[47]

Methyl 2-(thiophen-3-ylethynyl)benzoate (1f). Method A. Methyl-2-iodobenzoate (200 mg, 0.76 mmol) in anhydrous TEA (3 mL), 3-ethynylthiophene (99 mg, 0.91 mmol), *trans*-dichlorobis-(triphenylphosphine)palladium(II) (10.71 mg, 0.02 mmol) and CuI (1.45 mg, 0.007 mmol). Reaction time: 3 h. Eluent for chromatography: hexane/EtOAc 95:5. Yellow oil. Yield: 184 mg (100 %). **^{1}H-**NMR (300 MHz, $CDCl_3$): δ = 7.97 (d, *J* = 7.8 Hz, 1H, arom.), 7.63 (d, *J* = 7.7 Hz, 1H, arom.), 7.59–7.55 (m, 1H, arom.), 7.49 (td, *J* = 7.6, 1.2 Hz, 1H, arom.), 7.38 (td, *J* = 7.8, 1.1 Hz, 1H, arom.), 7.31 (dd, *J* = 4.9, 3.0 Hz, 1H, arom.), 7.24 (dd, *J* = 5.0, 0.8 Hz, 1H, arom.), 3.96 (s, 3H, -OCH_3). Spectral data are in good agreement with literature values.[28c]

Methyl 1-(*p*-tolylethynyl)-2-naphthoate (1g). Method A. Methyl 1-bromo-2-naphthoate (170 mg, 0.64 mmol) in anhydrous TEA (2.5 mL), 1-ethynyl-4-methylbenzene (89.4 mg, 0.76 mmol), *trans*-dichlorobis-(triphenylphosphine)palladium(II) (9 mg, 0.01 mmol) and CuI (1 mg, 0.007 mmol). Reaction time: 5 h. Eluent for chromatography: hexane/EtOAc 9:1. Orange oil. Yield 134 mg (69 %). **^{1}H-NMR** (300 MHz, $CDCl_3$): δ = 8.67 (ddd, *J* = 2.9, 1.5, 0.8 Hz, 1H, arom.), 7.99 (d, *J* = 8.7 Hz, 1H, arom.), 7.91–7.80 (m, 2H, arom.), 7.69–7.56 (m, 4H, arom.), 7.23 (d, *J* = 7.8 Hz, 2H, arom.), 4.03 (s, 3H, -OCH_3), 2.41 (s, 3H, -CH_3). **^{13}C-NMR** (75 MHz, $CDCl_3$): δ = 167.3 (C=O), 139.0 (C arom.), 134.5 (C arom.), 133.4 (C arom.), 131.7 (CH arom.), 130.2 (C arom.), 129.2 (CH arom.), 128.1 (CH arom.), 127.9 (CH arom.), 127.7 (CH arom.), 127.4 (CH arom.), 125.9 (CH arom.), 122.6 (C arom.), 120.4 (C arom.), 101.2 (C *sp*), 85.5 (C *sp*), 52.2 (-OCH_3), 21.6 (-CH_3) one signal obscured. **MS** ESI (+): *m/z* (%) = 323.3 $[M+Na]^+$ (100), 301.3 $[M+H]^+$ (87); $C_{21}H_{16}O_2$ [300.35]. Anal. Calcd for $C_{21}H_{16}O_2$: C, 83.98; H, 5.37. Found: C, 83.86; H, 5.34.

Methyl 3-((4-methoxyphenyl)ethynyl)thiophene-2-carboxylate (1h). Method A. Methyl 3-bromotiophene-2-carboxylate (200 mg, 0.90 mmol) in anhydrous TEA (4 mL), 1-ethynyl-4-methoxybenzene (131 mg, 1.00 mmol), *trans*-dichlorobis-(triphenylphosphine)palladium(II) (13 mg, 0.02 mmol) and CuI (1.7 mg, 0.009 mmol). Reaction time: 8.0 h. Eluent for chromatography: hexane/EtOAc 9:1. Yellow solid. Yield 208 mg (85%). **^{1}H-NMR** (300 MHz, $CDCl_3$): δ = 7.5 (d, *J* = 8.6 Hz, 2H, arom.), 7.47 (d, *J* = 5.1 Hz, 1H, arom.), 7.32 (d, *J* = 8.6 Hz, 2H, arom.), 7.19 (d, *J* = 5.1 Hz, 1H, arom.), 3.93 (s, 3H, -OCH_3). Spectral data are in good agreement with literature values.[48]

Methyl 2-((4-methoxyphenyl)ethynyl)nicotinate (1i). Method A. Methyl-2-bromonicotinate (200 mg, 0.75 mmol) in anhydrous TEA (3 mL), 1-ethynyl-4-methoxybenzene (120 mg, 0.90 mmol), *trans*-dichlorobis-(triphenylphosphine)palladium(II) (10.6 mg, 0.01 mmol) and CuI (1.45 mg, 0.007 mmol). Reaction time: 16 h. Eluent for chromatography: hexane/EtOAc 7:3. Orange oil. Yield: 200 mg (100%). **^{1}H-NMR** (300 MHz, $CDCl_3$): δ = 8.73 (dd, *J* = 4.8, 1.8 Hz, 1H, arom.), 8.27 (dd, *J* = 8.0, 1.8 Hz, 1H, arom.), 7.61 (d, *J* = 8.9 Hz, 2H, arom.), 7.31 (dd, *J* = 8.0, 4.8 Hz, 1H, arom.), 6.91 (d, *J* = 8.9 Hz, 2H, arom.), 4.00 (s, 3H, -$COOCH_3$), 3.84 (s, 3H, -OCH_3). Spectral data are in good agreement with literature values.[46]

Methyl 2-(pent-1-yn-1-yl)benzoate (1j). Method A. Methyl-2-iodobenzoate (300 mg, 1.14 mmol) in anhydrous TEA (4.6 mL), 1-pentyne (93 mg, 1.37 mmol), *trans*-dichlorobis-(triphenylphosphine)palladium(II) (16 mg, 0.02 mmol) and CuI (2.18 mg, 0.01 mmol). Reaction time: 48 h.

Eluent for chromatography: hexane/EtOAc 98:2. Colorless oil. Yield: 120 mg (52 %). **^{1}H-NMR** (300 MHz, $CDCl_3$): δ = 7.88 (dd, *J* = 7.6, 1.2 Hz, 1H, arom.), 7,51 (dd, *J* = 7.6, 1.2 Hz, 1H, arom.), 7.42 (td, *J* = 7.7, 1.5 Hz, 1H, arom.), 7.29 (td, *J* = 7.7, 1.5 Hz, 1H, arom.), 3.91 (s, 3H, -OCH_3), 2.45 (t, *J* = 7.2 Hz, 2H, -CH_2-), 1.66 (sex, *J* = 7.2 Hz, 2H, -CH_2-), 1.05 (t, *J* = 7.2 Hz, 3H, -CH_3). Spectral data are in good agreement with literature values.[49]

Methyl 2-(cyclopropylethynyl)benzoate (1k). Method A. Methyl-2-iodobenzoate (200 mg, 0.76 mmol) in anhydrous TEA (3 mL), ethynylcyclopropane (60.5 mg, 0.91 mmol), *trans*-dichlorobis-(triphenylphosphine)palladium(II) (10.71 mg, 0.02 mmol) and CuI (1.45 mg, 0.007 mmol). Reaction time: 20 h. Eluent for chromatography: hexane/EtOAc 95:5. Pale yellow oil. Yield: 152 mg (100 %). **^{1}H-NMR** (300 MHz, $CDCl_3$): δ = 7.87 (dd, *J* = 7.8, 1.4 Hz, 1H, arom.), 7.47 (dd, *J* = 7.8, 1.4 Hz, 1H, arom.), 7.39 (td, *J* = 7.6, 1.5 Hz, 1H, arom.), 7.27 (td, *J* = 7.6, 1.5 Hz, 1H, arom.), 3.90 (s, 3H, -OCH_3), 1.56–1.44 (m, 1H, -CH- sp^3), 0.96–0.79 (m, 4H, -CH_2-). Spectral data are in good agreement with literature values.[29c]

Methyl 2-(cyclopentylethynyl)benzoate (1l). Method A. Methyl-2-iodobenzoate (200 mg, 0.76 mmol) in anhydrous TEA (3 mL), ethynylcyclopentane (86.2 mg, 0.91 mmol), *trans*-dichlorobis-(triphenylphosphine)palladium(II) (10.71 mg, 0.02 mmol) and CuI (1.45 mg, 0.007 mmol). Reaction time: 20 h. Eluent for chromatography: hexane/EtOAc 95:5. Pale yellow oil. Yield 173 mg (100%). **^{1}H-NMR** (300 MHz, $CDCl_3$): δ = 7.86 (dd, J = 7.7, 1.3 Hz, 1H, arom.), 7.49 (dd, *J* = 7.7, 1.3 Hz, 1H, arom.), 7.40 (td, *J* = 7.6, 1.5 Hz, 1H, arom.), 7.29 (td, *J* = 7.6, 1.5 Hz, 1H, arom.), 3.91 (s, 3H, -OCH_3), 2.89 (quint, *J* = 7.1 Hz, 1H, -CH- sp^3), 2.08–1.95 (m, 2H, -CH_2-), 1.84–1.68 (m, 4H, -CH_2-), 1.66–1.59 (m, 2H, -CH_2-). **^{13}C-NMR** (75 MHz, $CDCl_3$): δ = 167.1 (C=O), 134.0 (CH arom.), 132.1 (C arom.), 131.3 (CH arom.), 130.1 (CH arom.), 127.0 (CH arom.), 124.5 (C arom.), 100.0 (C *sp*), 78.8 (C *sp*), 51.9 (-OCH_3), 33. 8 (-CH_2-), 31.1 (-CH-), 25.1 (-CH_2-). **MS** ESI (+): *m/z* (%) = 282.9 $[M+CH_3OH+Na]^+$(100); $C_{15}H_{16}O_2$ [228.29]. Anal. Calcd for $C_{15}H_{16}O_2$: C, 78.92; H, 7.06. Found: C, 78.77; H, 7.04.

Methyl 2-(3,3-dimethylbut-1-yn-1-yl)benzoate (1m). Method B. Methyl-2-iodobenzoate (250 mg, 0.95 mmol) in anhydrous DMF (3 mL), *N,N*-dimethyl-4-(prop-1-yn-1-yl)aniline (133 mg, 1.62 mmol, 1.7 eq.), *trans*-dichlorobis-(triphenylphosphine)palladium(II) (13.4 mg, 0.01 mmol), K_2CO_3 (621 mg, 4.77 mmol) and CuI (1.81 mg, 0.009 mmol). Reaction time: 16 h. Eluent for chromatography: hexane/EtOAc 95:5. Brown oil. Yield: 203 mg (99 %). **^{1}H-NMR** (300 MHz, $CDCl_3$): δ = 7.86 (dd, *J* = 7.8, 1.5 Hz, 1H, arom.), 7.48 (dd, *J* = 7.8, 1.4 Hz,1H, arom.), 7.40 (td, *J* = 7.6, 1.5 Hz, 1H, arom.), 7.30 (td, *J* = 7.5, 1.5 Hz, 1H, arom.), 3.92 (s, 3H, -OCH_3), 1.34 (s, 9H, -$(CH_3)_3$). Spectral data are in good agreement with literature values.[28d]

Methyl 2-((4-chlorophenyl)ethynyl)benzoate (1n). Method A. Methyl-2-iodobenzoate (200 mg, 0.76 mmol) in anhydrous TEA (3 mL), 1-chloro-4-ethynylbenzene (125 mg, 0.91 mmol), *trans*-dichlorobis-(triphenylphosphine)palladium(II) (10.7 mg, 0.01 mmol) and CuI (1.45 mg, 0.007 mmol). Reaction time: 2 h. Eluent for chromatography: hexane/EtOAc 95:5. Yellow oil. Yield: 204 mg (100 %). **^{1}H-NMR** (300 MHz, $CDCl_3$): δ = 7.99 (dd, *J* = 7.8, 1.4 Hz, 1H, arom.), 7.64 (dd, *J* = 7.7, 1.4 Hz, 1H, arom.), 7.54–7.48 (m, 3H, arom.), 7.40 (td, *J* = 7.6, 1.3 Hz, 1H, arom.), 7.34 (d, *J* = 8.4 Hz, 2H, arom.), 3.96 (s, 3H, -OCH_3). Spectral data are in good agreement with literature values.[45]

Methyl 2-((3-(trifluoromethyl)phenyl)ethynyl)benzoate (1o). Method A. Methyl-2-iodobenzoate (200 mg, 0.76 mmol) in anhydrous TEA (3 mL), 1-ethynyl-3-(trifluoromethyl)benzene (156 mg, 0.91 mmol), *trans*-dichlorobis-(triphenylphosphine)palladium(II) (10.71 mg, 0.01 mmol) and CuI (1.45 mg, 0.007 mmol). Reaction time: 1.5 h. Eluent for chromatography: hexane/EtOAc 95:5. Colorless oil. Yield: 230 mg (100 %). **^{1}H-NMR** (300 MHz, $CDCl_3$): δ = 8.01 (dd, *J* = 7.8, 0.8 Hz, 1H, arom.), 7.83 (s, 1H, arom.), 7.75 (d, *J* = 7.7 Hz, 1H, arom.), 7.66 (d, *J* = 7.7 Hz, 1H, arom.), 7.59 (d, *J* = 7.9 Hz, 1H, arom.), 7.50 (td, *J* = 11.1, 7.1 Hz, 2H, arom.), 7.42 (td, *J* = 7.7, 1.2 Hz, 1H, arom.), 3.97 (s, 3H, -OCH_3). Spectral data are in good agreement with literature values.[33]

Methyl 2-(pyridin-3-ylethynyl)benzoate (1p). Method A. Methyl-2-iodobenzoate (200 mg, 0.76 mmol) in anhydrous TEA (3 mL), 2-ethynylpyridine (94 mg, 0.91 mmol), *trans*-dichlorobis-(triphenylphosphine)palladium(II) (10.71 mg, 0.01 mmol) and CuI (1.45 mg, 0.007 mmol). Reaction time: 24 h. Eluent for chromatography: hexane/EtOAc 6:4. Yellow oil. Yield: 171 mg (95 %). **^{1}H-NMR** (300 MHz, $CDCl_3$): δ = 8.80 (s, 1H, arom.), 8.56 (dd, *J* = 4.8, 1.2 Hz, 1H, arom.), 8.00 (dd, *J* = 7.8, 1.0 Hz, 1H, arom.), 7.86 (td, *J* = 7.9, 1.8 Hz, 1H, arom.), 7.66 (dd, *J* = 7.7, 0.9 Hz, 1H, arom.), 7.52 (td, *J* = 7.6, 1.4 Hz, 1H, arom.), 7.42 (td, *J* = 7.7, 1.3 Hz, 1H, arom.), 7.30 (dd, *J* = 7.9, 4.9 Hz, 1H, arom.), 3.96 (s, 3H, -OCH_3). **^{13}C-NMR** (75 MHz, $CDCl_3$): δ = 166.4 (C=O), 152.2 (CH arom.), 148.7 (CH arom.), 138.7 (CH arom.), 134.1 (CH arom.), 131. 9 (C arom.), 131.8 (CH arom.), 130.6 (CH arom.), 128.5 (CH arom.), 123.1 (CH arom.), 123.0 (C arom.), 120.6 (C arom.), 91.5 (C *sp*), 90.7 (C *sp*), 52.3 (-OCH_3). **MS** ESI (+): *m/z* (%) = 260.3 $[M+Na]^+$ (100), 238.4 $[M+H]^+$ (89); $C_{15}H_{11}NO_2$ [237.27]. Anal. Calcd for $C_{15}H_{11}NO_2$: C, 75.94; H, 4.67; N, 5.90. Found: C, 76.10; H, 4.69; N, 5.93.

General procedure for cyclization of methyl 2-alkynyl(hetero)arylcarboxylates. ***Method A (thermal heating).*** Under a nitrogen atmosphere, the appropriate methyl 2-alkynyl(hetero)arylcarboxylate (0.18 mmol) was added to the selected DES (0.5 mL). AgOTf was added when required. The mixture was heated at 60°C by a typical oil-bath, until no more starting product was detected by TLC. Once the reaction was over, it was cooled at rt, poured into water and extracted with EtOAc for three times. The organic layers were dried over Na_2SO_4, filtered and freed from the solvent under reduced pressure. Unless other stated, the crude material was purified by flash column chromatography over silica gel. For yields, reaction times and catalyst loadings see tables 1 and 2 in the main text. ***Method B (microwave heating).*** In a microwave test tube, the appropriate methyl 2-alkynyl(hetero)arylcarboxylate (0.18 mmol) was added to the selected DES (0.5 mL). AgOTf was added when required. The mixture was heated at 90°C by microwave radiation, cooled at room temperature, poured in water (60 mL) and extracted with EtOAc (3 × 20 mL). The organic layers were dried over Na_2SO_4, filtered and freed from the solvent under reduced pressure. Unless other stated, the crude material was purified by flash column chromatography over silica gel. For yields, reaction times and catalyst loadings see tables 1 and 2 in the main text.

3-(*p*-Tolyl)-*1H*-isochromen-1-one (2a). Eluent for chromatography: hexane/EtOAc 9:1. White solid. **^{1}H-NMR** (300 MHz, $CDCl_3$): δ = 8.29 (dd, *J* = 8.1, 0.7 Hz, 1H, arom.), 7.76 (d, *J* = 8.3 Hz, 2H, arom.), 7.69 (td, *J* = 7.4, 1.3 Hz, 1H, arom.), 7.49–7.44 (m, 2H, arom.), 7.26 (d, *J* = 7.9 Hz, 3H, arom.), 6.89 (s, 1H, -CH_2- sp^2), 2.40 (s, 3H, -CH_3). Spectral data are in good agreement with literature values.[33]

3-(4-Methoxyphenyl)-*1H*-isochromen-1-one (2b). Eluent for chromatography: hexane/EtOAc 9:1. White solid. **^{1}H-NMR** (300 MHz, $CDCl_3$): δ = 8.27 (d, *J* = 8.4 Hz, 1H, arom.), 7.84–7.77 (m, 2H, arom.), 7.68 (td, *J* = 7.4, 1.3 Hz, 1H, arom.), 7.49–7.40 (m, 2H, arom.), 6.96 (d, *J* = 9.0 Hz, 2H, arom.), 6.82 (s, 1H, -CH- sp^2), 3.86 (s, 3H, -OCH_3). Spectral data are in good agreement with literature values.[33]

3-(2-methoxyphenyl)-*1H*-isochromen-1-one (2c). Eluent for chromatography: hexane/EtOAc 9:1. White solid. **^{1}H-NMR** (300 MHz,

$CDCl_3$): δ = 8.31 (dd, *J* = 7.8, 0.6 Hz, 1H, arom.), 7.98 (dd, *J* = 7.9, 1.7 Hz, 1H, arom.), 7.70–7.68 (m, 1H, arom.), 7.51–7.43 (m, 2H, arom.), 7.41–7.32 (m, 1H, arom. + -CH- sp^2), 7.07 (td, *J* = 7.6, 1.1 Hz, 1H, arom.), 7.03 (d, *J* = 8.3 Hz, 1H, arom.), 3.97 (s, 3H, $-OCH_3$). Spectral data are in good agreement with literature values.[33]

3-(3-hydroxyphenyl)-*1H*-isochromen-1-one (2d). Eluent for chromatography: hexane/EtOAc 6:4. Dark-red solid. **^{1}H-NMR** (300 MHz, d_6-acetone): δ = 8.64 (s, 1H, -OH), 8.22 (dd, *J* = 7.9, 0.6 Hz, 1H, arom.), 7.89–7.75 (m, 1H, arom.), 7.68 (d, *J* = 7.7 Hz, 1H, arom.), 7.63–7.53 (m, 1H, arom.), 7.45–7.39 (m, 2H, arom.), 7.35 (dd, *J* = 11.7, 4.5 Hz, 1H, arom.), 7.28 (s, 1H, -CH- sp^2), 7.00–6.91 (m, 1H, arom.). Spectral data are in good agreement with literature values.[33]

3-(4-(Dimethylamino)phenyl)-*1H*-isochromen-1-one (2e). Eluent for chromatography: hexane/EtOAc 8:2. Yellow solid. **^{1}H-NMR** (300 MHz, $CDCl_3$): δ = 8.26 (d, *J* = 7.7 Hz, 1H, arom.), 7.76 (d, *J* = 9.1 Hz, 2H, arom.), 7.63 (m, 1H, arom.), 7.43–7.37 (m, 2H, arom.), 6.73 (m, 3H, 2 arom. + -CH- sp^2), 3.03 (s, 6H, $-N(CH_3)_2$). Spectral data are in good agreement with literature values.[30d]

3-(thiophen-3-yl)-*1H*-isochromen-1-one (2f). Eluent for chromatography: hexane/EtOAc 9:1. White solid. **^{1}H-NMR** (300 MHz, $CDCl_3$): δ = 8.30 (d, *J* = 7.4 Hz, 1H, arom.), 7.89 (dd, *J* = 2.9, 1.3 Hz, 1H, arom.), 7.72 (td, *J* = 7.7, 1.3 Hz, 1H, arom.), 7.55–7.37 (m, 4H, arom.), 6.79 (s, 1H, -CH- sp^2). Spectral data are in good agreement with literature values.[33]

2-(*p*-Tolyl)-*4H*-benzo[f]isochromen-4-one (2g). Eluent for chromatography: hexane/EtOAc 9:1. Yellow solid. mp 187.7-188.8 °C. **^{1}H-NMR** (300 MHz, $CDCl_3$): δ = 8.39 (d, *J* = 8.6 Hz, 1H, arom.), 8.21 (d, *J* = 8.7 Hz, 1H, arom.), 7.96–7.78 (m, 4H, arom.), 7.75–7.64 (m, 2H, arom.), 7.62 (s, 1H, -CH- sp^2), 7.29 (d, *J* = 8.0 Hz, 2H, arom.), 2.42 (s, 3H, $-CH_3$). **^{13}C-NMR** (75 MHz, $CDCl_3$): δ = 162.7 (C=O), 155.1 (C arom.), 140.6 (C arom.), 136.9 (C arom.), 136.0 (C arom.), 129.6 (CH arom.), 129.32 (C arom.), 129.27 (CH arom.), 128.9 (CH arom.), 128.1 (CH arom.), 127.8 (C arom.), 127.2 (CH arom.), 125.4 (CH arom.), 124.2 (CH arom.), 124.0 (CH arom.), 117.3 (C arom.), 96.7 (CH sp^2), 21.4 ($-CH_3$). **MS ESI (+):** m/z (%) = 287.5 $[M+1]^+$ (100); $C_{20}H_{14}O_2$ [286.33]. Anal. Calcd for $C_{20}H_{14}O_2$: C, 83.90; H, 4.93. Found: C, 83.71; H, 4.90.

5-(4-Methoxyphenyl)-*7H*-thieno[2,3-c]pyran-7-one (2h). Eluent for chromatography: hexane/EtOAc 8:2. Pale green solid. **^{1}H-NMR** (300 MHz, $CDCl_3$): δ = 7.85–7.77 (m, 3H, arom.), 7.20 (d, *J* = 5.1 Hz, 1H, arom.), 7.01 (s, 1H, -CH- sp^2), 6.97 (d, *J* = 9.0 Hz, 2H, arom.), 3.87 (s, 3H, $-OCH_3$). Spectral data are in good agreement with literature values.[33]

7-(4-Methoxyphenyl)-*5H*-pyrano[4,3-b]pyridin-5-one (2i). Eluent for chromatography: hexane/EtOAc 1:1. Yellow solid. **^{1}H-NMR** (300 MHz, $CDCl_3$): δ = 8.88 (dd, *J* = 4.7, 1.8 Hz, 1H, arom.), 8.53-8.39 (m, 1H, arom.), 7.83 (d, *J* = 9.0 Hz, 2H, arom.), 7.35 (dd, *J* = 8.0, 4.7 Hz, 1H, arom.), 7.07 (s, 1H, -CH- sp^2), 6.97 (d, *J* = 9.0 Hz, 2H, arom.), 3.85 (s, 3H, $-OCH_3$). Spectral data are in good agreement with literature values.[45]

3-Propyl-*1H*-isochromen-1-one (2j). Eluent for chromatography: hexane/EtOAc 95:5. Colorless oil. **^{1}H-NMR** (300 MHz, $CDCl_3$): δ = 8.26 (d, *J* = 7.9 Hz, 1H, arom.), 7.68 (td, *J* = 7.9, 1.2 Hz, 1H, arom.), 7.45 (td, *J* = 7.8, 0.8 Hz, 1H, arom.), 7.36 (d, *J* = 7.8 Hz, 1H, arom.), 6.27 (s, 1H, -CH- sp^2), 2.51 (t, *J* = 7.5 Hz, 2H, $-CH_2-$ sp^3), 1.75 (sex, *J* = 7.8 Hz, 2H, $-CH_2-$ sp^3), 1.00 (t, *J* = 7.4 Hz, 3H, $-CH_3$). Spectral data are in good agreement with literature values.[33]

3-cyclopropyl-*1H*-isochromen-1-one (2k). Eluent for chromatography: hexane/EtOAc 9:1. Colorless oil. **^{1}H-NMR** (300 MHz, $CDCl_3$): δ = 8.19 (ddd, *J* = 8.0, 1.3, 0.7 Hz, 1H, arom.), 7.63 (td, *J* = 7.7, 1.4 Hz, 1H, arom.), 7.38 (ddd, *J* = 8.0, 7.4, 1.2 Hz, 1H, arom.), 7.30 (d, *J* = 7.9 Hz, 1H, arom.), 6.28 (s, 1H, -CH- sp^2), 1.79 (tt, *J* = 8.3, 8.3, 5.1, 5.1 Hz,1H, -CH- sp^3), 1.09–1.01 (m, 2H, $-CH_2-$ sp^3), 0.95–0.87 (m, 2H, $-CH_2-$ sp^3). Spectral data are in good agreement with literature values.[29e]

3-Cyclopentyl-*1H*-isochromen-1-one (2l). Eluent for chromatography: hexane/EtOAc 9:1. Orange oil. **^{1}H-NMR** (300 MHz, $CDCl_3$): δ = 8.23 (d, *J* = 8.0 Hz, 1H, arom.), 7.70–7.60 (m, 1H, arom.), 7.46–7.37 (m, 1H, arom.), 7.33 (d, *J* = 7.8 Hz, 1H, arom.), 6.26 (s, 1H, -CH- sp^2), 2.91 (quint, *J* = 7.9 Hz, 1H, -CH- sp^3), 2.08–1.92 (m, 2H, $-CH_2-$ sp^3), 1.86–1.61 (m, 6H, $-CH_2-$ sp^3). Spectral data are in good agreement with literature values.[50]

3-(*tert*-Butyl)-*1H*-isochromen-1-one (2m). Eluent for chromatography: hexane/EtOAc 9:1. Pale yellow oil. **^{1}H-NMR** (300 MHz, $CDCl_3$): δ = 8.25 (d, *J* = 7.9 Hz, 1H, arom.), 7.67 (td, *J* = 7.9, 1.5 Hz, 1H, arom.), 7.45 (td, *J* = 7.8, 1.5 Hz, 1H, arom.), 7.38 (d, *J* = 7.8 Hz, 1H, arom.), 6.30 (s, 1H, -CH- sp^2), 1.33 (s, 10H, $-(CH_3)_3$). Spectral data are in good agreement with literature values.[51]

3-(4-Chlorophenyl)-*1H*-isochromen-1-one (2n) and 3-(4-chlorobenzylidene)isobenzofuran-1(*3H*)-one (3n). Eluent for chromatography: hexane/EtOAc 9:1. Compounds **2n** and **3n** were only partially separable by column chromatography. Despite a lot of different attempts with many eluent mixtures they are always isolated as mixtures. White solid. **2n: ^{1}H-NMR** (300 MHz, $CDCl_3$): δ = 8.30 (d, *J* = 7.8 Hz, 1H, arom.), 7.80 (d, *J* = 8.7 Hz, 2H, arom.), 7.71 (td, *J* = 7.6, 1.2 Hz, 1H, arom.), 7.50 (t, *J* = 7.7 Hz, 1H, arom.), 7.42 (d, *J* = 8.7 Hz, 2H, arom.), 6.92 (s, 1H, -CH- sp^2). **2n + 3n: ^{1}H-NMR** (300 MHz, $CDCl_3$): δ = 8.30 (d, *J* = 7.8 Hz, 1H, arom. of **2n**), 7.87–7.78 (m, 2H, arom. of **2n**), 7.87 (d, *J* = 7.8 Hz, 1H, arom. of **3n**), 7.73 (td, *J* = 7.6, 1.2 Hz, 1H, arom. of **2n**), 7.70 (d, *J* = 8.8 Hz, 2H, arom. of **3n**), 7.68 (m, 1H, arom. of **3n**), 7.54 (m, 1H, arom. of **3n**), 7.53 (d, *J* = 7.8 Hz, 1H, arom. of **3n**), 7.51 (t, *J* = 7.7 Hz, 2H, arom. of **2n**), 7.47–7.40 (m, 2H, arom. of **2n**), 7.30 (d, *J* = 8.8 Hz, 2H, arom. of **3n**), 6.93 (s, 1H, -CH- sp^2 of **2n**), 6.30 (s, 1H, -CH- sp^2 of **3n**). Spectral data of compounds [52] are in good agreement with literature values.

3-(3-(Trifluoromethyl)phenyl)-*1H*-isochromen-1-one (2o) and 3-(3-(trifluoromethyl)-benzylidene)isobenzofuran-1(*3H*)-one (3o). Eluent for chromatography: hexane/EtOAc 9:1. Compounds **2o** and **3o** are not separable by column chromatography. Despite a lot of different attempts with many eluent mixtures they are always isolated as mixtures. White solid. **^{1}H-NMR** (300 MHz, $CDCl_3$): δ = 8.32 (d, *J* = 8.2 Hz, 1H, arom. of **2o**), 8.12 (s, 1H, arom. of **2o**), 8.09 (m, 1H, arom. of **3o**), 8.05 (d, *J* = 7.8 Hz, 1H, arom. of **2o**), 7.96-7.93 (m, 2H, arom. of **3o**), 7.74 (m, 1H, arom. of **2o** and m, 2H, arom. of **3o**), 7.67 (d, *J* = 7.8 Hz, 1H, arom. of **2o**), 7.59 (d, *J* = 7.8 Hz, 1H, arom. of **2o**), 7.54 (m, 2H, arom. of **2o** and m, 3H, arom. of **3o**), 7.01 (s, 1H, -CH- sp^2 of **2o**), 6.41 (s, 1H, -CH- sp^2 of **3o**). **^{13}C-NMR** (75 MHz, $CDCl_3$): δ = 166.6 (C=O of **3o**), 161.8 (C=O of **2o**), 151.9 (C arom. of **2o**), 145.8 (C arom. of **3o**), 141.4 (q, $^2J(C,F)$ = 33 Hz, 1C, C-CF_3 of **2o**), 140.1 (C arom. of **3o**), 136.9 (C arom. of **2o**), 135.1 (CH arom. of **2o**), 134.6 (CH arom. of **3o**), 133.9 (C arom. of **3o**), 132.9 (CH arom. of **3o**), 132.7 (C arom. of **2o**), 131.1 (q, $^2J(C,F)$ = 32 Hz, 1C, C-CF_3 of **3o**), 130.3 (CH arom. of **3o**), 129.8 (CH arom. of **2o**), 129.5 (CH arom. of **2o**), 129.3 (CH arom. of **3o**), 128.7 (CH arom. of **2o**), 128.3 (CH arom. of **2o**), 126.5 (q, $^3J(C,F)$ = 3.9 Hz, 1C, CH-C-CF_3 of **3o**), 126.4 (q, $^3J(C,F)$ = 3.8 Hz, 1C, CH-C-CF_3 of **2o**), 126.2 (CH arom. of **2o**), 125.7 (CH arom. of **3o**), 125.6 (C, arom. of **3o**), 124.7 (q, $^3J(C,F)$ = 3.8 Hz, 1C, CH-C-CF_3 of **3o**), 122.0 (q, $^3J(C,F)$ = 3.9 Hz, 1C, CH-C-CF_3 of **2o**), 120.7 (C, arom. of **2o**), 120.3 (q, $^1J(C,F)$ = 272 Hz, 1C, CF_3 of **3o**), 120.0 (CH arom. of **3o**), 120.0 (q, $^1J(C,F)$ = 272 Hz, 1C, CF_3 of **2o**), 105.2 (-CH- sp^2 of **3o**), 102.9 (-CH- sp^2

of **2o**). The data of compound **2o** are in good agreement with literature values.[33] Compound **3o** is a new compound.

3-(Pyridin-3-yl)-*1H*-isochromen-1-one (2p) and 3-(pyridin-3-ylmethylene)isobenzofuran-1(*3H*)-one (3p). Eluent for chromatography: hexane/EtOAc 8:2. Compounds **2p** and **3p** are not separable by column chromatography. Despite a lot of different attempts with many eluent mixtures they are always isolated as mixtures. White solid. **^{1}H-NMR** (300 MHz, $CDCl_3$): δ = 9.08 (s, 1H, arom. of **2p**), 8.81 (s, 1H, arom. of **3p**), 8.63 (d, *J* = 4.2 Hz, 1H, arom. of **2p**), 8.50 (s, 1H, arom. of **3p**), 8.36 (td, *J* = 8.1, 1.6 Hz, 1H, arom. of **3p**), 8.29 (ddd, *J* = 7.9, 1.2, 0.5 Hz, 1H, arom. of **2p**), 8.16 (ddd, *J* = 8.1, 2.3, 1.6 Hz, 1H, arom. of **2p**), 7.93 (td, *J* = 7.7, 0.9 Hz, 1H, arom. of **3p**), 7.81-7.71 (m, 1H, arom. of **2p** and m, 2H, arom. of **3p**), 7.60-7.49 (m, 2H, arom. of **2p** and m, 1H, arom. of **3p**), 7.39 (dd, *J* = 4.8, 8.0 Hz, 1H, arom. of **2p**), 7.34 (dd, *J* = 4.8, 8.0 Hz, 1H, arom. of **3p**), 7.00 (s, 1H, -CH_2- *sp*^{2} of **2p**), 6.38 s, 1H, -CH_2- *sp*^{2} of **3p**). **^{13}C-NMR** (75 MHz, $CDCl_3$): 166.5 (C=O of **3p**), 161.7 (C=O of **2p**), 151.0 (C arom. of **2p**), 150.7 (CH arom. of **3p**), 150.6 (CH arom. of **2p**), 148.9 (CH arom. of **3p**), 146.5 (CH arom. of **2p**), 146.4 (CH arom. **3p**), 139.9 (C arom. of **2p**), 136.8 (C arom. of **2p**), 135.1 (CH arom. of **2p**), 134.8 (CH arom. of **3p**), 132.8 (CH arom. of **3p**), 132.6 (CH arom. of **2p**), 130.4 (CH arom. of **3p**), 129.8 (CH arom. of **2p**), 129.4 (C arom. of **3p**), 128.8 (CH arom. of **2p**), 128.0 (C arom. of **3p**), 126.2 (CH arom. of **2p**), 125.7 (CH arom. of **3p**), 123.7 (CH arom. of **3p**), 123.5 (C arom. of **3p**), 123.5 (CH arom. of **2p**), 120.8 (C arom. of **2p**), 120.0 (CH arom. of **3p**), 103.3 (-CH- *sp*^{2} of **3p**), 102.9 (-CH- *sp*^{2} of **2p**). The data of compound **2p** are in good agreement with literature values.[51] Compound **3p** is a new compound.

Recycling trials: The reactions were performed as described above (*General procedure for cyclization of methyl 2-alkynyl(hetero)arylcarboxylates. Method B-dielectric heating*). The first cycle was performed with methyl 2-(*p*-tolylethynyl)benzoate **1a** (83 mg, 0.33 mmol) in 4 mL of PTSA/BTMAMes. After usual aqueous work-up and isolation of the product **2a**, the aqueous phase containing the DES was freed from water under vacuum. The next run was performed under identical reaction conditions as reported in the following table:

Trial	**1a** (mmol, mg)	**PTSA/BTMAMes** (mL)	**Yield 2a** (%)
1	0.331, 83	4	95
2	0.328, 82	2.8	98
3	0.308, 77	2.2	95
4	0.324, 81	1.3	93

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