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p-Toluenesulfonic acid-promoted selective functionalization of unsymmetrical arylalkynes: a regioselective access to various arylketones and heterocycles

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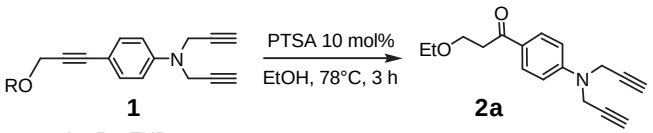
ABSTRACT

Regioselective hydration of a wide range of internal alkynes has been afforded in high to good yields by using PTSA in EtOH. The scope of the reaction of alkynes has been delineated. Arylaliphatic alkynes and diarylalkynes were regioselectively hydrated in good to excellent yields and short reaction times when the reaction was achieved under microwave irradiation. Moreover, diarylalkynes, arylenynes as well as diaryldiynes bearing a methoxy- or a thiomethyl substituent on the *ortho* position underwent a regioselective 5-*endo*-dig-cyclization to give a variety of 2-aryl- and 2-styrylbenzofuran or benzothiophene derivatives. We believe that, this new environmentally metal-free procedure combined to microwave irradiation would be in importance in the search of green laboratory-scale synthesis.

1. Introduction

The hydration of alkynes is an important tool to construct a carbon–oxygen bond,[1] and provides a direct access to carbonyl compounds with a perfect atom economy. Historically, this reaction was described by Kucherov since 1881,[2] and required the use of mercury(II) salts. The necessity of strongly acidic conditions however, associated to the use of stoichiometric amounts of toxic mercury salts had always been an inherent problem of the process, making this reaction unsuitable for modern applications. In recent years, numerous attempts have been made to develop non-mercury alkyne hydration methodology. To this end, transition-metal complex catalysts including Au,[3] Ru,[4] Ir,[5] Rh,[6] Pt,[7] and Pd[8] have been employed with varying degrees of success, but the use of high loading of expensive transition-metal catalysts limits the exploitation of these methods. Beside enzymatic hydration of alkynes,[9] metal-free procedures using a catalytic Brønsted acid such as TfOH or Tf_2NH[10] or concentrated H_2SO_4,[11] or HCO_2H[12] have been reported. While these latter hydration reactions are suitable in the case of robust substrates, they are limited to terminal alkynes and are not applicable for oxygenated alkynes[12] where the triple bond remained absolutely inert.

As part of our research program directed to a selective functionalization of unsymmetrically disubstituted alkynes,[13] we had to investigate the tetrahydropyranyl/ether cleavage of **1a** in EtOH under *p*-toluenesulfonic acid (PTSA) conditions.[14] Contrary to our expectations, the reaction did not afford **1b**. We serendipitously found that, besides the THP/ether cleavage, the internal carbon–carbon triple bond of **1a** was hydrated together with a concomitant etherification to give regioselectively **2a** as the only product in a 90% yield. Under these conditions, performing the reaction from **1b** assisted both etherification of free hydroxyl group and carbonyl formation, producing **2a** in an excellent 94% isolated yield. One can note that in both cases, the hydration reaction is chemoselective, as it occurred exclusively on the internal carbon–carbon triple bond keeping terminal alkynes unchanged (Scheme 1).



1

1a: R = THP
1b: R = H

2a

Scheme 1.

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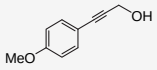
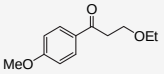
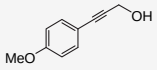
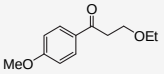
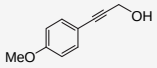
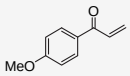
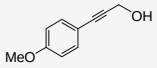
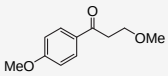
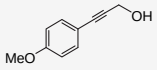
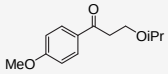
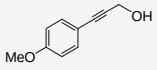
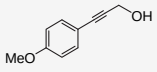
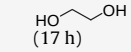
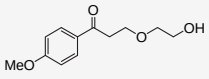
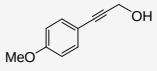
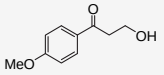
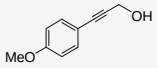
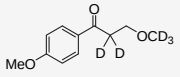
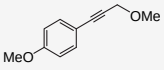
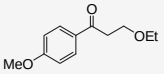
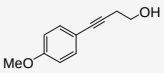
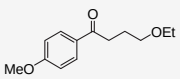
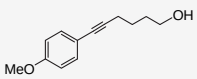
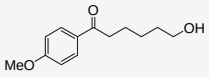
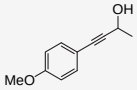
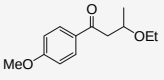
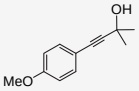
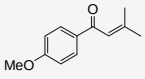
Because the discovery of metal-free alkynes hydration procedures remain as an intriguing challenge, the above observations led us to experiment the PTSA/alcohol system as a new and regioselective access to carbonyl compounds. Herein we wish to detail our results with a variety of unsymmetrical internal alkynes including, aliphatic arylalkynes or alkynols, diarylalkynes, 1,3-enynes and 1,3-diynes.

2. Results and discussion

2.1. Hydration/etherification of aliphatic arylalkynols[15]

The required alkynols **1c–h** were readily prepared by Sonogashira/Linstrumelle (S/L) coupling reactions.[16] The reactivity of model alkyne **1c** was first examined in the presence of different Brønsted acids and solvents; the results are listed in Table 1. Thus,

Table 1
Screening of catalysts and solvents for hydration of 4-methoxyphenyl alkynols **1c–h**

Entry	Alkyne **1**		Catalyst (20 mol %)	ROH (time)		Ketone **2**	Yield[a] (%)
1		**1c**	PTSA	EtOH (5 h)	**2b**		94
2		**1c**	$MeSO_3H$	EtOH (5 h)	**2b**		85
3		**1c**	CF_3SO_3H[b]	EtOH (5 h)	**3a**		60
4		**1c**	PTSA	MeOH (6 h)	**2c**		98
5		**1c**	PTSA	^{i}PrOH (7 h)	**2d**		66
6		**1c**	PTSA	^{t}BuOH (24 h)		—	0
7		**1c**	PTSA	 (17 h)	**2e**		33
8		**1c**	PTSA	H_2O (10 h)	**2f**		79
9		**1c**	PTSA	CD_3OD (5 h)	***D*-2c**		96
10		**1d**	PTSA	EtOH (8 h)	**2b**		90
11		**1e**	PTSA	EtOH (24 h)	**2g**		85
12		**1f**	PTSA	EtOH (36 h)	**2h**		90
13		**1g**	PTSA	EtOH (24 h)	**2i**		91
14		**1h**	PTSA	EtOH (10 h)	**3b**		73

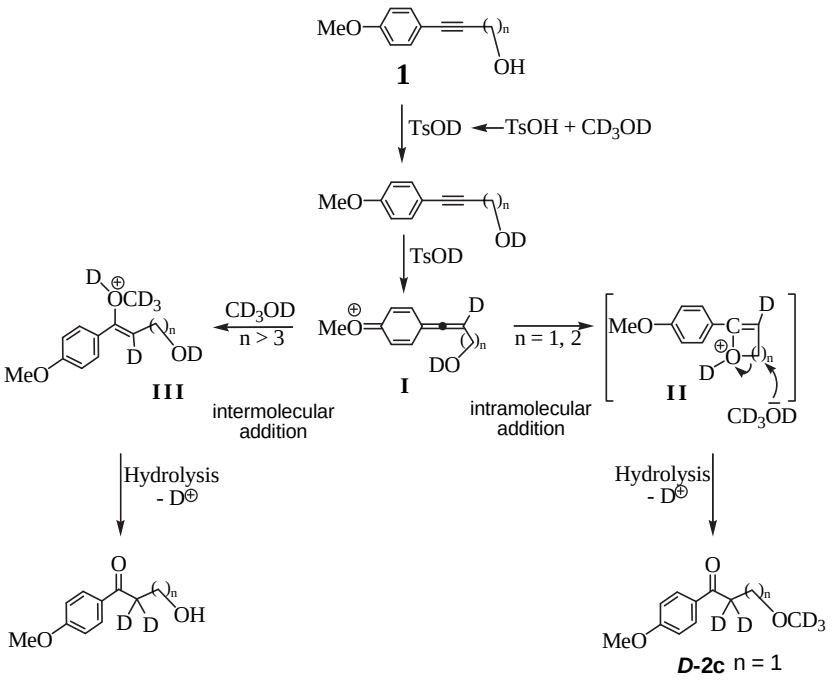
[a] Isolated yield.
[b] 30 mol % of catalyst were used.

reaction of **1c** with PTSA or $MeSO_3H$ (20 mol %) in refluxing EtOH for 5 h provides **2b** resulting from a regioselective hydration and etherification of the free alcohol (entries 1 and 2). It is noteworthy that enone **3a** was formed when CF_3SO_3H was used as catalyst (entry 3, 60%). All of the other tested catalytic systems (H_2SO_4, CF_3COOH, HCO_2H) were unsuccessful, and in better cases, yields in hydration products **2** were not satisfactory (e.g., HCOOH, 50%, data not shown). The influence of the solvent was next examined with **1c** and PTSA (entries 4–9). The hydration and etherification of **1c** occurred efficiently in refluxing MeOH (entry 4) yielding **2c** in 98%. The process was slower and less effective in ^{i}PrOH or 1,2-ethyleneglycol (entries 5 and 7) whereas, in ^{t}BuOH no reaction occurred, even after a prolonged reaction time (entry 6). Interestingly, when the hydration was performed in refluxing water for 10 h, the triple bond was regioselectively hydrated giving ketone **2f** with a free-alcohol function in a 79% yield (entry 8). Carrying out the reaction with **1c** in CD_3OD as a solvent, besides a deuterated methylether formed, a quantitative deuterium incorporation on the α-carbon of the keto group was observed yielding ***D*-2c** (entry 9, 96%).

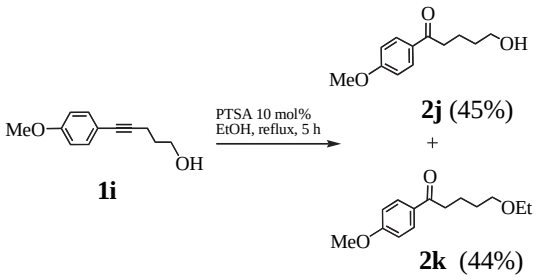
Next, the PTSA/EtOH system was used for the hydration of alkyne **1d** bearing a methylether function. In this case, **1d** also underwent hydration of the triple bond together with a *trans*-etherification reaction by the solvent resulting in a 90% yield of the ethylether carbonyl compound **2b** (entry 10). Finally, the influence of alkynol chains on the hydration/etherification process was investigated. As shown in entry 11, compound **1e** bearing on the aromatic ring a butyn-4-ol chain, was transformed into the expected ketone **2g** in a good yield but with a prolonged reaction time (24 h). Similarly, hydration of alkyne **1f** having on the aromatic nucleus a hexyn-6-ol chain was still effective (entry 12). In this case, no etherification of the hydroxyl group occurred and **2h** with a free-alcohol function was isolated in a good 90% yield. Reaction from arylalkyne **1g** having a secondary propargylic alcohol function provided the expected carbonyl ether **2i** (91%, entry 13). Under these conditions, tertiary propargyl alcohol **1h** leads in 73% yield to the corresponding conjugated ketone **3b**, well known as the Rupe's rearrangement[17] adduct (entry 14).

2.2. Mechanism of PTSA-catalyzed hydration and etherification of arylalkynols in CD_3OD

The formation of arylketones **2** is believed to proceed initially through a deuterium exchange between CD_3OD and PTSA followed by acidic deuterium activation of the triple bond as outline in Scheme 2. The intermediate species of type **I** should evolve according to an intra or an intermolecular addition process depending on the longer alkynol chains. With substrates having a propyn-3-ol or a butyn-4-ol chain (**1c**; n=1 or **1e**; n=2) the reaction would evolved according to an intramolecular oxygen atom-addition to provide a four or a five membered cyclic oxonium intermediate **II**. Nucleophilic ring opening with CD_3OD and subsequent hydrolysis regenerated the catalyst and produced a deuterated enol intermediate immediately rearranged to the corresponding keto tautomer ***D*-2c** (entry 9, Table 1). From substrate **1f** having longer alkynol chain (n=4, entry 12, Table 1), direct alcoholic media addition[7c,18] on **I** is preferred in comparison with thermodynamically disfavored seven-membered cyclic oxonium intermediate formation, keeping free the hydroxyl group. As a check on our mechanistic interpretation, we also examined hydration of a substrate **1i** bearing a pentyl-5-ol chain (n=3). Under the same reaction conditions, hydration of **1i** evolved according to the two routes to give a mixture of alcohol **2j** and ether **2k** (Scheme 3).



Scheme 2. Mechanism proposed for PTSA-catalyzed hydration of alkynols in CD_3OD.

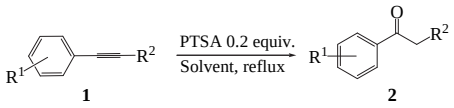


Scheme 3. Hydration of alkynol **1i**.

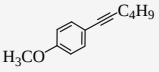
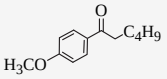
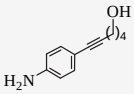
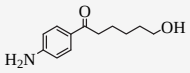
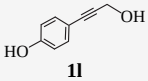
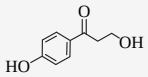
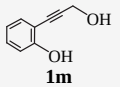
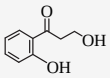
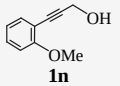
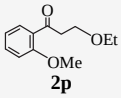
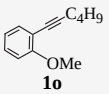
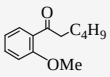
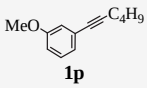
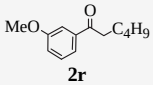
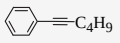
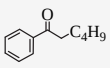
2.3. Hydration of aliphatic arylalkynes

The scope of this PTSA-catalyzed hydration reaction was next investigated with several arylalkyne substrates and the results of this study are summarized in Table 2.

Table 2
PTSA catalyzed synthesis of various arylketones **2**

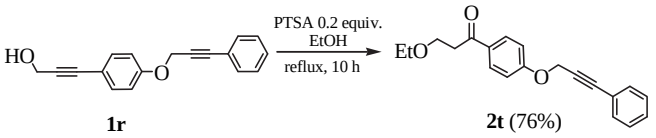


1 **2**

Entry	Alkyne **1**	ROH (reflux) Time	Ketone **2**	Yield[a] (%)
1	 **1j**	EtOH 60 h	 **2l**	90
2	 **1k**	EtOH 6 h	 **2m**	78[b]
3	 **1l**	H_2O 8 h	 **2n**	79
4	 **1m**	H_2O 12 h	 **2o**	73
5	 **1n**	EtOH 144 h	 **2p**	73
6	 **1o**	EtOH 144 h	 **2q**	80[c]
7	 **1p**	EtOH 144 h	 **2r**	0
8	 **1q**	EtOH 72 h	 **2s**	0

[a] Isolated yield.
[b] When the reaction was achieved with the corresponding *ortho*-NH_2 derivative, 12 h were required to give the ketone with a modest 30% yield.
[c] 1.2 equiv of PTSA were used.

Arylalkyne **1j** bearing a hexynyl side chain was successfully hydrated (entry 1, 90%) but 60 h were required for complete conversion. Next, other *p*-electron-donating groups on the aromatic ring were evaluated to assist the hydration process. As shown in entries 2 and 3, a *para* NH_2 and a *para*-OH substituents on the aromatic ring activated the triple bond, as suggested in the mechanism, and the corresponding ketones **2m** and **2n** were obtained in EtOH or H_2O in good yields. On switching the electron-donating OH-group from the *para* to the *ortho* position on the aromatic nucleus, the hydration in H_2O was still efficient but required a prolonged reaction time (compare entries 3 and 4, Table 2). In refluxing EtOH, *ortho* anisole alkyne derivatives **1n** and **1o** reacted smoothly to give arylketones **2p** and **2q**. In this latter case, 1.2 equiv of PTSA were necessary to achieve the complete hydration of the alkyne substrate **1o** (entry 6). However, in agreement with the proposed mechanism, *meta* anisole derivative **1p** as well as non-substituted arylalkyne **1q** did not react under the above experimental conditions, even with stoechiometric amount of PTSA and prolonged reaction times. In these cases, starting arylalkynes were recovered unchanged (entries 7 and 8). These findings were illustrated with the selective hydration of alkyne **1r** having two carbon–cabon triple bonds. As expected, besides the etherification of the free-alcohol function by the solvent, only the activated triple bond underwent the hydration reaction leading to **2t** in 76% yield (Scheme 4).



1r **2t** (76%)

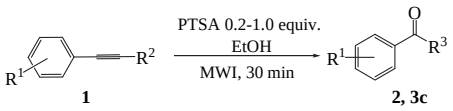
Scheme 4. Selectivity in triple bond hydration of **1r**.

To circumvent the low reactivity of *ortho*-substituted arylalkynes and the lack of reactivity of non-substituted arylalkynes as well as *meta*-substituted derivatives, we envisioned to use microwave irradiation (MWI)[19] that could enhance this process and expand the substrate scope. Moreover, with cooperative *para*-substituted arylalkynes, the use of MWI should accelerate the rate of this hydration reaction.

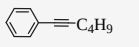
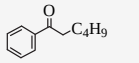
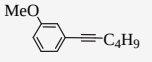
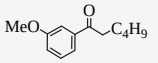
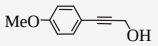
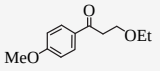
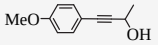
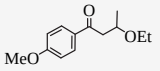
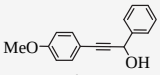
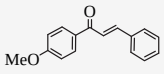
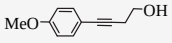
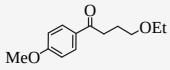
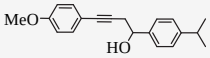
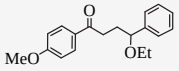
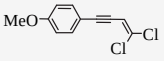
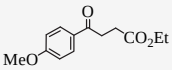
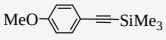
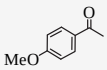
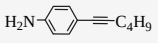
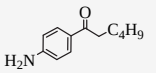
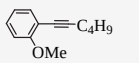
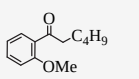
Initial efforts focused on optimizing microwave conditions for the formation of **2s** from **1q**. After screening the quantity of PTSA, temperature and reaction time, we found that complete conversion of **1q** required the use of PTSA (1 equiv) in EtOH, for 30 min at 170 °C under MWI to give **2s** in 89% yield (entry 1, Table 3). Performing the reaction at a lower temperature (120 °C or 150 °C) or using a catalytic amount of PTSA (20 mol %) resulted in lower yields of **2s** (15–35%, data not shown). The optimized reaction conditions found for **1q** were applied to *meta* substituted arylalkyne **1p**, which was transformed into **2r** within 30 min in a satisfactory 60% yield (entry 2, Table 3). To evaluate the significant benefit of MWI, model arylalkyne **1c** with a cooperative *para* methoxy substituent was heated in EtOH and PTSA (0.2 equiv) at different temperatures. The best result was obtained when **1c** was heated at 120 °C for 30 min under MWI (entry 3, 98%). Similarly, we have applied this protocol to various arylalkynes. In most cases studied, hydration and etherification process successfully occurred (entries 3, 4, 6, and 7), except with secondary propargylic alcohol **1s** (entry 5) where the Rupe's rearrangement predominated to give the conjugated ketone **3c**. With 1,1-dichloroenyne **1u**, beside the triple bond hydration, alcoholysis of the carbon–chlorine bonds occurred to produce the ketoester **2v** in a 51% isolated yield (entry 8). Silylated arylalkyne **1v** reacted well and furnished 4-methoxyacetophenone **2w** in 77% yield (entry 9). Replacing the 4-methoxy by a 4-NH_2 substituent has no deleterious effect on this acidic hydration process and ketone **2x** was obtained in a 91% yield (entry 10) Finally hydration of *ortho* methoxyarylalkyne **1o** successfully occurred within only 1 h at 170 °C (entry 11), whereas under conventional heating (entry 6 Table 2) 144 h were required to complete the hydration of the alkyne substrate.

The PTSA-assisted hydration of unsymmetrical diarylalkynes **4a–f** under MWI was next evaluated (Table 4, entries 1–6). By using 1.2 equiv of PTSA at 120 °C in EtOH, diarylalkyne **4a** was regioselectively hydrated within 30 min (entry 1, 97%). As shown in entry 2, the presence of a bromine atom was tolerated and ketone **5b** was regioselectively obtained in a nearly quantitative yield (entry 2, 98%). Diarylalkynes **4c** and **4d**, bearing respectively a methyl and a NH_2-substituent on the aromatic rings reacted smoothly under the previous conditions (120 °C). After some trials, we were pleased

Table 3
PTSA-promoted hydration of arylalkynes **1** under MWI



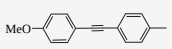
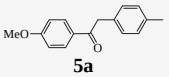
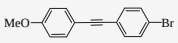
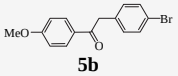
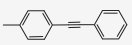
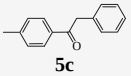
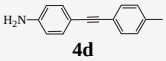
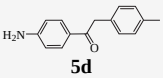
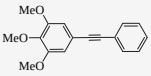
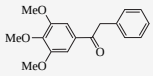
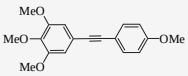
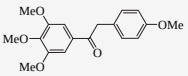
1 **2, 3c**

Entry	Alkyne **1**	PTSA (equiv) Temp	Ketone **2**	Yield[a] (%)
1	 **1q**	(1.0) 170 °C	 **2s**	89
2	 **1p**	(1.0) 170 °C	 **2r**	60
3	 **1c**	(0.2) 120 °C	 **2b**	98
4	 **1g**	(0.2) 120 °C	 **2i**	51[b]
5	 **1s**	(0.2) 120 °C	 **3c**	90
6	 **1e**	(0.2) 120 °C	 **2g**	79
7	 **1t**	(0.2) 120 °C	 **2u**	69
8	 **1u**	(0.2) 120 °C	 **2v**	51
9	 **1v**	(0.2) 120 °C	 **2w**	77
10	 **1w**	(0.2) 120 °C	 **2x**	91
11	 **1o**	(1.0) 170 °C	 **2q**	60

[a] Isolated yield.
[b] 27% of conjugated ketone (Rupe's rearrangement) was also isolated.

to observe the total conversion of these substrates into the corresponding ketones **5c** and **5d** within 30 min using 1.0 equiv of PTSA under microwave heating at 150 °C (entries 3 and 4). Surprisingly, the 3,4,5-trimethoxyphenyl nucleus frequently found in many anticancer substances,[13g,20] deactivated the triple bond. In these cases, a microwave heating at 170 °C in the presence of 1 equiv of PTSA were needed to achieve a total conversion. Substrate **4e** furnished regioselectively ketone **5e** (entry 5) whereas, a mixture of ketones was obtained from alkyne **4f** having methoxy substituents on both aromatic nucleus (entry 6).

Table 4
PTSA-promoted hydration of substituted diarylalkynes **4** under MWI

Entry	Diarylalkyne **4**	(Equiv) *T* (°C)	Product **5**	Yield[a] (%)
1	 **4a**	(1.2) 120 °C	 **5a**	97[b]
2	 **4b**	(1.2) 120 °C	 **5b**	98[c]
3	 **4c**	(1.0) 150 °C	 **5c**	80
4	 **4d**	(1.0) 150 °C	 **5d**	79
5	 **4e**	(1.0) 170 °C	 **5e**	68
6	 **4f**	(1.0) 170 °C	 **5f**	55[d]

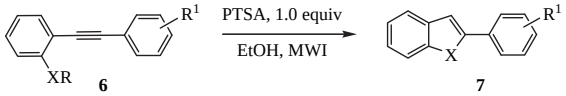
[a] Isolated yield.
[b] Obtained as an inseparable 90/10 mixture with the other regioisomer.
[c] Reaction was run for 1 h.
[d] Obtained as an inseparable 87/13 mixture with the other regioisomer.

2.4. PTSA-promoted hydration of *ortho*-substituted arylalkynes under MWI

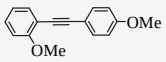
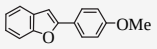
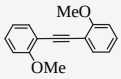
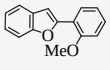
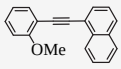
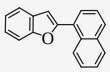
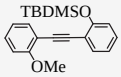
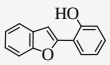
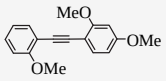
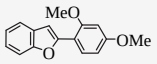
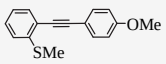
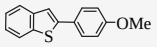
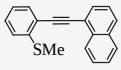
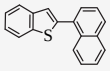
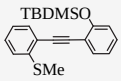
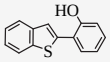
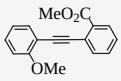
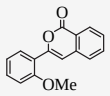
Having succeeded in developing an efficient hydration process of low reactive diarylalkynes, we next examined the reaction with *ortho* substituted diarylalkynes under MWI at 170 °C in the presence of 1 equiv of PTSA in EtOH.[21] The results of this study are summarized in Table 5. Under the above conditions, diarylalkyne **6a** bearing an *ortho* methoxy substituent on the aromatic ring surprisingly, provided the cyclized 2-arylbenzo[*b*]furan **7a** with no trace of the hydration products (entry 1, 76%). This result clearly showed that the nature of the substituents attached to the triple bond has a major impact on the behavior of the reaction (cyclization versus hydration). A *para* methoxyphenyl ring attached to the triple bond of **6a** favors the benzofuran formation whereas, alkyne **1o** with an aliphatic chain fail to undergo cyclization but provides exclusively the hydration adduct (see entry 11, Table 3). The unique formation of **7a** is believed to proceed according to an electrophilic activation of the alkyne carbon–carbon triple bond with PTSA to give hypothetic species **IV** or **VI** (Scheme 5). Subsequent intramolecular oxygen cyclization from **IV** would form the furan nucleus of type **V**, which evolves into **7a** via a dealkylation step by the solvent. According to this hypothesis, the intermolecular ethanol addition from species **VI** is disfavored.

The scope and limitation of this cyclization was next studied with a variety of *ortho* substituted diarylalkynes. Substrates **6b–e** bearing in the *ortho* position a methoxy substituent were successfully transformed into the corresponding benzofuran derivatives **7b–e** in good yields (entries 2–5, Table 5). One can note that a regioselective cyclization occurred from **6e** to give a single benzofuran product **7e** although alkyne substrate contains two *ortho* methoxy substituents (entry 5). We believe that the aromatic ring with two methoxy groups increase the electron density on the

Table 5
PTSA-promoted cyclization of *ortho* substituted diarylalkynes **6** in EtOH under MWI



6 **7**

Entry	Diarylalkyne **7**	Time (h) *T* (°C)	Product **8**	Yield[a] (%)
1	 **6a**	1 130	 **7a**	76
2	 **6b**	2 160	 **7b**	83
3	 **6c**	2 160	 **7c**	93
4	 **6d**	1 160	 **7d**	61
5	 **6e**	1 160	 **7e**	65
6	 **6f**	1 130	 **7f**	94
7	 **6g**	2 160	 **7g**	93
8	 **6h**	1 160	 **7h**	88
9	 **6i**	1 130	 **7i**	95

[a] Isolated yield.

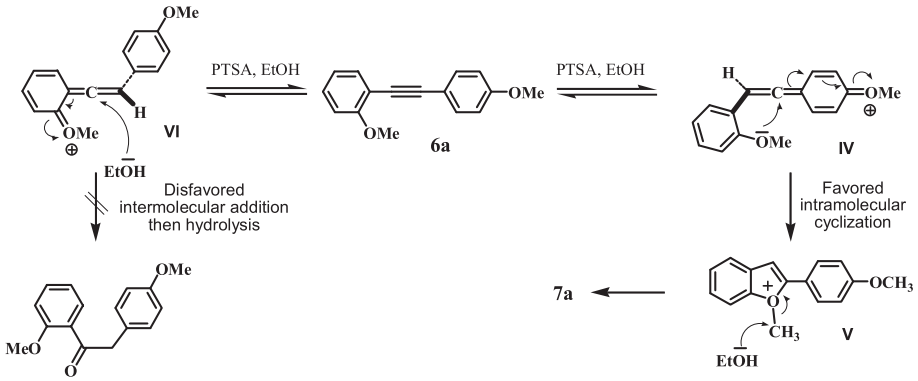
distal end of the triple bond. Subsequent electrophilic attack occurred with the *ortho* methoxy group of the other aromatic ring. This protocol was applied to *ortho*-(alkynyl)thioanisole derivatives **6f–h**. As expected, in EtOH, the reaction provided the benzothiophenes **7f–h** in good to excellent yields (88 to 94%, entries 6–8). It should be noted, that this metal-free procedure, which proceeds under environmentally friendly conditions is amenable for large scale synthesis of 2-arylbenzofuran and 2-arylbenzothiphene derivatives, which are prevalent in many compounds of biological interest.[22] The reaction with substrate **6i** bearing both an *ortho* electron-donating methoxy and an electron-withdrawing methoxycarbonyl substituent was also examined. The cyclization proceeded with high selectivity and isocoumarin **7i** was obtained as the sole product[23] (95%, entry 9). This result corroborates our mechanism hypothesis as the methoxy substituent regioselectively directed the activation of the triple bond thus allowing the electrophilic cyclization to proceed by the *ortho* methoxycarbonyl group.

2.5. PTSA-promoted hydration of enynes 8 and diynes 9 under MWI

In addition to the above substrates, 1,3-enynes and 1,3-diynes were subjected to the previously established and already optimized electrophilic cyclization (Table 6). Enyne **8a** was readily prepared by Pd/Cu-catalyzed coupling[16b] of 2-methoxyphenyl acetylene with 1-bromo-2-methylpropene in a 72% yield.

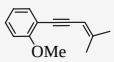
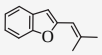
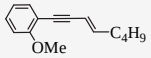
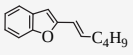
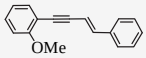
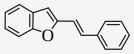
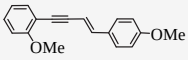
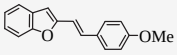
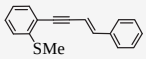
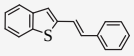
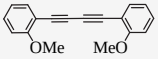
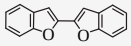
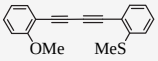
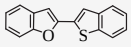
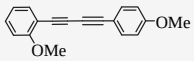
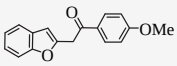
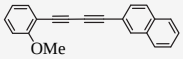
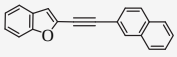
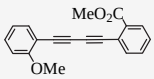
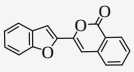
For enynes **8b–e**, they were obtained in good yields (See Experimental section) from iron[24] or palladium[25] catalyzed reaction of (*E*)-chloroenynes[16] and Grignard reagents. The desired diynes **9a–e** were synthesized by the coupling of 1-iodoethynyl-2-methoxybenzene with terminal arylalkynes in good yields (64–81%).[26]

The PTSA protocol for the cyclization of *ortho*-substituted arylalkynes **6** was then applied to enynes **8** and diynes **9**. The results of this study are reported in Table 6. Reaction of enyne **8a** was carried out with PTSA (1 equiv) under MWI in EtOH and gave 2-alkenylbenzofuran **10a** in a satisfactory 72% yield (entry 1). Similarly, the reaction of (*E*)-enynes **8b–e** gave also the corresponding 2-substituted benzofuran derivatives **10b–e** with comparable yields. All the compounds synthesized were characterized by the *E* double bond geometry as judged by ^{1}H NMR analysis (entries 2–5). The present approach seems undoubtedly promising because it allows a quick entry to a variety of 2-alkenylbenzofurans of biological interest.[27] The reaction was then applied to 1,3-diynes **9**. Compounds **9a** and **9b** were readily transformed into the corresponding bisbenzofuran **11a** and 2-(benzothiophenyl) benzofuran derivative **11b** (entries 6 and 7). One can note that no reaction occurred when



Scheme 5. Mechanism proposed for the formation of **7a**.

Table 6
Reaction of enynes **8** and diynes **9** with PTSA in EtOH under MWI[a]

Entry	Alkyne	Product	Yield[b] (%)
1	 **8a**	 **10a**	72
2	 **8b**	 **10b**	47[c]
3	 **8c**	 **10c**	73
4	 **8d**	 **10d**	75
5	 **8e**	 **10e**	78
6	 **9a**	 **11a**	58[d]
7	 **9b**	 **11b**	76
8	 **9c**	 **11c**	94
9	 **9d**	 **11d**	28[e]
10	 **9e**	 **11e**	0[f]

[a] Reaction conditions: **8** or **9** (0.2 mmol); PTSA (0.2 mmol); EtOH (2 mL); 160 °C; 2 h.
[b] Isolated yield.
[c] Reaction time 0.5 h.
[d] 24% of 2-(benzofuran-2-yl)-1-(2-methoxyphenyl)ethanone were also isolated.
[e] Unoptimized yield.
[f] Mixture of unidentified products.

heating **9a** at 160 °C under MWI in acidic solvents (e.g., AcOH, HCOOH, TFA). Starting material **9a** was recovered totally unchanged (data not shown). 1,3-Diyne **9c** bearing a 4-methoxy substituent on one of the aromatic rings was next evaluated (entry 8). As expected, the cyclization-process occurred together with the regioselective hydration of the second carbon–carbon triple bond to furnish **11c**. With a less electron-donating 2-naphtyl substituent attached to the triple bond (entry 9), the process was less efficient and benzofuran **11d** was isolated with a modest 28% yield. Finally, when carrying out the reaction with diyne **9e**, bearing both a methoxy and carbomethoxy substituents on the *ortho* position of the aromatic rings, no trace of benzofuran or isocoumarin derivatives were detected.

3. Conclusion

In summary, the use of PTSA in alcoholic media is a simple and efficient protocol, that is, easy to carry out. It appears to be predictable, regardless of the diverse array of starting materials that can be employed. Electron-rich aliphatic arylalkynes are regioselectively hydrated using a catalytic amount of PTSA in refluxing EtOH to provide carbonyl compounds. The substrate scope of this friendly procedure was successfully extended to non cooperative alkynes when carrying out the reaction under microwave irradiation. Moreover, unsymmetrical diarylalkynes bearing various functional groups on the aromatic nucleus were regioselectively and rapidly hydrated in good to excellent yields. Under the optimized conditions, diarylalkynes bearing on the *ortho* position a methoxy- or a thiomethyl substituent allowed an electrophilic cyclization to produce a variety of benzofuran and benzothiophene derivatives. Similarly, *ortho*-methoxy arylenynes were successfully transformed into the corresponding 2-alkenylbenzofurans in good yields. Although, this procedure requires high temperatures (from 80 °C to 170 °C), it involves non-toxic PTSA, EtOH as solvent, short reaction times, high to excellent yields, low cost and with minimum waste. All of these advantages are in a total agreement with the green chemistry philosophy.

4. Experimental

4.1. Instrumentation

The compounds were all identified by usual physical methods, i.e., ^{1}H NMR, ^{13}C NMR, IR, and elemental analysis. ^{1}H and ^{13}C NMR spectra were measured in $CDCl_3$ with a Bruker Avance 300 (300 MHz). ^{1}H chemical shifts are reported in parts per million from an internal standard TMS or of residual chloroform (7.27 ppm). The following abbreviations are used: m (multiplet), s (singlet), d (doublet), t (triplet), dd (doublet of doublet). ^{13}C chemical shifts are reported in parts per million from the central peak of deuteriochloroform (77.14). IR spectra were measured on a Bruker Vector 22 spectrophotometer (neat, cm^{-1}). Mass spectra were obtained with a Esquire LC Bruker spectrometer. Elemental analyses were performed with a Perkin-Elmer 240 analyzer. Analytical TLC were performed on Merck precoated silica gel 60F plates. Merck silica gel 60 (230–400 mesh) was used for column chromatography. Melting points (mp) were recorded on a Büchi B-450 apparatus and were uncorrected.

4.2. Preparation of arylalkynes

4.2.1. N,N-di(prop-2-ynyl)-4-(3-(tetrahydro-2H-pyran-2-yloxy)prop-1-ynyl)benzenamine ***1a***. To a stirred solution of 4-iodo-aniline (2.19 g, 10 mmol) in THF (20 mL) under an argon atmosphere was added, CuI (190 mg, 1.0 mmol), $PdCl_2(PPh_3)_2$ (350 mg, 0.5 mmol), Et_2NH (7.3 g, 100 mmol), and 2-(prop-2-ynyloxy)-tetrahydro-2*H*-pyran (16.8 g, 12 mmol). The stirred mixture was stirred for a 5 h at room temperature and ether (30 mL) was added. After filtration on a pad of Celite, the organic layer was washed with H_2O. After extraction and concentration to dryness, the crude mixture was dissolved in DMF (30 mL). Then, propargyl bromide (3 mL; 27.6 mmol; 80% in toluene), K_2CO_3 (3.24 g), KI (0.3 g) were added to the mixture, which was stirred at 50 °C for 15 h. After cooling, the crude mixture was diluted in diethylether (30 mL), filtered. The organic layer was washed with H_2O (3×10 mL), dried with $MgSO_4$, and evaporated to dryness. Purification by flash chromatography afforded **1a** (675 mg, 2.22 mmol calculated from 4-iodoaniline).

Yield: 22%. IR (cm^{-1}) 3287, 2942, 1606, 1514, 1340. ^{1}H NMR ($CDCl_3$, 300 MHz, 298 K): δ ppm 1.40–1.90 (m, 6H), 2.25 (t, 2H, J=2.3 Hz), 3.50–3.90 (m, 2H), 4.11 (d, 4H, J=2.3 Hz), 4.47 (d, 2H, J=3.3 Hz), 4.89 (t, 1H, J=3.3 Hz), 6.84 (d, 2H, J=9.0 Hz), 7.37 (d, 2H, J=9.0 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz, 298 K): δ ppm 18.9, 25.2, 30.1, 40.0 (2), 54.7, 61.8, 72.7 (2), 78.7 (2), 83.4, 85.9, 96.5, 112.9, 114.4 (2), 132.8 (2), 147.2. Anal. Calcd for $C_{20}H_{21}NO_2$: C, 78.15; H, 6.89; N, 4.56. Found C, 78.01; H, 6.71; N, 4.49.

4.2.2. 6-(4-Aminophenyl)hex-5-yn-1-ol ***1k***. TEA (1.5 equiv) was used in place of Et_2NH.

Yield: 45%. IR (cm^{-1}) 3367, 2936, 1608, 1513, 1431, 1288, 1176, 1059, 829. ^1H NMR ($CDCl_3$, 300 MHz, 298 K): δ ppm 1.50–1.85 (m, 4H), 2.40 (t, 2H, J=5.9 Hz), 3.70 (t, 2H, J=5.2 Hz), 6.58 (d, 2H, J=6.7 Hz), 7.19 (d, 2H, J=6.7 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz, 298 K): δ ppm 19.2, 25.2, 31.9, 62.5, 81.4, 87.2, 114.7 (2), 132.7 (2), 145.9 (one C missing). Anal. Calcd for $C_{12}H_{15}NO$: C, 76.16; H, 7.99; N, 7.40. Found C, 76.05; H, 8.15; N, 7.19.

4.2.3. 2-(3-Hydroxyprop-1-ynyl)phenol ***1m***. Compound **1m** was prepared from the coupling of *tert*-butyl(2-iodophenoxy)-dimethylsilane with 1-propyn-3-ol as above and the crude mixture was desilylated using TBAF (5 equiv) in THF at room temperature.

Yield: 59% (for the two steps). IR (cm^{-1}) 3290, 2938, 1605, 1510. ^1H NMR ($CDCl_3$, 300 MHz, 298 K): δ ppm 4.70–4.90 (br s, 3H), 7.01–7.23 (m, 2H), 7.45 (td, 1H, J=7.8 Hz, J=1.3 Hz), 7.51 (dd, 1H, J=7.8 Hz, J=1.2 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz, 298 K): δ ppm 50.4, 79.9, 93.3, 109.9, 115.3, 119.5, 129.8, 132.5, 157.9. Anal. Calcd for $C_9H_8O_2$: C, 72.96; H, 5.44. Found C, 72.87; H, 5.34.

4.2.4. 1-(4-isoPropylphenyl)-4-(4-methoxyphenyl)but-3-yn-1-ol ***1t***. Yield: 88%. Mp 72–73 °C. IR (cm^{-1}) 3454, 2967, 1607, 1508, 1283, 1242, 1175, 1065, 1037, 1016, 830. ^1H NMR ($CDCl_3$, 300 MHz, 298 K): δ ppm 1.24 (d, 6H, J=6.9 Hz), 2.42 (d, 1H, J=3.3 Hz), 2.82 (d, 2H, J=6.3 Hz), 2.91 (q, 1H, J=6.9 Hz), 3.79 (s, 3H), 4.88–4.93 (m, 1H), 6.81 (d, 2H, J=8.5 Hz), 7.22 (d, 2H, J=8.1 Hz), 7.32 (d, 2H, J=8.5 Hz), 7.35 (d, 2H, J=8.1 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz, 298 K): δ ppm 24.0, 30.6, 33.8, 55.3, 72.5, 82.9, 84.6, 113.7, 115.4, 125.8, 126.5, 133.0, 140.1, 148.6, 159.3. MS (ESI^+) m/z=317 $[M+Na]^+$. Anal. Calcd for $C_{20}H_{22}O_2$: C, 81.60; H, 7.53. Found C, 81.47; H, 7.31.

4.2.5. 4-(Hex-1-ynyl)benzenamine ***1w***. Yield: 65%. IR (cm^{-1}) 3374, 2957, 2931, 1620, 1512, 828. ^1H NMR ($CDCl_3$, 300 MHz, 298 K): δ ppm 0.94 (t, 3H, J=7.0 Hz), 1.46–1.65 (m, 4H), 2.38 (t, 2H, J=6.8 Hz), 3.35 (s, 2H), 6.58 (d, 2H, J=8.4 Hz), 7.20 (d, 2H, J=8.4 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz, 298 K): δ ppm 13.6, 19.0, 21.9, 31.0, 80.7, 87.7, 113.6 (2), 114.7, 132.6 (2), 146.9. MS (ESI^+) m/z=192.3 $[M+Na]^+$. Anal. Calcd for $C_{12}H_{15}N$: C, 83.19; H, 8.73; N 8.08. Found C, 82.66; H, 8.44; N 7.68.

4.2.6. 4-(p-Tolylethynyl)benzenamine ***4d***. Yield: 92%. White solid mp 172–174 °C. IR (cm^{-1}) 3467, 3375, 2209, 1616, 1599, 1515, 1295, 814. ^1H NMR ($CDCl_3$, 300 MHz, 298 K): δ ppm 2.35 (s, 3H), 3.81 (s, 2H), 6.63 (d, 2H, J=8.5 Hz), 7.12 (d, 2H, J=8.0 Hz), 7.33 (d, 2H, J=8.5 Hz), 7.38 (d, 2H, J=8.0 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz, 298 K): δ ppm 21.4, 87.4, 89.3, 112.8, 114.7, 120.8 (2), 129.0 (2), 131.2 (2), 132.8 (2), 137.7, 146.4. MS (APCI) m/z=208 $[M+H]^+$. Anal. Calcd for $C_{15}H_{13}N$: C, 86.92; H, 6.32; N, 6.76. Found C, 86.68; H, 6.33; N, 6.66.

4.2.7. 1-(2-(2-Methoxyphenyl)ethynyl)naphthalene ***6c***. Yield: 79%; yellow oil. IR (cm^{-1}) 3057, 2834, 1574, 1491, 1461, 1433, 1397, 1275, 1242, 1180, 1161, 1113, 1047, 1022, 934, 799, 772. ^1H NMR ($CDCl_3$, 300 MHz, 298 K): δ ppm 3.82 (s, 3H), 6.80 (s, 2H), 7.18 (ddd, 1H, J=1.7 Hz, J=7.5 Hz, J=8.3 Hz), 7.38 (m, 4H), 7.67 (m, 3H), 8.41 (dd, 1H, J=1.7 Hz, J=8.3 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz, 298 K): 56.0, 90.9, 91.8, 110.8, 112.8, 120.2, 120.6, 121.4, 125.3, 126.4, 126.6, 126.8, 128.3, 128.6, 129.9, 130.1, 133.3, 133.4, 160.2. MS (APCI) m/z=259 $[M+H]^+$. Anal. Calcd for $C_{19}H_{14}O$: C, 88.34; H, 5.46. Found C, 88.04; H, 5.28.

4.2.8. tert-Butyl(2-((2-methoxyphenyl)ethynyl)phenoxy)dimethyl silane ***6d***. Yield: 45%; brown oil. IR (cm^{-1}) 2930, 2857, 1593, 1574, 1497, 1482, 1461, 1444, 1285, 1249, 1181, 1161, 1113, 1096, 1025, 916, 838, 806, 780. ^1H NMR ($CDCl_3$, 300 MHz, 298 K): δ ppm 0.00 (s, 6H), 0.77 (s, 9H), 3.63 (s, 3H), 6.60 (m, 4H), 6.98 (m, 2H), 7.23 (dt, 2H, J=1.7 Hz, J=7.7 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz, 298 K): −4.1 (2), 18.4, 25.8 (3), 55.7, 89.2, 90.9, 110.7, 113.1, 116.3, 119.8, 120.4, 121.1, 129.3, 129.5, 133.5, 133.8, 156.3, 160.0. MS (APCI) m/z=339 $[M+H]^+$. Anal. Calcd for $C_{21}H_{26}O_2Si$: C, 74.51; H, 7.74. Found C, 74.16; H, 7.48.

4.2.9. 2,4-Dimethoxy-1-((2-methoxyphenyl)ethynyl)benzene ***6e***. Yield: 69%; brown solid; mp 98 °C. IR (cm^{-1}) 2934, 1606, 1508, 1457, 1299, 1243, 1208, 1161, 1024, 751. ^1H NMR ($CDCl_3$, 300 MHz, 298 K): δ ppm 3.82 (s, 3H), 3.90 (s, 3H), 3.92 (s, 3H), 6.45–6.50 (m, 2H), 6.86–6.96 (m, 2H), 7.22–7.31 (m, 1H), 7.45 (dt, 1H, J=8.7 Hz, J=1.2 Hz), 7.50 (dd, 1H, J=7.5 Hz, J=1.6 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz, 298 K): δ ppm 55.5, 56.1, 88.5, 90.0, 98.6, 104.9, 105.6, 110.8, 113.3, 120.5, 129.3, 133.5, 134.4, 159.9, 161.2, 161.3. MS (APCI) m/z=269 $[M+H]^+$. Anal. Calcd for $C_{17}H_{16}O_3$: C, 76.10; H, 6.01. Found C, 75.87; H, 5.88.

4.2.10. Methyl(2-(2-(naphthalen-1-yl)ethynyl)phenyl)sulfane ***6g***. Yield: 30%; colorless oil. ^1H NMR ($CDCl_3$, 300 MHz, 298 K): δ 2.71 (s, 3H), 7.33 (m, 2H), 7.49 (dt, 1H, J=1.2 Hz, J=7.9 Hz), 7.69 (m, 4H), 7.99 (m, 3H), 8.77 (d, 1H, J=8.3 Hz). MS (APCI) m/z=275 $[M+H]^+$. Anal. Calcd for $C_{19}H_{14}S$: C, 83.17; H, 5.14. Found C, 82.82; H, 4.95.

4.2.11. tert-Butyldimethyl(2-(2-(2-(methylthio)phenyl)ethynyl) phenoxy)silane ***6h***. Yield: 52%; yellow oil. IR (cm^{-1}) 2361, 2218, 1994, 1574, 1497, 1482, 916, 838, 806, 780, 744. ^1H NMR ($CDCl_3$, 300 MHz, 298 K): δ 0.06 (s, 6H), 0.83 (s, 9H), 2.29 (s, 3H), 6.64 (dd, 1H, J=1.0 Hz, J=8.2 Hz), 6.73 (dt, 1H, J=1.0 Hz, J=7.5 Hz), 6.89 (dt, 1H, J=1.2 Hz, J=7.4 Hz), 7.06 (m, 3H), 7.24 (dd, 1H, J=1.4 Hz, J=7.6 Hz), 7.34 (dd, 1H, J=1.8 Hz, J=7.7 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz, 298 K): −4.0 (2), 15.2, 18.4 (3), 25.9, 88.5, 90.6, 112.9, 119.9, 121.3, 124.2, 128.5, 129.7, 132.0, 133.9, 134.5. MS (APCI) m/z=355 $[M+H]^+$. Anal. Calcd for $C_{21}H_{26}OSSi$: C, 71.13; H, 7.39. Found C, 70.89; H, 7.10.

4.2.12. (E)-1-Methoxy-2-(oct-3-en-1-ynyl)benzene ***8b***. Yield: 82%; yellow oil. IR (cm^{-1}) 1673, 1603, 1510. ^1H NMR ($CDCl_3$, 300 MHz, 298 K): δ ppm 0.95 (t, 3H, J=6.9 Hz), 1.34–1.44 (m, 4H), 2.16 (q, 2H, J=6.8 Hz), 3.89 (s, 3H), 5.75 (d, 1H, J=15.5 Hz), 6.21–6.31 (m, 1H), 6.85–6.92 (m, 2H), 7.23–7.29 (m, 1H), 7.39 (d, 1H, J=7.5 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz, 298 K): δ ppm 14.0, 22.3, 31.0, 33.0, 55.9, 84.1, 92.6, 109.9, 110.6, 112.9, 120.5, 129.4, 133.5, 145.1, 159.8. MS (ESI) m/z=237.3 $[M+Na]^+$. Anal. Calcd for $C_{15}H_{18}O$: C, 84.07; H, 8.47. Found C, 83.93; H, 8.33.

4.2.13. (E)-1-Methoxy-2-(4-phenylbut-3-en-1-ynyl)benzene ***8c***. Yield: 91%; yellow oil. IR (cm^{-1}) 3029, 1592, 1489, 1462, 1433, 1274, 1258, 1239, 1119, 1024, 951, 745, 690. ^1H NMR ($CDCl_3$, 300 MHz, 298 K): δ ppm 3.92 (s, 3H), 6.47 (d, 1H, J=16.2 Hz), 6.90 (d, 1H, J=8.3 Hz), 6.94 (td, 1H, J=7.5 Hz, J=0.8 Hz), 7.07 (d, 1H, J=16.2 Hz), 7.27–7.38 (m, 4H), 7.42–7.48 (m, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz, 298 K): δ ppm 56.0, 88.2, 93.1, 108.6, 110.8, 112.8, 120.7, 126.4, 128.6, 128.8, 129.8, 133.6, 136.6, 141.1, 160.0. MS (APCI) m/z=235 $[M+H]^+$. Anal. Calcd for $C_{17}H_{14}O$: C, 87.15; H, 6.02. Found C, 87.01; H, 5.97.

4.2.14. (E)- 4-(2-Methoxyphenyl)-1-(4-methoxyphenyl)but-1-en-3-yne ***8d***. Yield: 59%; yellow solid; mp 69 °C. IR (cm^{-1}) 2935, 1604, 1510, 1491, 1247, 1028, 752. ^1H NMR ($CDCl_3$, 300 MHz, 298 K): δ ppm 3.82 (s, 3H), 3.91 (s, 3H), 6.31 (d, 1H, J=16.2 Hz), 6.86–6.95 (m, 4H), 7.02 (d, 1H, J=16.2 Hz), 7.26–7.31 (m, 1H), 7.37 (d, 2H, J=8.7 Hz), 7.44 (dd, 1H, J=7.5 Hz, J=1.6 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz, 298 K): δ ppm 55.5, 56.0, 87.4, 93.5, 106.2, 110.7, 112.9, 114.3 (2), 120.6, 127.8 (2), 129.5, 129.6, 133.6, 140.7, 159.9, 160.1. MS (APCI) m/z=265 $(M+H)^+$. Anal. Calcd for $C_{18}H_{16}O_2$: C, 81.79; H, 6.10. Found C, 81.55; H, 5.91.

4.2.15. (E)-Methyl(2-(4-phenylbut-3-en-1-ynyl)phenyl)sulfane ***8e***. Yield: 82%; yellow oil. IR (cm^{-1}) 3026, 1463, 1434, 952, 746, 690. ^1H NMR ($CDCl_3$, 300 MHz, 298 K): δ ppm 2.52 (s, 3H), 6.47 (d, 1H, J=16.2 Hz), 7.08–7.19 (m, 3H), 7.27–7.38 (m, 4H), 7.43–7.46 (m, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz, 298 K): δ ppm 15.3, 89.3, 95.5, 108.1, 116.9,

121.7, 124.3, 124.4, 126.5 (2), 128.8 (2), 128.9, 132.4, 136.5, 141.6. MS (APCI) m/z=251 $(M+H)^+$. Anal. Calcd for $C_{17}H_{14}S$: C, 81.56; H, 5.64. Found C, 81.39; H, 5.51.

4.2.16. (2-(4-(2-Methoxyphenyl)buta-1,3-diynyl)phenyl)(methyl) sulfane ***9b***. Yield: 70%; light brown solid; mp 82–83 °C. IR (cm^{-1}) 2938, 1594, 1492, 1464, 1433, 1248, 1022, 703. ^1H NMR ($CDCl_3$, 300 MHz, 298 K): δ ppm 2.51 (s, 3H), 3.91 (s, 3H), 6.89 (d, 1H, J=8.7 Hz), 6.92 (t, 1H, J=7.5 Hz), 7.09 (t, 1H, J=7.5 Hz), 7.17 (d, 1H, J=7.9 Hz), 7.29–7.36 (m, 2H), 7.48–7.51 (m, 2H). IR (cm^{-1}) 15.4, 56.0, 77.7, 79.5, 80.1, 80.4, 110.8, 111.2, 120.5, 120.7, 124.5, 124.6, 129.5, 130.9, 133.7, 134.6, 143.2, 161.5. MS (APCI) m/z=279 $[M+H]^+$. Anal. Calcd for $C_{18}H_{14}OS$: C, 77.66; H, 5.07. Found C, 77.66; H, 5.01.

4.2.17. 1-(2-Methoxyphenyl)-4-(4-methoxyphenyl)buta-1,3-diyne ***9c***. Yield: 64%; colorless solid; mp 109–110 °C. IR (cm^{-1}) 2936, 2837, 1601, 1508, 1489, 1247, 1171, 1024, 750. ^1H NMR ($CDCl_3$, 300 MHz, 298 K): δ ppm 3.82 (s, 3H), 3.90 (s, 3H), 6.84–6.94 (m, 4H), 7.32 (t, 1H, J=7.6 Hz), 7.45–7.48 (m, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz, 298 K): δ ppm 55.4, 55.9, 73.2, 77.7, 78.0, 82.5, 110.8, 111.3, 114.0, 114.2 (2), 120.6, 130.6, 134.1 (2), 134.4, 160.4, 161.5. MS (APCI) m/z=263 $[M+H]^+$. Anal. Calcd for $C_{18}H_{14}O_2$: C, 82.42; H, 5.38. Found C, 82.11; H, 5.20.

4.2.18. 1-(4-(2-Methoxyphenyl)buta-1,3-diynyl)naphthalene ***9d***. Yield: 75%; beige solid; mp 82–83 °C. IR (cm^{-1}) 3059, 1491, 1279, 1253, 748. ^1H NMR ($CDCl_3$, 300 MHz, 298 K): δ ppm 3.93 (s, 3H), 6.89–6.96 (m, 2H), 7.32–7.38 (m, 1H), 7.49–7.55 (m, 4H), 7.78–7.83 (m, 3H), 8.06 (s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz, 298 K): δ ppm 56.0, 74.7, 77.9, 78.5, 82.7, 110.8, 111.2, 119.4, 120.7, 126.9, 127.3, 127.9, 128.0, 128.3, 128.6, 130.9, 133.0, 133.3, 134.6, 161.6. MS (APCI) m/z=283 $(M+H)^+$. Anal. Calcd for $C_{21}H_{14}O$: C, 89.34; H, 5.00. Found C, 89.01; H, 4.79.

4.3. Typical procedure for the PTSA-catalyzed hydration of arylalkynes under classical heating

To a stirred solution of alkyne **1a** (307 mg; 1 mmol) in EtOH (2 mL), was added PTSA monohydrate (38 mg; 0.2 mmol). The mixture was refluxed for 3 h, diluted in H_2O and extracted with EtOAc. The combined organic layer was washed with brine and dried over Na_2SO_4. After removal of the solvent under vacuo, the crude product was purified by column chromatography on silica gel to afford 242 mg of **2a**.

4.3.1. 1-(4-(Diprop-2-ynylamino)phenyl)-3-ethoxypropan-1-one ***2a***. Yield: 90%; yellow solid; mp 90 °C. IR (cm^{-1}) 3271, 2957, 2871, 1655, 1595, 1562. ^1H NMR ($CDCl_3$, 300 MHz, 298 K): δ ppm 1.18 (t, 3H, J=7.0 Hz), 2.27 (t, 2H, J=2.3 Hz), 3.16 (t, 2H, J=6.8 Hz), 3.51 (q, 2H, J=7.0 Hz), 3.82 (t, 2H, J=6.8 Hz), 4.17 (d, 4H, J=2.3 Hz), 6.88 (d, 2H, J=9.1 Hz), 7.91 (d, 2H, J=9.1 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz, 298 K): δ ppm 14.9, 38.1, 39.8 (2), 65.9, 66.2, 72.9 (2), 78.3 (2), 112.9 (2), 127.6, 129.9 (2), 150.6, 196.3. MS (ESI) m/z=292 $[M+Na]^+$. Anal. Calcd for $C_{17}H_{19}NO_2$: C, 75.81; H, 7.11; N, 5.20. Found C, 75.66; H, 7.02; N, 5.05.

4.3.2. 3-Ethoxy-1-(4-methoxyphenyl)propan-1-one ***2b***[19e]. Yield: 94%; yellow oil. IR (cm^{-1}) 2974, 1673, 1599, 1575, 1510. ^1H NMR ($CDCl_3$, 300 MHz, 298 K): δ ppm 1.14 (t, 3H, J=7.0 Hz), 3.14 (t, 2H, J=6.7 Hz), 3.47 (d, 2H, J=8.9 Hz), 3.78 (s, 3H), 3.79 (t, 2H, J=6.8 Hz), 6.87 (d, 2H, J=8.9 Hz), 7.89 (d, 2H, J=8.9 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz, 298 K): δ ppm 14.9, 38.4, 55.2, 65.8, 66.3, 113.5 (2), 130.0, 130.2 (2), 163.3, 196.7. MS (EI) m/z=208 (18%) $[M]^+$.

4.3.3. 3-Methoxy-1-(4-methoxyphenyl)propan-1-one ***2c***[15]. Yield: 98%; yellow oil. IR (cm^{-1}) 2986, 2905, 2842, 2816, 1665, 1598, 1513. ^1H NMR ($CDCl_3$, 300 MHz, 298 K): δ ppm 3.14 (t, 2H, J=6.6 Hz), 3.32 (s, 3H), 3.76 (t, 2H, J=6.6 Hz), 3.81 (s, 3H), 6.88 (d, 2H, J=8.9 Hz), 7.90 (d, 2H, J=8.9 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz, 298 K): δ ppm 38.1, 55.2, 58.6, 67.9, 113.5 (2), 130.0, 130.2 (2), 163.4, 196.6. MS (EI) m/z=194 (23%) $[M]^+$.

4.3.4. 3- (2H)-Methoxy-1-(4-methoxyphenyl)-(2,2-2H)propan-1-one ***D-2c***. Yield: 98%; yellow oil. ^1H NMR ($CDCl_3$, 300 MHz, 298 K): δ ppm 3.77 (s, 2H), 3.83 (s, 3H), 6.91 (d, 2H, J=8.8 Hz), 7.92 (d, 2H, J=8.8 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz, 298 K): δ ppm 37.5 (q, J=19.3 Hz), 55.2, 57.8 (m, J=21.5 Hz), 67.8, 113.6 (2), 130.0, 130.2 (2), 163.4, 196.7. MS (ES) m/z=222 $[M+Na]^+$.

4.3.5. 3-Isopropoxy-1-(4-methoxyphenyl)propan-1-one ***2d***[15]. Yield: 66%; pale yellow oil. ^1H NMR ($CDCl_3$, 300 MHz, 298 K): δ ppm 1.13 (d, 6H, J=6.1 Hz), 3.15 (t, 2H, J=6.8 Hz), 3.59 (m, 1H), 3.81 (s, 3H), 3.82 (t, 2H, J=6.8 Hz), 6.89 (d, 2H, J=8.9 Hz), 7.92 (d, 2H, J=8.9 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz, 298 K): δ ppm 21.7 (2), 38.6, 55.0, 63.2, 71.4, 113.3 (2), 129.9, 130.0 (2), 163.1, 196.6. MS (ESI) m/z=245 $[M+Na]^+$.

4.3.6. 3-(2-Hydroxyethoxy)-1-(4-methoxyphenyl)propan-1-one ***2e***[15]. Yield: 33%; colorless oil. ^1H NMR ($CDCl_3$, 300 MHz, 298 K): δ ppm 2.50–2.70 (s, 1H), 3.17 (t, 2H, J=6.2 Hz), 3.56 (t, 2H, J=4.8 Hz), 3.69 (t, 2H, J=4.8 Hz), 3.83 (s, 3H), 3.88 (t, 2H, J=6.2 Hz), 6.89 (d, 2H, J=8.9 Hz), 7.91 (d, 2H, J=8.9 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz, 298 K): δ ppm 38.1, 55.3, 61.5, 65.9, 72.0, 113.7 (2), 129.9, 130.3 (2), 163.6, 196.9. MS (ESI) m/z=225 $[M+Na]^+$.

4.3.7. 3-Hydroxy-1-(4-methoxyphenyl)propan-1-one ***2f***[28]. Yield: 75%; yellow solid; mp 62 °C. ^1H NMR ($CDCl_3$, 300 MHz, 298 K): δ ppm 2.50–2.70 (s, 1H), 3.16 (t, 2H, J=5.5 Hz), 4.72 (s, 3H), 4.00 (t, 2H, J=5.5 Hz), 6.93 (d, 2H, J=9.0 Hz), 7.93 (d, 2H, J=9.0 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz, 298 K): δ ppm 39.9, 55.4, 58.1, 113.7 (2), 129.8, 130.3 (2), 163.7, 198.9. MS (ESI) m/z=181 $[M+H]^+$.

4.3.8. 4-Ethoxy-1-(4-methoxyphenyl)butan-1-one ***2g***[15]. Yield: 85%; yellow oil. ^1H NMR ($CDCl_3$, 300 MHz, 298 K): δ ppm 1.16 (t, 3H, J=7.0 Hz), 1.17 (m, 2H), 2.99 (t, 2H, J=7.2 Hz), 3.35–3.50 (m, 4H), 3.83 (s, 3H), 6.90 (d, 2H, J=8.7 Hz), 7.93 (d, 2H, J=8.7 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz, 298 K): δ ppm 15.0, 24.4, 34.6, 55.2, 65.4, 69.5, 113.5 (2), 130.0, 130.1 (2), 163.3, 198.4. MS (ESI) m/z=245 $[M+Na]^+$.

4.3.9. 6-Hydroxy-1-(4-methoxyphenyl)hexan-1-one ***2h***[15]. Yield: 90%; yellow solid; mp 60 °C. ^1H NMR ($CDCl_3$, 300 MHz, 298 K): δ ppm 1.40–1.60 (m, 6H), 2.92 (t, 2H, J=7.3 Hz), 3.65 (t, 2H, J=6.4 Hz), 3.85 (s, 3H), 6.91 (d, 2H, J=8.9 Hz), 7.92 (d, 2H, J=8.9 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz, 298 K): δ ppm 24.1, 25.5, 32.5, 38.0, 55.4, 62.6, 113.7 (2), 130.1, 130.2 (2), 163.4, 199.0. MS (EI) m/z=222 $[M]^+$.

4.3.10. 3-Ethoxy-1-(4-methoxyphenyl)butan-1-one ***2i***[15]. Yield: 91%; yellow oil. IR (cm^{-1}) 2973, 2930, 1675, 1600, 1576, 1510. ^1H NMR ($CDCl_3$, 300 MHz, 298 K): δ ppm 1.14 (t, 3H, J=7.0 Hz), 1.24 (d, 3H, J=6.1 Hz), 2.86 (dd, 1H, J=6.2 Hz, J=15.8 Hz), 3.28 (dd, 1H, J=6.2 Hz, J=15.8 Hz), 3.50 (quint, 1H, J=7.0 Hz), 3.51 (dd, 1H, J=7.0 Hz, J=7.0 Hz), 3.86 (s, 3H), 4.06 (m, 1H), 6.92 (d, 2H, J=8.9 Hz), 7.94 (d, 2H, J=8.9 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz, 298 K): δ ppm 15.5, 20.4, 45.5, 55.4, 64.1, 72.0, 113.7 (2), 130.5, 130.6 (2), 163.5, 197.4. MS (ESI) m/z=223 $[M+H]^+$.

4.3.11. 5-Hydroxy-1-(4-methoxyphenyl)pentan-1-one ***2j***[29]. Yield: 45%; colorless solid; mp 50 °C. IR (cm^{-1}) 3470, 1671, 1605. ^1H NMR ($CDCl_3$, 300 MHz, 298 K): δ ppm 1.50–2.05 (m, 5H), 3.01 (t, 2H, J=6.5 Hz), 3.80–3.60 (m, 2H), 3.75 (s, 3H), 6.85 (d, 2H, J=8.8 Hz), 7.92 (d, 2H, J=8.8 Hz).

4.3.12. 5-Ethoxy-1-(4-methoxyphenyl)pentan-1-one ***2k***[29]. Yield: 44%; colorless solid; mp 46 °C. IR (cm^{-1}) 1673, 1603, 1510. ^1H NMR ($CDCl_3$, 300 MHz, 298 K): δ ppm 1.20 (t, 3H, J=7.1 Hz), 1.50–2.01 (m,

4H), 2.95 (t, 2H, *J*=6.5 Hz), 3.45 (t, 2H, *J*=6.5 Hz), 3.50 (q, 2H, *J*=7.1 Hz), 3.86 (s, 3H), 6.92 (d, 2H, *J*=8.9 Hz), 7.91 (d, 2H, *J*=8.9 Hz).

4.3.13. 1-(4-Methoxyphenyl)hexan-1-one **2l**[30]. Yield: 81%; yellow solid; mp 60 °C. IR (cm^{-1}) 3077, 3011, 2956, 2931, 1676, 1601, 1254. ^1H NMR ($CDCl_3$, 300 MHz, 298 K): δ ppm 0.90 (t, 3H, *J*=5.6 Hz), 1.36 (m, 4H), 1.70 (quint, 2H, *J*=7.3 Hz), 2.89 (t, 2H, *J*=7.3 Hz), 3.85 (s, 3H), 6.91 (d, 2H, *J*=8.8 Hz), 7.93 (d, 2H, *J*=8.8 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz, 298 K): δ ppm 13.8, 22.4, 24.2, 31.5, 38.1, 55.3, 113.5 (2), 130.2 (3), 163.2, 199.0. MS (EI) *m*/*z*=206 $[M]^+$.

4.3.14. 1-(4-Aminophenyl)-6-hydroxyhexan-1-one **2m**[15]. Yield: 72%; yellow solid; mp 114 °C. ^1H NMR (CD_3OD, 300 MHz, 298 K): δ ppm 1.20–1.80 (m, 6H), 2.87 (t, 2H, *J*=7.6 Hz), 3.55 (t, 2H, *J*=6.4 Hz), 6.63 (d, 2H, *J*=8.8 Hz), 7.75 (d, 2H, *J*=8.8 Hz). ^{13}C NMR (CD_3OD, 75 MHz, 298 K): δ ppm 26.1, 26.7, 33.5, 38.6, 62.3, 114.3 (2), 126.8, 132.1(2), 153.6, 201.5. MS (ESI) *m*/*z*=230 $[M+Na]^+$.

4.3.15. 3-Hydroxy-1-(4-hydroxyphenyl)propan-1-one **2n**[30]. Yield: 79%; white solid; mp 140 °C. IR (cm^{-1}) 3462, 3114, 1643, 1596. ^1H NMR (CD_3OD, 300 MHz, 298 K): δ ppm 3.14 (t, 2H, *J*=6.2 Hz), 3.93 (t, 2H, *J*=6.2 Hz), 6.84 (d, 2H, *J*=8.9 Hz), 7.89 (d, 2H, *J*=8.9 Hz). ^{13}C NMR (CD_3OD, 75 MHz, 298 K): δ ppm 41.7, 58.9, 116.2, 130.2, 131.8, 163.8, 199.7. MS (ESI) *m*/*z*=167 $[M+H]^+$.

4.3.16. 3-Hydroxy-1-(2-hydroxyphenyl)propan-1-one **2o**. Yield: 73%. ^1H NMR (CD_3COCD_3, 300 MHz, 298 K): δ ppm 2.80 (br s, 1H), 3.31 (t, 2H, *J*=8.8 Hz), 4.01 (m, 2H), 6.87–7.01 (m, 2H), 7.55 (td, 1H, *J*=7.9 Hz, *J*=1.3 Hz), 7.98 (dd, 1H, *J*=7.9 Hz, *J*=1.3 Hz), 12.40 (br s, 1H). ^{13}C NMR (CD_3COCD_3, 75 MHz, 298 K): δ ppm 41.0, 57.3, 117.7, 118.8, 120.1, 130.7, 136.2, 205.1. Anal. Calcd for $C_9H_{10}O_3$: C, 65.05; H, 6.07. Found C, 64.87; H, 5.90.

4.3.17. 3-Ethoxy-1-(2-methoxyphenyl)propan-1-one **2p**. Yield: 73%; yellow oil. IR (cm^{-1}) 2974, 2868, 1672, 1597. ^1H NMR ($CDCl_3$, 300 MHz, 298 K): δ ppm 1.13 (t, 3H, *J*=7.0 Hz), 3.23 (t, 2H, *J*=6.8 Hz), 3.45 (q, 2H, *J*=7.0 Hz), 3.76 (t, 2H, *J*=6.7 Hz), 3.83 (s, 3H), 6.85–7.00 (m, 2H), 7.35–7.45 (m, 1H), 7.65 (dd, 1H, *J*=7.8 Hz, *J*=1.8 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz, 298 K): δ ppm 14.9, 43.9, 55.2, 65.6, 66.0, 111.3, 120.3, 127.9, 130.0, 133.2, 158.4, 200.0. MS (EI) *m*/*z*=208 $[M]^+$. Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found C, 69.00; H, 7.52.

4.3.18. 1-(2-Methoxyphenyl)hexan-1-one **2q**[31]. Yield: 80%; colorless oil. IR (cm^{-1}) 2928, 2858, 1674, 1597. ^1H NMR ($CDCl_3$, 300 MHz, 298 K): δ ppm 0.87 (t, 3H, *J*=6.9 Hz), 1.25–1.35 (m, 4H), 1.55–1.75 (m, 2H), 2.92 (t, 2H, *J*=7.5 Hz), 3.84 (s, 3H), 6.85–7.00 (m, 2H), 7.30–7.45 (m, 1H), 7.61 (dd, 1H, *J*=7.6 Hz, *J*=1.8 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz, 298 K): δ ppm 13.7, 22.3, 23.9, 31.4, 43.5, 55.2, 111.4, 120.4, 128.7, 129.9, 132.8, 158.1, 202.9. MS (EI) *m*/*z*=206 $[M]^+$.

4.3.19. 3-Ethoxy-1-(4-(3-phenylprop-2-ynyloxy)phenyl)propan-1-one **2t**. Yield: 76%; yellow solid; mp 61 °C. IR (cm^{-1}) 2939, 2803, 1669, 1595. ^1H NMR ($CDCl_3$, 300 MHz, 298 K): δ ppm 1.18 (t, 3H, *J*=7.0 Hz), 3.20 (t, 2H, *J*=6.7 Hz), 3.52 (q, 2H, *J*=7.0 Hz), 3.84 (t, 2H, *J*=6.7 Hz), 4.96 (s, 2H), 7.06 (d, 2H, *J*=9.0 Hz), 7.30–7.40 (m, 3H), 7.40–7.50 (m, 2H), 7.97 (d, 2H, *J*=9.0 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz, 298 K): δ ppm 15.0, 38.6, 56.6, 65.8, 66.4, 83.0, 87.7, 114.6 (2), 121.9, 128.2 (2), 128.8, 130.3 (2), 130.7, 131.7 (2), 161.5, 196.9. MS (ESI) *m*/*z*=309 $[M+H]^+$. Anal. Calcd for $C_{20}H_{20}O_3$: C, 77.90; H, 6.54. Found C, 77.54; H, 6.23.

4.4. Typical procedure for the synthesis of ketones under microwaves irradiation

To an Emrys Optimizer 0.5–2 mL Pyrex reaction vessel were added alkyne (1 mmol) and PTSA (see tables for quantity) in EtOH (1 mL). The reaction vessel was then placed in the Emrys Optimizer and exposed to microwave irradiation according to the following specifications: temperature, time (see tables), fixed hold time: on, sample absorption: high, pre-stirring: 60 s. After cooling to room temperature, H_2O (3 mL) was added to the crude and the mixture was extracted with EtOAc (3×2 mL). Organic layers were dried, concentrated and the crude mixture was purified by column chromatography on silica gel.

4.4.1. 1-(3-Methoxyphenyl)-hexan-1-one **2r**. Yield: 60%. IR (cm^{-1}) 2954, 2932, 1684, 1596, 1260. ^1H NMR ($CDCl_3$, 300 MHz, 298 K): δ ppm 0.89 (t, 3H, *J*=7.6 Hz), 1,27–1.40 (m, 4H), 1.70 (m, 2H), 2.92 (t, 2H, *J*=7.6 Hz), 3.81 (s, 3H), 7.07 (ddd, 1H, *J*=8.1 Hz, *J*=2.8 Hz, *J*=0.9 Hz), 7.35 (dd, 1H, *J*=8.1 Hz, *J*=8.1 Hz), 7.46 (dd, 1H, *J*=2.8 Hz, *J*=1.7 Hz), 7.51 (ddd, 1H, *J*=8.1 Hz, *J*=1.7 Hz, *J*=0.9 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz, 298 K): δ ppm 14.0, 22.6, 24.2, 31.6, 38.7, 55.4, 112.3, 119.2, 120.6, 129.4, 138.4, 159.7, 202.2. Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found C, 75.35; H, 8.54.

4.4.2. 1-Phenylhexan-1-one **2s**[30]. Yield: 89%; colorless oil. IR (cm^{-1}) 2930, 1683, 1597, 1448, 745. ^1H NMR ($CDCl_3$, 300 MHz, 298 K): δ ppm 0.91 (t, 3H, *J*=7.2 Hz), 1.34–1.44 (m, 4H), 1.75 (quint, 2H, *J*=7.2 Hz), 2.96 (t, 2H, *J*=7.2 Hz), 7.40–7.59 (m, 3H), 7.93–7.98 (dt, 2H, *J*=5.8 Hz, *J*=1.4 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz, 298 K): δ ppm 13.9, 22.5, 24.1, 31.5, 38.6, 128.0 (2), 128.5 (2), 132.8, 137.2, 200.5.

4.4.3. 4-Ethoxy-4-(4-isopropylphenyl)-1-(4-methoxyphenyl)-butan-1-one **2u**. Yield: 69%. IR (cm^{-1}) 2960, 1672, 1596, 1509, 1261, 1165, 987, 828. ^1H NMR ($CDCl_3$, 300 MHz, 298 K): δ ppm 1.15 (t, 3H, *J*=6.9 Hz), 1.24 (d, 6H, *J*=6.6 Hz), 2.08–2.17 (m, 2H), 2.90 (q, 1H, *J*=6.9 Hz), 3.01 (td, 2H, *J*=7.2 Hz, *J*=1.8 Hz), 3.26 (m, 2H), 3.86 (s, 3H), 4.31 (t, 1H, *J*=6.3 Hz), 6.92 (d, 2H, *J*=8.8 Hz), 7.12–7.25 (m, 4H), 7.92 (d, 2H, *J*=8.8 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz, 298 K): δ ppm 15.3, 24.0 (2), 32.9, 33.8, 34.4, 55.4, 64.1, 80.8, 113.6 (2), 126.4 (4), 130.3 (3), 139.9, 148.0, 163.3, 198.8. Anal. Calcd for $C_{22}H_{28}O_3$: C, 77.61; H, 8.29. Found C, 77.62; H, 8.36.

4.4.4. Ethyl 4-(4-methoxyphenyl)-4-oxobutanoate **2v**[30]. Yield: 51%. IR (cm^{-1}) 2980, 2841, 1730, 1599, 1576, 1510, 1249, 1217, 1163, 1023, 833, 799. ^1H NMR ($CDCl_3$, 300 MHz, 298 K): δ ppm 1.25 (t, 3H, *J*=7.1 Hz), 2.72 (t, 2H, *J*=6.7 Hz), 3.25 (t, 2H, *J*=6.7 Hz), 3.85 (s, 3H), 4.10 (q, 2H, *J*=7.1 Hz), 6.90 (d, 2H, *J*=9.0 Hz), 7.95 (d, 2H, *J*=9.0 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz, 298 K): δ ppm 14.1, 28.4, 33.0, 55.4, 60.5, 113.7 (2), 129.7 (2), 130.2, 163.5, 173.0, 196.6.

4.4.5. 1-(4-Methoxyphenyl)-ethanone **2w**[30]. Yield: 77%. IR (cm^{-1}) 1672, 1600, 1312, 1205. ^1H NMR ($CDCl_3$, 300 MHz, 298 K): δ ppm 2.55 (s, 3H), 3.87 (s, 3H), 6.92 (d, 2H, *J*=8.9 Hz), 7.95 (d, 2H, *J*=8.9 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz, 298 K): δ ppm 26.7, 55.9, 114.1 (2), 130.7, 131.0 (2), 163.9, 197.2.

4.4.6. 1-(4-Aminophenyl)-hexan-1-one **2x**[30]. Yield: 91%. IR (cm^{-1}) 3462, 3355, 2933, 1627, 1587, 1560, 1318, 1258, 1210, 1176, 818. ^1H NMR ($CDCl_3$, 300 MHz, 298 K): δ ppm 0.90 (t, 3H, *J*=6.6 Hz), 1.36 (m, 4H), 1.73 (q, 2H, *J*=7.3 Hz), 2.85 (t, 2H, *J*=7.3 Hz), 4.06 (br s, 2H, NH_2), 6.64 (d, 2H, *J*=8.5 Hz), 7.81 (d, 2H, *J*=8.5 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz, 298 K): δ ppm 13.8, 22.4, 24.5, 31.5, 37.8, 113.5 (2), 127.2, 130.3 (2), 151.2, 198.8.

4.4.7. 1-(4-Methoxyphenyl)-2-p-tolyl-ethanone **5a**[19i]. Yield: 97%. IR (cm^{-1}) 3005, 2901, 1678, 1596, 1501, 1321, 1254, 1177, 1027, 995, 829, 774. ^1H NMR ($CDCl_3$, 300 MHz, 298 K): δ ppm 2.32 (s, 3H), 3.86 (s, 3H), 4.19 (s, 2H), 6.92 (d, 2H, *J*=8.7 Hz), 7.12 (d, 2H, *J*=8.1 Hz), 7.16 (d, 2H, *J*=8.1 Hz), 7.98 (d, 2H, *J*=8.7 Hz).

^{13}C NMR ($CDCl_3$, 75 MHz, 298 K): δ ppm 21.0, 44.9, 55.4, 113.7 (2), 129.2 (2), 129.3 (2), 129.7, 130.9 (2), 131.8, 136.3, 163.4, 196.4.

4.4.8. 1-(4-Methoxyphenyl)-2-(4-bromophenyl)-ethanone ***5b***[19i]. Yield: 98%. IR (cm^{-1}) 33017, 1675, 1598, 1573, 1257, 1177. ^{1}H NMR ($CDCl_3$, 300 MHz, 298 K): δ ppm 3.89 (s, 3H), 4.18 (s, 2H), 6.93 (dd, 2H, J=6.6 Hz, J=1.8 Hz), 7.14 (dd, 2H, J=7.5 Hz, J=2.2 Hz), 7.44 (dd, 2H, J=6.6 Hz, J=1.8 Hz), 7.97 (dd, 2H, J=7.5 Hz, J=2.2 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz, 298 K): δ ppm 44.5, 55.5, 113.9 (2), 120.8, 128.5, 130.8 (2), 131.2 (2), 131.7 (2), 134.0, 163.7, 195.5.

4.4.9. 2-Phenyl-1-p-tolyl-ethanone ***5c***[19i]. Yield: 80%. IR (cm^{-1}) 1680, 1603, 1334, 1222, 1198, 1172, 814, 729. ^{1}H NMR ($CDCl_3$, 300 MHz, 298 K): 2.42 (s, 3H), 4.29 (s, 2H), 7.25–7.44 (m, 7H), 7.95 (d, 2H, J=8.1 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz, 298 K): δ ppm 21.6, 45.3, 126.7, 128.6 (2), 128.7 (2), 129.2 (2), 129.4 (2), 134.0, 134.7, 143.9, 197.3.

4.4.10. 1-(4-Aminophenyl)-2-p-tolyl-ethanone ***5d***[19i]. Yield: 79%. IR (cm^{-1}) 3472, 3356, 1656, 1630, 1587, 1567, 1335, 1316, 1232, 1174, 814. ^{1}H NMR ($CDCl_3$, 300 MHz, 298 K): δ ppm 2.31 (s, 3H), 4.14 (m, 4H), 6.62 (d, 2H, J=8.7 Hz), 7.11 (d, 2H, J=7.8 Hz), 7.16 (d, 2H, J=7.8 Hz), 7.86 (d, 2H, J=8.7 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz, 298 K): δ ppm 21.0, 44.6, 113.7 (2), 127.1, 129.1 (2), 129.2 (2), 131.1 (2), 132.3, 136.1, 151.1, 196.0.

4.4.11. 2-Phenyl-1-(3,4,5-trimethoxyphenyl)-ethanone ***5e***[19i]. Yield: 68%. IR (cm^{-1}) 2940, 2360, 1676, 1582, 1504, 1453, 1411, 1331, 1152, 1000, 697. ^{1}H NMR ($CDCl_3$, 300 MHz, 298 K): δ ppm 3.85 (s, 6H), 3.87 (s, 3H), 4.22 (s, 2H), 7.23–7.33 (m, 7H). ^{13}C NMR ($CDCl_3$, 75 MHz, 298 K): δ ppm 45.6, 56.2 (2), 60.9, 106.3 (2), 126.9, 128.7 (2), 129.2 (2), 131.7, 134.8, 141.6, 153.0 (2), 196.4.

4.4.12. 1-(4-Methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)-ethanone ***5f***[19e]. Yield: 55%. IR (cm^{-1}) 2935, 2834, 1675, 1596, 1509, 1122. ^{1}H NMR ($CDCl_3$, 300 MHz, 298 K): δ ppm 3.81 (s, 3H), 3.83 (s, 6H), 3.86 (s, 3H), 4.15 (s, 2H), 6.46 (s, 2H), 6.93 (d, 2H, J=8.9 Hz), 7.98 (d, 2H, J=8.9 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz, 298 K): δ ppm 45.4, 55.4, 56.1 (2), 60.8, 106.4 (2), 113.8 (2), 129.6, 130.5 (2), 130.9, 136.8, 153.3 (2), 163.6, 196.1.

4.4.13. 2-(4-Methoxyphenyl)benzofuran ***7a***[32]. Yield: 79%; colorless solid; mp 148–150 °C. IR (cm^{-1}) 2960, 2837, 1606, 1502, 1451, 1241, 1022, 835, 818, 700. ^{1}H NMR ($CDCl_3$, 300 MHz, 298 K): δ ppm 3.87 (s, 3H), 6.89 (d, 1H, J=0.9 Hz), 6.99 (d, 2H, J=9.0 Hz), 7.19–7,29 (m, 2H), 7.50–7.58 (m, 2H), 7.81 (d, 2H, J=9.0 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz, 298 K): δ ppm 55.3, 99.7, 111.0, 114.2 (2), 120.5, 122.8, 123.3, 123.7, 126.4 (2), 129.5, 154.7, 156.0, 159.9. MS (APCI) m/z=225 $(M+H)^+$.

4.4.14. 2-(2-Methoxyphenyl)benzofuran ***7b***[32]. Yield: 83%; colorless solid; mp 78–80 °C. IR (cm^{-1}) 2939, 1492, 1446, 1282, 1247, 1015, 742. ^{1}H NMR ($CDCl_3$, 300 MHz, 298 K): δ ppm 3.89 (s, 3H), 6.90 (d, 1H, J=8.3 Hz), 6.98 (td, 1H, J=7.6 Hz, J=1.0 Hz), 7.09–7.26 (m, 4H), 7.40–7.43 (m, 1H), 7.48–7.51 (m, 1H), 7.98 (dd, 1H, J=7.8 Hz, J=1.7 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz, 298 K): δ ppm 55.6, 106.5, 111.0, 111.2, 119.5, 120.9, 121.2, 122.8, 124.2, 127.2, 129.4, 129.9, 152.3, 154.0, 166.7. MS (APCI) m/z=225 $(M+H)^+$.

4.4.15. 2-(Naphthalen-1-yl)benzofuran ***7c***[32]. Yield: 93%; yellow solid; mp 161–162 °C. IR (cm^{-1}) 3055, 1452, 1257, 979, 793, 771, 737. ^{1}H NMR ($CDCl_3$, 300 MHz, 298 K): δ ppm 7.11 (s, 1H), 7.29–7.40 (m, 2H), 7.55–7.64 (m, 4H), 7.69 (d, 1H, J=7.8 Hz), 7.91–7.95 (m, 3H), 8.50 (d, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz, 298 K): δ ppm 106.1, 111.4, 121.1, 123.1, 124.5, 125.4, 125.7, 126.3, 127.0, 127.5, 128.4, 128.8, 129.2, 129.7, 130.9, 134.1, 155.1, 155.8. MS (APCI) m/z=245 $(M+H)^+$.

4.4.16. 2-(Benzofuran-2-yl)phenol ***7d***[33]. Yield: 61%; colorless solid; mp 97 °C. IR (cm^{-1}) 3451, 3352, 1590, 1446, 1212, 1017, 743. ^{1}H NMR ($CDCl_3$, 300 MHz, 298 K): δ ppm 6.72–6.78 (m, 2H), 6.84 (s, 1H), 6.91 (s, 1H), 6.99–7.09 (m, 3H), 7.28 (m, 1H), 7.35 (m, 1H), 7.46 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz, 298 K): δ ppm 103.5, 111.2, 116.2, 117.5, 120.9, 121.1, 123.6, 124.6, 127.3, 128.6, 130.4, 153.5, 154.1, 154.4. MS ($APCI^+$) m/z=211 $[M+H]^+$.

4.4.17. 2-(2,4-Dimethoxyphenyl)benzofuran ***7e***. Yield: 65%; colorless solid; mp 49–52 °C. IR (cm^{-1}) 2937, 2836, 1610, 1502, 1252, 1208, 1158, 1029, 796, 740. ^{1}H NMR ($CDCl_3$, 300 MHz, 298 K): δ ppm d 3.90 (s, 3H), 4.01 (s, 3H), 6.61–6.68 (m, 2H), 7.22–7.32 (m, 3H), 7.54 (dt, 1H, J=6.6 Hz, J=1.1 Hz), 7.62 (m, 1H), 8.03 (d, 1H, J=8.6 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz, 298 K): δ ppm 55.6 (2), 98.9, 104.4, 105.0, 110.7, 112.9, 120.8, 122.7, 123.7, 128.1, 130.2, 152.6, 153.8, 157.9, 161.1. MS ($APCI^+$) m/z=255.0 $(M+H)^+$. Anal. Calcd for $C_{16}H_{14}O_3$: C, 75.57; H, 5.55. Found C, 75.39; H, 5.41.

4.4.18. 2-(4-Methoxyphenyl)benzo[b]thiophene ***7f***[30]. Yield: 94%; colorless solid; mp 199–201 °C. IR (cm^{-1}) 2357, 1604, 1497, 1434, 1244, 1077, 1030, 820, 746. ^{1}H NMR ($CDCl_3$, 300 MHz, 298 K): δ ppm 3.86 (s, 3H), 6.96 (d, 2H, J=8.8 Hz), 7.28–7.37 (m, 2H), 7.43 (s, 1H), 7.65 (d, 2H, J=8.7 Hz), 7.74 (d, 1H, J=7.2 Hz), 7.81 (d, 1H, J=7.7 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz, 298 K): δ ppm 55.4, 114.3 (2), 118.2, 122.2, 123.2, 123.9, 124.4, 127.0, 127.7 (2), 139.2, 140.9, 144.1, 159.8. MS (APCI) m/z=241 $(M+H)^+$.

4.4.19. 2-(Naphthalen-1-yl)benzo[b]thiophene ***7g***[34]. Yield: 94%; beige solid; mp 106–108 °C. IR (cm^{-1}) 3051, 1456, 1435, 1390, 1155, 799, 772, 743, 725. ^{1}H NMR ($CDCl_3$, 300 MHz, 298 K): δ ppm 7.38–7.48 (m, 2H), 7.49 (s, 1H), 7.53–7.58 (m, 3H), 7,69 (d, 1H, J=7,0 Hz), 7.87–7.96 (m, 4H), 8.32–8.35 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz, 298 K): δ ppm 122.2, 123.7, 124.2, 124.4, 124.6, 125.3, 125.9, 126.3, 126.8, 128.5, 128.6, 129.0, 131.9, 132.5, 133.9, 140.3, 140.4, 142.3. MS (APCI) m/z=261 $(M+H)^+$.

4.4.20. 2-(Benzo[b]thiophen-2-yl)phenol ***7h***. Yield: 88%; colorless solid; mp 91–94 °C. IR (cm^{-1}) 3511, 3054, 1481, 1449, 1432, 1333, 1290, 1173, 747. ^{1}H NMR ($CDCl_3$, 300 MHz, 298 K): δ ppm 5.63 (s, 1H), 6.99–7.05 (m, 2H), 7.27–7.43 (m, 3H), 7.40 (dd, 1H, J=7.6 Hz, J=1.6 Hz), 7.56 (s, 1H), 7.81–7.89 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz, 298 K): δ ppm 116.5, 121.0, 121.2, 122.3, 123.0, 123.8, 124.7, 124.8, 130.0, 130.4, 139.4, 140.0, 140.4, 152.9. MS ($APCI^+$) m/z=227.0 $(M+H)^+$. Anal. Calcd for $C_{14}H_{10}OS$: C, 74.31; H, 4.45. Found C, 74.01; H, 4.22.

4.4.21. 3-(2-Methoxyphenyl)-1H-isochromen-1-one ***7i***[23]. Yield: 95%; white solid; mp 122–124 °C. IR (cm^{-1}) 1724, 1625, 1493, 1225, 1021, 754. ^{1}H NMR ($CDCl_3$, 300 MHz, 298 K): δ ppm 3.96 (s, 3H), 7.00 (d, 1H, J=8.3 Hz), 7.07 (t, 1H, J=8.0 Hz), 7.36–7.40 (m, 2H), 7.45–7.51 (m, 2H), 7.70 (t, 1H, J=8.3 Hz), 7.97 (dd, 1H, J=7.9, J=1.7 Hz), 8.30 (d, 1H, J=7.9 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz, 298 K): δ ppm 55.8, 107.1, 111.5, 120.8, 120.9, 121.0, 126.4, 128.1, 129.0, 129.5, 130.9, 134.8, 138.2, 150.6, 157.4, 162.8. MS (APCI) m/z=253 $(M+H)^+$.

4.4.22. 2-(2-Methylprop-1-enyl)benzofuran ***10a***[35]. Yield: 72%; colorless solid; mp 44–48 °C. IR (cm^{-1}) 2929, 1453, 1196, 1055, 847, 790, 748. ^{1}H NMR ($CDCl_3$, 300 MHz, 298 K): δ ppm 1.98 (s, 3H), 2.13 (s, 3H), 6.20 (s, 1H), 6.51 (s, 1H), 7.17–7.25 (m, 2H), 7.43 (d, 1H, J=7.5 Hz), 7.43 (d, 1H, J=7.5 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz, 298 K):

δ ppm 20.7, 27.5, 103.8, 110.9, 114.7, 120.5, 122.7, 123.7, 129.2, 139.7, 154.2, 155.8. MS (APCI$^+$) m/z=173.0 (M+H)$^+$.

4.4.23. (E)-2-(Hex-1-enyl)benzofuran ***10b***. Yield: 47%. ^{1}H NMR ($CDCl_3$, 300 MHz, 298 K): δ ppm 0.93–0.98 (m, 3H), 1.37–1.53 (m, 4H), 2.27 (q, 2H, *J*=6.8 Hz), 6.33 (d, 1H, *J*=16.0 Hz), 6.47–6.60 (m, 2H), 7.15–7.26 (m, 2H), 7.41–7.50 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz, 298 K): δ ppm 14.1, 22.4, 31.3, 32.8, 102.7, 110.9, 118.7, 120.7, 122.8, 124.1, 129.3, 134.1, 154.7, 155.4. Anal. Calcd for $C_{14}H_{16}O$: C, 83.96; H, 8.05. Found C, 83.66; H, 7.82.

4.4.24. (E)-2-Styrylbenzofuran ***10c***[30]. Yield: 73%; colorless solid; 124–126mp °C. IR (cm^{-1}) 3057, 1450, 1256, 958, 907, 804, 738, 691. ^{1}H NMR ($CDCl_3$, 300 MHz, 298 K): δ ppm 6.70 (s, 1H), 7.03 (d, 1H, *J*=16.2 Hz), 7.20–7.42 (m, 6H), 7.50 (d, 1H, *J*=8.0 Hz), 7.55 (d, 3H, *J*=7.4 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz, 298 K): δ ppm 105.3, 111.0, 116.6, 121.0, 123.0, 124.8, 126.8 (2), 128.3, 128.9, 129.3, 130.4, 136.7, 155.0, 155.2. MS (APCI$^+$) m/z=221.0 (M+H)$^+$.

4.4.25. (E)-2-(4-Methoxystyryl)benzofuran ***10d***. Yield: 75%; colorless solid; mp 143 °C. IR (cm^{-1}) 2996, 1600, 1506, 1450, 1238, 1176, 1025, 965, 944, 826, 816, 743. ^{1}H NMR ($CDCl_3$, 300 MHz, 298 K): δ ppm 3.85 (s, 3H), 6.63 (s, 1H), 6.86–6.94 (m, 3H), 7.18–7.32 (m, 3H), 7.47–7.54 (m, 4H). ^{13}C NMR ($CDCl_3$, 75 MHz, 298 K): δ ppm 55.5, 104.4, 110.9, 114.4 (2), 114.5, 120.8, 122.9, 124.4, 128.2 (2), 129.4, 129.5, 130.1, 154.9, 155.6, 159.9. MS (APCI$^+$) m/z=251.0 (M+H)$^+$. Anal. Calcd for $C_{17}H_{14}O_2$: C, 81.58; H, 5.64. Found C, 81.44; H, 5.52.

4.4.26. (E)-2-Styrylbenzo[b]thiophene ***10e***[36]. Yield: 78%; beige solid; mp 198 °C. IR (cm^{-1}) 2926, 1447, 1432, 947, 818, 739, 725, 690. ^{1}H NMR ($CDCl_3$, 300 MHz, 298 K): δ ppm 7.01 (d, 1H, *J*=16.0 Hz), 7.26–7.40 (m, 7H), 7.52 (d, 2H, *J*=7.4 Hz), 7.70 (m, 1H), 7.78 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz, 298 K): δ ppm 122.4, 122.5, 123.4, 123.6, 124.7, 124.9, 126.7 (2), 128.2, 128.9 (2), 131.0, 136.8, 139.1, 140.4, 143.1. MS (APCI$^+$) m/z=237.0 (M+H)$^+$.

4.4.27. 2,2′-Bibenzofuran ***11a***. Yield: 58%; colorless solid; mp 177–178 °C. IR (cm^{-1}) 1439, 1255, 1172, 1048, 875, 814, 748, 611. ^{1}H NMR ($CDCl_3$, 300 MHz, 298 K): δ ppm 6.92–6.96 (m, 2H), 7.03 (m, 1H), 7.07 (m, 1H), 7.18–7.27 (m, 3H), 7.46 (m, 1H), 7.54 (m, 1H), 7.65 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz, 298 K): δ ppm 103.8, 111.4, 121.5, 123.5, 125.2, 128.7, 147.8, 155.2. MS (APCI$^+$) m/z=235.0 (M+H)$^+$. Anal. Calcd for $C_{16}H_{10}O_2$: C, 82.04; H, 4.30. Found C, 81.77; H, 4.12.

4.4.28. 2-(Benzo[b]thiophen-2-yl)benzofuran ***11b***. Yield: 76%; colorless solid; mp 207–209 °C. IR (cm^{-1}) 3055, 1426, 1202, 988, 932, 878, 827, 799, 737, 625. ^{1}H NMR ($CDCl_3$, 300 MHz, 298 K): δ ppm 7.03 (s, 1H), 7.29–7.44 (m, 4H), 7.57 (d, 1H, *J*=8.0 Hz), 7.62 (d, 1H, *J*=7.4 Hz), 7.76 (s, 1H), 7.85 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz, 298 K): δ ppm 103.4, 111.3, 121.1, 121.2, 122.4, 123.4, 124.1, 124.9, 125.0, 125.1, 129.0, 133.0, 139.7, 140.2, 151.1, 155.5. MS (APCI$^+$) m/z=251.0 (M+H)$^+$. Anal. Calcd for $C_{16}H_{10}OS$: C, 76.77; H, 4.03. Found C, 76.44; H, 3.80.

4.4.29. 2-(Benzofuran-2-yl)-1-(4-methoxyphenyl)ethanone ***11c***. Yield: 94%; colorless solid; mp 104–106 °C. IR (cm^{-1}) 2936, 1678, 1454, 1251, 1219, 1170, 751. ^{1}H NMR ($CDCl_3$, 300 MHz, 298 K): δ ppm 3.87 (s, 3H), 4.40 (s, 2H), 6.62 (s, 1H), 6.95 (d, 2H, *J*=8.7 Hz), 7.16–7.26 (m, 2H), 7.43 (d, 1H), 7.50 (d, 1H), 8.04 (d, 2H, *J*=8.7 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz, 298 K): δ ppm 38.8, 55.7, 105.3, 111.2, 114.1 (2), 120.8, 122.8, 123.9, 128.8, 129.3, 131.2 (2), 152.0, 155.1, 164.0, 193.1. MS (APCI$^+$) m/z=289.0 (M+Na)$^+$. Anal. Calcd for $C_{17}H_{14}O_3$: C, 76.68; H, 5.30. Found C, 76.39; H, 4.99.

4.4.30. 2-(Naphthalen-2-ylethynyl)benzofuran ***11d***. Yield: 28%; beige solid; mp 136–137 °C. IR (cm^{-1}) 3058, 2934, 1448, 1258, 1165, 906, 819, 739. ^{1}H NMR ($CDCl_3$, 300 MHz, 298 K): δ ppm 7.07 (d, 1H, *J*=0.7 Hz), 7.27–7.32 (m, 1H), 7.38 (m, 1H), 7.51–7.57 (m, 3H), 7.60–7.66 (m, 2H), 7.85–7.88 (m, 3H), 8.15 (s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz, 298 K): δ ppm 80.2, 95.7, 111.4, 111.8, 119.3, 121.4, 123.5, 125.8, 126.9, 127.3, 128.0, 128.1, 128.4, 132.1, 133.1, 133.3, 139.0, 150.5, 155.1. MS (APCI$^+$) m/z=269.0 (M+H)$^+$. Anal. Calcd for $C_{20}H_{12}O$: C, 89.53; H, 4.51. Found C, 89.11; H, 4.32.

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