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TBAF-Catalyzed Cyclization Reactions of *o*-(Alkynyl)phenyl Propargyl Alcohols with Malonate Esters: A Possible Cation-π Interaction as The Activation Approach

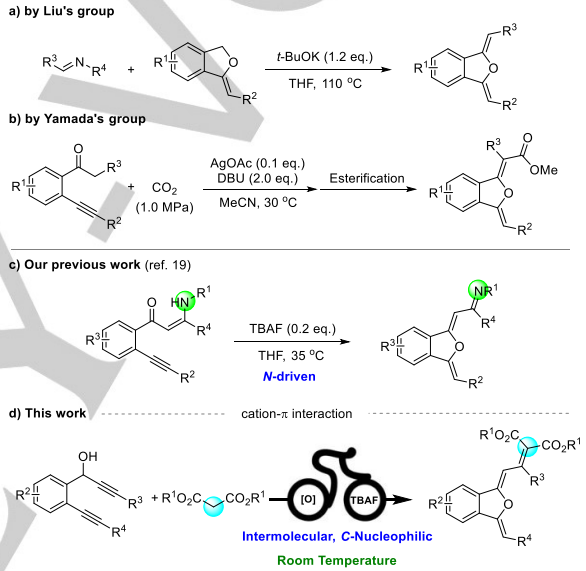
Yulei Zhao,*[a] Xuqiang Guo,[a] Zongkang Wang,[a] Duyi Shen,*[a] Tingting Chen,[a] Nan Wu,[a] Shina Yan,[a] and Jinmao You[a,b]

Dedication ((optional))

Abstract: An efficient method has been devised for the synthesis of dihydroisobenzofuran derivatives through the reaction of *in situ* generated ynones with potentially *C*-nucleophilic malonate esters. All of the products are capable to be prepared by applying the tandem strategy at room temperature. The reaction was realized through a combination of the pivotal TBAF-catalyzed conjugate addition and selective *O*-nucleophilic cyclization. As revealed by the control experiments, both the basicity of fluoride anion and ammonium cation-π interaction with alkyne unit might play crucial roles in the cyclization reaction.

Introduction

Tetrabutylammonium fluoride (TBAF), known as a soluble source of fluoride,[1] has been widely applied as fluorinated reagent,[2] reagent for the cleavage of silyl ethers,[3] basic catalyst,[4] *etc.*[5-7] The application of TBAF is primarily dependent on the effect of fluoride anion. However, due to its noticeable catalytic activity for the cyclization of alkyne, the effect of tetraalkylammonium ion has recently drawn increasing attention for research.[8] In 2011, Lepore et al. reported a unique cyclization of β-alkynyl hydrazines to synthesize azaproline derivatives, which was mediated by nonmetal ammonium cation catalysts.[8b] Subsequently, they came up with the direct evidence for ammonium cation-π interaction with a non-conjugated alkyne by Raman spectroscopy.[8a] As demonstrated by their study on the homogeneous systems, the ammonium agent is conducive to the formation of nitrogen-carbon bond[8b] (cyclization process) through a cation-π interaction with the alkyne unit.[8a] In 2017, Lepore's group further developed a TBAF-catalyzed approach to the synthesis of isoxazolines and pyrazolines through the cyclization of alkyne substrates.[8c] Although cation-π interaction is known as a sort of intermolecular force,[9] this cation binding force was demonstrated more in aromatic systems.[10] For the characteristics of ammonium cation-π interaction with alkyne, experimental exploration remains limited.



Scheme 1. Construction of dihydroisobenzofuran structures.

Dihydroisobenzofuran is key structural subunit and widely present in a variety of different biologically active structures.[11] Despite advances, the synthetic routes to dihydroisobenzofuran derivatives are primarily concentrated on high temperatures[12] or precious metal-catalyzed[13] approaches (Scheme 1a and 1b). It remains essential to explore new convenient procedures to synthesize dihydroisobenzofuran derivatives using accessible starting materials and low-cost catalyst under mild conditions. Enaminone, exhibiting high *N*-[14], *C*-[15] and *O*-nucleophilicity[16], shows a wide range of synthetic applications[17]. Based on our research on tandem reactions,[18] a bifunctional TBAF catalyzed selective *O*-nucleophilic cyclization of enaminone was reported recently for the synthesis of dihydroisobenzofuran derivatives (Scheme 1c),[19] wherein a cation-π interaction as the activated process might be necessitated. In this intramolecular isomerization reaction, the nitrogen atom of enaminone acts as an electron-donor to initiate the nucleophilic cyclization to intramolecular alkyne moiety. Accordingly, it is speculated that an appropriate independent *C*-nucleophile is also suited to the construction of dihydroisobenzofuran derivatives. Herein, the intermolecular cyclization reaction of *o*-(alkynyl)phenyl propargyl alcohols with potentially *C*-nucleophilic malonate esters is

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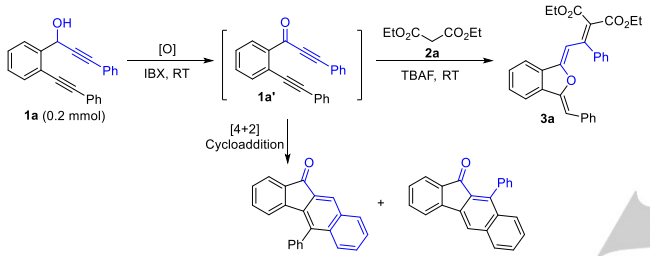
developed to construct dihydroisobenzofurans through a possible ammonium cation-π interaction process (Scheme 1d).

Results and Discussion

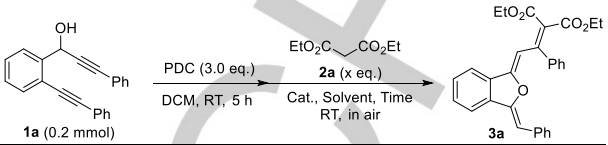
Our initial efforts focused on the reaction of *o*-(alkynyl)phenyl propargyl alcohol[20] **1a** and diethyl malonate **2a** using 2-Iodoxybenzoic acid (IBX) as the oxidant and TBAF as the subsequent catalyst (Scheme 2). Nevertheless, it was inevitable for all the attempts to partly result in intramolecular [4+2] cycloaddition[21]. Acidic IBX has a potential to promote the occurrence of this side reaction. In order to inhibit the undesired cycloaddition, pyridinium dichromate (PDC) was taken as the oxidant. To our delight, when PDC was employed, only an extremely small amount of [4+2] cycloaddition was detected as the oxidation process proceeded. This result encouraged us to optimize the reaction conditions with **1a** and **2a** as model substrates (Table 1).



Scheme 2. Initial exploration with IBX as oxidant.

Firstly, a variety of different catalysts were examined for the subsequent addition-cyclization process (Table 1, entries 1-9). When the reaction occurred in the presence of 2.0 equiv of TBAF as the catalyst at room temperature, the desired product **3a** was obtained in 91% yield within 2 hours (entry 1). Nevertheless, other quaternary ammonium salt represented by tetrabutylammonium bromide (TBAB), tetrabutylammonium chloride (TBAC) and tetrabutylammonium iodide (TBAI) were identified as ineffective for the formation of **3a** (entries 2-4). As demonstrated by these results (entry 1 vs entries 2-4), the basicity offered by fluoride anion may play a significant role. Based on this discovery, the alkaline Bu_4NOH was employed, and **3a** was obtained in 64% yield (entry 5). When $TBAF{\cdot}3H_2O$ was taken as the catalyst, 88% yield could be achieved within 2 hours (entry 6). Despite the investigation conducted into other common Brønsted base (such as, sodium carbonate, triethylamine or potassium hydroxide), no significant catalytic activity was observed for the cyclization process (entries 7-9). Secondly, different varieties of solvents (such as, ethyl acetate, dichloromethane, toluene and acetonitrile) were screened, only resulting in 78-84% yields for the desired dihydroisobenzofuran (entries 10-13). Finally, the optimization usage of reagents was scheduled. When the amount of TBAF declined from 2.0 equiv to 0.5 equiv, the yield of **3a** was found to be slightly up-regulated to 91% (entry 14). When the amount of **2a** was reduced to 1.2 equiv from 2.0 equiv, 91% yield could also be achieved (entry 15). Further reduce the dosage of TBAF to 0.2 equiv led to a slightly raised yield (entry 16, 92%). Without TBAF, no **3a** was detected (entry 17), which suggested that TBAF was requisite for the cyclization process to take place. In addition, it is worth noting that the slight [4+2] cycloaddition as the side reaction exists in most investigations catalyzed by TBAF. X-ray crystallography was performed to confirm the structure of **3a**.[22]

Table 1. Optimization of the reaction conditions[a]



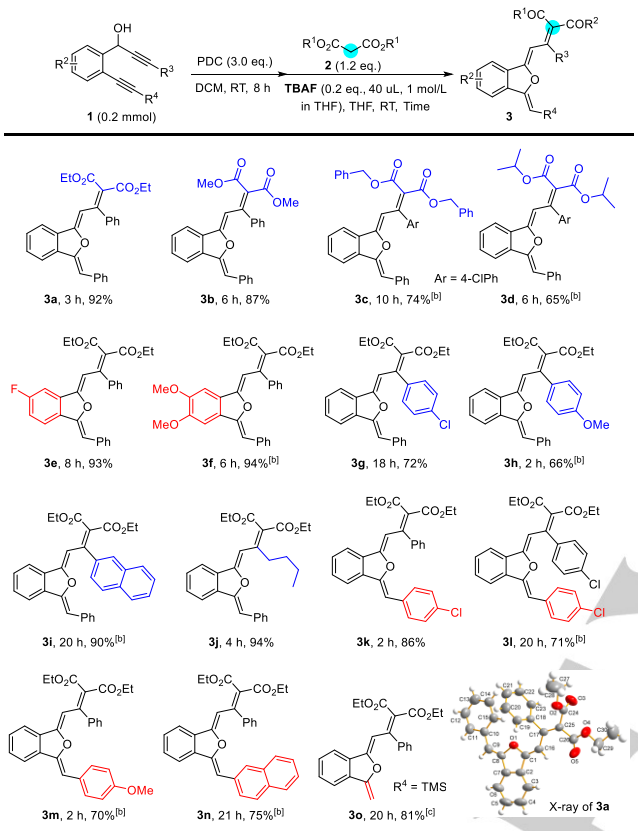
Entry	Cat.	Solvent	**2** (x eq.)	Time (h)	Yield (%)
1	TBAF (2 eq.)	THF	2	2	91
2	TBAB (2 eq.)	THF	2	2	0
3	TBAC (2 eq.)	THF	2	2	0
4	TBAI (2 eq.)	THF	2	2	0
5	Bu_4NOH[b] (2 eq.)	THF	2	2	64
6	$TBAF{\cdot}3H_2O$ (2 eq.)	THF	2	2	88
7	Na_2CO_3 (2 eq.)	THF	2	2	0
8	Et_3N (2 eq.)	THF	2	2	0
9	KOH (2 eq.)	THF	2	2	ND
10	TBAF (2 eq.)	EtOAc	2	2	84
11	TBAF (2 eq.)	DCM	2	2	78
12	TBAF (2 eq.)	PhMe	2	2	81
13	TBAF (2 eq.)	MeCN	2	2	83
14	TBAF (0.5 eq.)	THF	2	2	91
15	TBAF (0.5 eq.)	THF	1.2	2	91
16	**TBAF (0.2 eq.)**	**THF**	**1.2**	**3**	**92**
17	TBAF (0 eq.)	THF	1.2	20	0

[a] TBAF (1 mol/L in THF) was used. RT = room temperature. ND = no desired product was detected. [b] 50wt.% in water.

With the optimal reaction conditions established (Table 1, entry 16), the scope and generality of this methodology was then explored (Table 2). Firstly, an investigation was conducted into the effect of different malonate esters. It was discovered that dimethyl malonate or dibenzyl malonate substrates underwent the reaction smoothly to afford **3b** and **3c** in 87% and 74% yield, respectively. When sterically-hindered diisopropyl malonate was involved in for the reaction, the corresponding product **3d** could also be derived in 65% yield as well. Next, the electronic effect of R^2 substituents was closely examined. The substrates with electron-withdrawing (e.g., **3e**, R^2 = 6-F, 93%) or electron-donating (e.g., **3f**, R^2 = 5,6-dimethoxy, 94%) groups were all tolerable to furnish the corresponding products in excellent yields. Then, the electronic effect of R^3 was explored. Substrates with both *p*-ClPh and *p*-OMePh groups were suitable for the reaction, thus offering the desired isobenzofuran diesters in moderate to good yields (**3g**, 72%; **3h**, 66%). When R^3 was 2-naphthyl group, the corresponding **3i** was formed in 90% yield. n-Butyl also exhibited an excellent compatibility, thus offering the corresponding product **3j** in 94% yields. For R^4, the *p*-ClPh, *p*-OMePh, and 2-naphthyl were all well tolerated, furnishing **3k-3n**

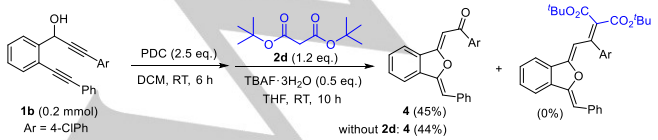
in 70-86% yields. However, alkyl-substituted (R^4 = n-butyl) propargyl alcohol failed to give the desired product. Additionally, trimethylsilyl (R^4) was compatible to generate the corresponding terminal olefin **3o** in 81% yield (In this reaction, 1.5 equiv of TBAF·3H_2O was taken both as the catalyst and as the reagent for the cleavage of C-Si bond).

Table 2. The scope of the reaction.[a]

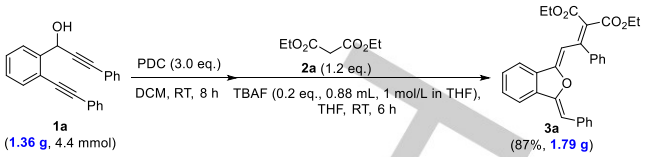


[a] Reaction conditions: (1) **1** (0.2 mmol) and PDC (0.6 mmol) in DCM (4.0 mL) at RT for 8 h; (2) **2** (0.24 mmol), TBAF (0.04 mmol, 40 uL, 1 mol/L in THF) and THF (2.0 mL) was used. Isolated yield. RT = room temperature. [b] 0.5 eq. of TBAF (1 mol/L in THF) was used. [c] 1.5 eq. of TBAF-3H_2O was used.

When R^1 substituent was sterically hindered t-butyl group, no desired diester product was observed. Interestingly, when TBAF·3H_2O was taken as the catalyst, ketone **4** was obtained instead (Scheme 3, 45%). In the absence of di-tert-butyl malonate (**2d**), **4** could also be generated in a moderate yield (44%). These results showed in Scheme 3 indicated a possibility that ketone **4** is derived from a certain amount of H_2O and propargyl alcohol **1b**. A similar reaction between ynones and water is under investigation in our laboratory. In addition, the scalability of this method was demonstrated in the reaction occurring between propargyl alcohol **1a** and diethyl malonate **2a**, thus providing a gram quantity of the dihydroisobenzofuran **3a** with a good yield (Scheme 4, 87%).



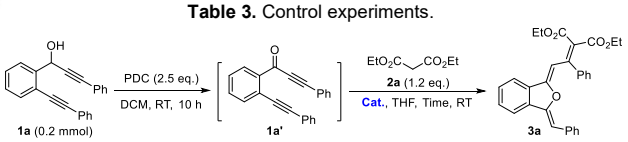
Scheme 3. Formation of ketone **4**.



Scheme 4. Gram-Scale Preparation.

In order for deepened understanding as to the reaction mechanism, a series of control experiments were conducted using propargyl alcohol **1a** and diethyl malonate **2a** (Table 3). Under the standard reaction conditions, **3a** was obtained in 91% yield (entry 1). Nevertheless, no further *O*-nucleophilic cyclization reaction occurred only with TBAC as the sole catalyst (entry 2), indicating that fluoride anion was vital for the onset of the cyclization reaction (entry 2 vs 1). It is noteworthy that an excessively long reaction time could result in slightly undesired intramolecular [4+2] cycloaddition from ynone **1a'** (Scheme 2). When the reaction was carried out with NaF (0.5 equiv) as the base, intermediate **1a'** was isolated in 84% yield but no **3a** was detected (entry 3). It was initially suspected that the failure of NaF could be attributable to its poor solubility in THF. In order to improve the solubility of sodium salt, 15-crown-5 was introduced. However, no desired *O*-nucleophilic cyclization reaction was observed to take place in the presence of 15-crown-5 (0.5 eq.) and NaF (0.5 eq.) (entry 4), which implied that the ammonium salt not only played a single role in phase transfer catalysis, but also promoted an additional catalytic activity for subsequent cyclization process (entry 4 vs 1). To further validate our hypothesis, the reaction was carried out by using TBAC (0.5 eq.), 15-crown-5 (0.5 eq.) and NaF (0.5 eq.) as the catalyst, based on which **3a** could be isolated in 28% yield (entry 5). These mentioned above results (entries 1-5) implied that both the fluoride anion and ammonium cation might play the significant roles in the efficient tandem cyclization. In addition, it has also been proved that acidic conditions are ineffective for the cyclization reaction (entries 6-8).

Table 3. Control experiments.

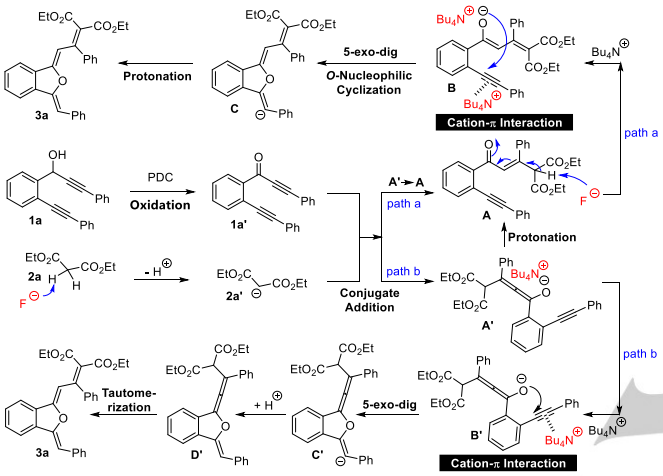


Entry	Catalyst	Time (h)	Yield of **1a'** (%)	Yield of **3a** (%)
1[a]	TBAF (0.5 eq.)	2	0	91
2	TBAC (0.5 eq.)	30	82	0
3	NaF (0.5 eq.)	30	84	0
4	NaF (0.5 eq.), 15-crown-5 (0.5 eq.)	30	89	0
5	NaF (0.5 eq.), 15-crown-5 (0.5 eq.), TBAC (0.5 eq.)	30	57	28
6	HF (0.5 eq.)	24	91	0
7	TsOH (0.5 eq.)	10	92	0
8	HF (0.5 eq.), TBAC (0.5 eq.)	10	91	0

[a] TBAF (0.5 eq., 100 uL, 1 mol/L in THF) was used in the reaction.

On the basis of all the above controlled experiments and the previous literature[23], a plausible reaction mechanism has been proposed (Scheme 5). Initially, propargyl alcohol **1a** is oxidized by PDC to generate ynone intermediate **1a'**. Then, a nucleophilic attack of deprotonated diethyl malonate **2a'** to **1a'** gives rise to intermediate **A** (path a). Subsequently, **A** is further

converted to the oxygen anion intermediate **B** *via* a deprotonation-rearrangement process (**A** to **B**). Under a possible activation initiated by cation-π interaction,[8a] the formed oxygen anion launched attacks on the intramolecular alkyne moiety (**B** to **C**, 5-exo-dig) to furnish **C**. Tetrabutylammonium cation was also speculated to serve as a noncoordinating cation to stabilize oxygen anion intermediate **B**. Finally, the desired product **3a** was obtained after the protonation process. Alternatively, allenoate ion **A'** could be formed by nucleophilic attack of **2a'** to **1a'** (path b). Then, the produced allenoate ion can directly attack to the activated alkyne moiety (**B'** to **C'**). The resulting anion **C'** can be protonated and tautomerized to furnish the product **3a**.



Scheme 5. The possible reaction mechanism.

Conclusions

In conclusion, an efficient method has been developed to construct dihydroisobenzofuran derivatives starting from malonate esters and *o*-(alkynyl)phenyl propargyl alcohols. All resulting products can be prepared by applying this tandem strategy at room temperature. These dihydroisobenzofuran diesters were selectively formed *via* the oxidation process of propargyl alcohols, and the subsequent bifunctional TBAF catalyzed conjugate addition and selective *O*-nucleophilic cyclization processes. This methodology is characterized by fluoride anion as a Brønsted base and a possible cation-π interaction as the approach to activation.

Experimental Section

General Methods. All reactions were carried out in air except noted. The TBAF (1 mol/L in THF) was purchased from Sigma-Aldrich Co. and Sun Chemical Technology (Shanghai) Co., Ltd. Unless noted, all commercial reagents were used without further purification. Reactions were monitored by thin layer chromatography using UV light to visualize the course of reaction. Purification of reaction products was carried out by flash chromatography on silica gel (300~400 mesh). ^{1}H NMR spectra were recorded at 500 or 300 MHz, ^{13}C NMR spectra were recorded at 125 MHz, and in $CDCl_3$ or $(CD_3)_2SO$ (containing 0.03% TMS) solutions. ^{1}H NMR spectra were recorded with Me_4Si (δ = 0.00) as the internal reference and ^{13}C NMR spectra were recorded with $CDCl_3$ (δ = 77.00) or DMSO-d_6 (δ = 39.52) as the internal reference. High-resolution mass spectra were obtained using a Bruker Maxis Impact mass spectrometer with a TOF (for ESI) analyzer. Single crystal X-ray diffraction data was collected in Bruker SMARTAPEX diffractiometers with molybdenum cathodes. The compounds **1** are known compounds and are prepared according to the reported literature methods.[24]

A typical procedure for the synthesis of dihydroisobenzofurans 3

To a well-dried 25 mL Schlenk tube containing a magnetic stirring bar was added PDC (225 mg, 0.6 mmol). Then, the vessel was evacuated and refilled with N_2 for three times. Under a stream of N_2, to this vessel were added DCM (4 mL) and propargyl alcohol **1** (0.2 mmol). The mixture was stirred at room temperature till **1** disappeared by TLC analysis (about 8 hours). The resulting mixture was then filtered and washed with DCM (about 20 mL). The filtrate was concentrated under reduced pressure and transferred to a vial using THF (2 mL). Subsequently, to the vial was added 1,3-dicarbonyl compound **2** (0.24 mmol) and TBAF (the corresponding amount of TBAF, see: Table 2). The mixture was stirred at room temperature till ynone intermediate **1'** disappeared by TLC analysis. The resulting mixture was concentrated under reduced pressure and subjected to column chromatography for purification directly, using petroleum ether/ethyl acetate (20:1-10:1) as the eluent.

diethyl 2-(2-((*Z*)-3-((*Z*)-benzylidene)isobenzofuran-1(3*H*)-ylidene)-1-phenylethylidene)malonate (3a): Yellow solid; 92% yield (86 mg); mp 141-143 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.77 (d, *J* = 7.5 Hz, 1H), 7.57 (d, *J* = 7.3 Hz, 1H), 7.48-7.42 (m, 7H), 7.25 (s, 1H), 7.16-7.12 (m, 3H), 6.78 (d, *J* = 6.5 Hz, 2H), 6.03 (s, 1H), 4.31 (q, *J* = 7.1 Hz, 2H), 3.94 (q, *J* = 7.1 Hz, 2H), 1.33 (t, *J* = 7.1 Hz, 3H), 0.98 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.0, 164.6, 157.6, 151.3, 150.6, 139.2, 134.9, 133.7, 133.1, 130.6, 129.2, 129.0, 128.7, 128.5, 128.4, 128.3, 126.6, 123.6, 121.2, 119.5, 102.2, 97.0, 61.0, 60.9, 14.2, 13.7; IR (KBr): 2972, 2901, 1622, 1406, 1394, 1250, 1066, 880, 759 cm^{-1}; HRMS (ESI) calcd for $C_{30}H_{27}O_5$ $[M+H]^+$: 467.1853, found 467.1849.

dimethyl 2-(2-((*Z*)-3-((*Z*)-benzylidene)isobenzofuran-1(3*H*)-ylidene)-1-phenylethylidene)malonate (3b): Yellow solid; 87% yield (76 mg); mp 121-122 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.80 (d, *J* = 7.4 Hz, 1H), 7.58 (d, *J* = 7.3 Hz, 1H), 7.49-7.43 (m, 7H), 7.30 (s, 1H), 7.14-7.12 (m, 3H), 6.79-6.77 (m, 2H), 6.04 (s, 1H), 3.83 (s, 3H), 3.45 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.7, 164.9, 158.0, 152.2, 150.6, 139.1, 134.9, 133.7, 133.0, 130.7, 129.3, 129.1, 128.7, 128.4, 128.3, 128.3, 126.7, 122.6, 121.3, 119.6, 102.3, 96.8, 52.1, 52.0; IR (KBr): 2970, 1630, 1210, 1081, 755, 584 cm^{-1}; HRMS (ESI) calcd for $C_{28}H_{23}O_5$ $[M+H]^+$: 439.1540, found 439.1546.

dibenzyl 2-(2-((*Z*)-3-((*Z*)-benzylidene)isobenzofuran-1(3*H*)-ylidene)-1-(4-chlorophenyl)ethylidene) malonate (3c): Yellow solid; 74% yield (93 mg); mp 130-132 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.60-7.56 (m, 2H), 7.48-7.45 (m, 1H), 7.41-7.32 (m, 8H), 7.31-7.26 (m, 5H), 7.18-7.17 (m, 4H), 7.10-7.08 (m, 2H), 6.80-6.79 (m, 2H), 6.05 (s, 1H), 5.29 (s, 2H), 4.92 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.6, 164.2, 158.1, 150.7, 150.4, 137.4, 135.8, 135.1, 135.1, 134.9, 133.5, 132.8, 130.9, 129.9, 129.3, 128.7, 128.6, 128.6, 128.5, 128.4, 128.3, 128.1, 127.9, 127.1, 122.8, 121.3, 119.6, 102.7, 96.5, 67.1, 66.6; IR (KBr): 2980, 1724, 1626, 1549, 1187, 1005, 762, 699 cm^{-1}; HRMS (ESI) calcd for $C_{40}H_{30}ClO_5$ $[M+H]^+$: 625.1776, found 625.1782.

diisopropyl 2-(2-((*Z*)-3-((*Z*)-benzylidene)isobenzofuran-1(3*H*)-ylidene)-1-(4-chlorophenyl)ethylidene) malonate (3d): Yellow solid; 65% yield (69 mg); mp 151-152 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.76 (d, *J* = 7.4 Hz, 1H), 7.58 (d, *J* = 7.6 Hz, 1H), 7.48-7.38 (m, 6H), 7.24-7.18 (m, 4H), 6.82 (d, *J* = 6.9 Hz, 2H), 6.05 (s, 1H), 5.20-5.15 (m, 1H), 4.89-4.84 (m, 1H), 1.32 (d, *J* = 6.2 Hz, 6H), 1.07 (d, *J* = 6.3 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.2, 164.0, 157.5, 150.5, 149.0, 137.7, 134.8, 133.6, 133.0, 130.7, 130.1, 129.3, 128.5, 128.5, 127.0, 124.6, 121.1, 119.6, 102.3, 96.5, 68.6, 68.5, 21.8, 21.3; IR (KBr): 2942, 1630, 1210, 1081, 756, 584 cm^{-1}; HRMS (ESI) calcd for $C_{32}H_{30}ClO_5$ $[M+H]^+$: 529.1776, found 529.1781.

diethyl 2-(2-((*Z*)-3-((*Z*)-benzylidene)-6-fluoroisobenzofuran-1(3*H*)-ylidene)-1-phenylethylidene) malonate (3e): Yellow solid; 93% yield (90 mg); mp 129-130 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.73 (dd, *J* = 8.5, 4.6 Hz, 1H), 7.47-7.43 (m, 5H), 7.22-7.21 (m, 2H), 7.15-7.12 (m, 4H), 6.77-6.76 (m, 2H), 5.98 (s, 1H), 4.30 (q, *J* = 7.1 Hz, 2H), 3.94 (q, *J* = 7.2 Hz, 2H), 1.32 (t, *J* = 7.1 Hz, 3H), 0.98 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.0, 164.6, 164.5 (d, $J_{C\text{-}F}$ = 249.6 Hz), 156.8, 151.1, 149.7 (d, $J_{C\text{-}F}$ = 4.6 Hz), 139.1, 136.9 (d, $J_{C\text{-}F}$ = 9.9 Hz), 133.3, 129.2, 129.0, 128.9, 128.5, 128.4, 128.3, 127.0, 123.7, 123.2 (d, $J_{C\text{-}F}$ = 9.6 Hz), 117.6 (d, $J_{C\text{-}F}$ = 24.6 Hz), 106.0 (d, $J_{C\text{-}F}$ = 24.5 Hz), 103.2, 96.8, 61.0, 61.0, 14.2, 13.7; IR (KBr): 2928, 1718, 1618, 1534, 1479, 1298, 1192, 1011, 768, 692 cm^{-1}; HRMS (ESI) calcd for $C_{30}H_{26}FO_5$ $[M+H]^+$: 485.1759, found 485.1764.

diethyl 2-(2-((*Z*)-3-((*Z*)-benzylidene)-5,6-dimethoxyisobenzofuran-1(3*H*)-ylidene)-1-phenylethylidene) malonate (3f): Yellow solid; 94% yield (99 mg); mp 182-183 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.47-7.42 (m, 5H), 7.15-7.09 (m, 5H), 6.95 (s, 1H), 6.76-6.74 (m, 2H), 5.89 (s, 1H), 4.30 (q, *J* = 7.1 Hz, 2H), 4.00 (s, 3H), 3.99 (s, 3H), 3.93 (q, *J* = 7.2 Hz, 2H), 1.33 (t, *J* = 7.1 Hz, 3H), 0.98 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.2, 164.8, 158.1, 152.6, 151.9, 151.4, 150.6, 139.5, 133.9, 128.9, 128.7, 128.5, 128.4, 128.2, 126.3, 126.2, 122.5, 101.9, 100.9, 100.6, 95.8, 60.9, 60.8, 56.4, 56.3, 14.2, 13.7; IR (KBr): 2931, 1701, 1618, 1499, 1310, 1213, 1024, 829, 697 cm^{-1}; HRMS (ESI) calcd for $C_{32}H_{31}O_7$ $[M+H]^+$: 527.2064, found 527.2059.

diethyl 2-(2-((*Z*)-3-((*Z*)-benzylidene)isobenzofuran-1(3*H*)-ylidene)-1-(4-chlorophenyl)ethylidene) malonate (3g): Red solid; 72% yield (72 mg); mp 135-137 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.75 (d, *J* = 7.5 Hz, 1H), 7.57 (d, *J* = 7.6 Hz, 1H), 7.48-7.38 (m, 6H), 7.22-7.18 (m, 4H), 6.82-6.81 (m, 2H), 6.05 (s, 1H), 4.31 (q, *J* = 7.2 Hz, 2H), 3.98 (q, *J* = 7.2 Hz, 2H), 1.33 (t, *J* = 7.1 Hz, 3H), 1.04 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.8, 164.5, 157.8, 150.4, 149.8, 137.7, 134.9, 134.8, 133.5, 132.9, 130.8, 130.0, 129.3, 128.6, 128.5, 128.5, 127.0, 123.7, 121.2, 119.6, 102.5, 96.4, 61.1, 61.0, 14.2, 13.7; IR (KBr): 2926, 1707, 1620, 1491, 1366, 1207, 760, 700 cm^{-1}; HRMS (ESI) calcd for $C_{30}H_{26}ClO_5$ $[M+H]^+$: 501.1463, found 501.1460.

diethyl 2-(2-((*Z*)-3-((*Z*)-benzylidene)isobenzofuran-1(3*H*)-ylidene)-1-(4-methoxyphenyl)ethylidene) malonate (3h): Yellow solid; 66% yield (66 mg); mp 133-135 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.95-7.90 (m, 2H), 7.64-7.57 (m, 2H), 7.33 (d, *J* = 8.5 Hz, 2H), 7.20-7.10 (m, 3H), 7.05 (d, *J* = 8.5 Hz, 2H), 6.95 (s, 1H), 6.91-6.80 (m, 2H), 6.47 (s, 1H), 4.22 (q, *J* = 7.0 Hz, 2H), 3.95 (q, *J* = 7.0 Hz, 2H), 3.76 (s, 3H), 1.22 (t, *J* = 7.1 Hz, 3H), 0.98 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.4, 164.8, 160.2, 157.5, 151.2, 150.6, 134.8, 133.7, 133.2, 131.5, 130.6, 130.0, 129.2, 128.8, 128.3, 126.7, 123.0, 121.2, 119.6, 113.8, 102.0, 97.4, 60.9, 60.8, 55.1, 14.2, 13.8; IR (KBr): 2978, 1708, 1624, 1480, 1444, 1193, 1069, 1014, 768, 698 cm^{-1}; HRMS (ESI) calcd for $C_{31}H_{29}O_6$ $[M+H]^+$: 497.1959, found 497.1955.

diethyl 2-(2-((*Z*)-3-((*Z*)-benzylidene)isobenzofuran-1(3*H*)-ylidene)-1-(naphthalen-2-yl)ethylidene) malonate (3i): Red solid; 90% yield (93 mg); mp 141-143 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.01 (s, 1H), 7.93-7.92 (m, 1H), 7.85-7.81 (m, 3H), 7.57-7.54 (m, 4H), 7.50-7.44 (m, 2H), 7.36 (s, 1H), 6.77-6.74 (m, 1H), 6.46 (d, *J* = 7.7 Hz, 2H), 6.18-6.15 (m, 2H), 5.98 (s, 1H), 4.33 (q, *J* = 7.1 Hz, 2H), 3.83 (q, *J* = 7.1 Hz, 2H), 1.34 (t, *J* = 7.1 Hz, 3H), 0.81 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.1, 164.6, 157.7, 151.1, 150.4, 137.0, 134.8, 133.6, 133.2, 133.1, 133.0, 130.6, 129.2, 128.5, 128.3, 128.0, 128.0, 127.8, 127.4, 126.5, 126.4, 126.3, 123.8, 121.1, 119.5, 102.2, 96.6, 60.9, 60.9, 14.2, 13.5; IR (KBr): 3061, 2974, 1695, 1619, 1544, 1212, 1107, 1013, 760, 670 cm^{-1}; HRMS (ESI) calcd for $C_{34}H_{29}O_5$ $[M+H]^+$: 517.2010, found 517.2016.

diethyl 2-(1-((*Z*)-3-((*Z*)-benzylidene)isobenzofuran-1(3*H*)-ylidene)hexan-2-ylidene)malonate (3j): Yellow oil; 94% yield (84 mg); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.73 (d, *J* = 7.8 Hz, 2H), 7.68 (d, *J* = 7.7 Hz, 1H), 7.64 (d, *J* = 7.7 Hz, 1H), 7.48-7.45 (m, 1H), 7.43-7.41 (m, 1H), 7.39-7.36 (m, 2H), 7.26-7.23 (m, 1H), 7.12 (s, 1H), 6.23 (s, 1H), 4.31 (q, *J* = 7.1 Hz, 2H), 4.27 (q, *J* = 7.1 Hz, 2H), 3.02 (t, *J* = 7.9 Hz, 2H), 1.68-1.62 (m, 2H), 1.46-1.39 (m, 2H), 1.35 (t, *J* = 7.1 Hz, 3H), 1.32 (t, *J* = 7.1 Hz, 3H), 0.85 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.0, 165.3, 156.0, 153.2, 151.1, 134.4, 134.1, 133.5, 130.4, 129.3, 128.7, 128.5, 127.1, 122.3, 121.0, 119.6, 101.7, 96.3, 61.0, 60.7, 32.7, 32.0, 22.9, 14.1, 14.1, 14.0; IR (KBr): 2959, 1726, 1621, 1561, 1210, 1012, 759, 691 cm^{-1}; HRMS (ESI) calcd for $C_{28}H_{31}O_5$ $[M+H]^+$: 447.2166, found 447.2162.

diethyl 2-(2-((*Z*)-3-((*Z*)-4-chlorobenzylidene)isobenzofuran-1(3*H*)-ylidene)-1-phenylethylidene) malonate (3k): Yellow solid; 86% yield (86 mg); mp 143-144 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.74 (d, *J* = 7.2 Hz, 1H), 7.52 (d, *J* = 7.2 Hz, 1H), 7.46-7.41 (m, 7H), 7.24 (s, 1H), 7.07 (d, *J* = 8.5 Hz, 2H), 6.66 (d, *J* = 8.5 Hz, 2H), 5.94 (s, 1H), 4.31 (q, *J* = 7.2 Hz, 2H), 3.95 (q, *J* = 7.1 Hz, 2H), 1.33 (t, *J* = 7.2 Hz, 3H), 0.99 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.9, 164.6, 157.4, 151.0, 150.9, 139.2, 134.6, 133.2, 132.3, 132.1, 130.7, 129.9, 129.5, 129.0, 128.5, 128.5, 128.3, 123.9, 121.2, 119.6, 100.8, 97.3, 61.0, 61.0, 14.2, 13.7; IR (KBr): 2977, 1702, 1623, 1546, 1489, 1206, 1068, 752, 696 cm^{-1}; HRMS (ESI) calcd for $C_{30}H_{26}ClO_5$ $[M+H]^+$: 501.1463, found 501.1469.

diethyl 2-(2-((*Z*)-3-((*Z*)-4-chlorobenzylidene)isobenzofuran-1(3*H*)-ylidene)-1-(4-chlorophenyl) ethylidene)malonate (3l): Red solid; 71% yield (76 mg); mp 149-151 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.77 (d, *J* = 7.2 Hz, 1H), 7.57 (d, *J* = 7.2 Hz, 1H), 7.50-7.44 (m, 2H), 7.41 (s, br, 4H), 7.23 (s, 1H), 7.17 (d, *J* = 8.5 Hz, 2H), 6.74 (d, *J* = 8.5 Hz, 2H), 6.01 (s, 1H), 4.31 (q, *J* = 7.1 Hz, 2H), 3.99 (q, *J* = 7.2 Hz, 2H), 1.33 (t, *J* = 7.1 Hz, 3H), 1.05 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.7, 164.5, 157.6, 150.8, 149.6, 137.6, 135.1, 134.6, 133.0, 132.6, 132.1, 130.9, 130.0, 129.6, 129.5, 128.7, 128.6, 124.0, 121.3, 119.6, 101.1, 96.8, 61.2, 61.1, 14.2, 13.7; IR (KBr): 2980, 1727, 1617, 1489, 1203, 1013, 843, 759 cm^{-1}; HRMS (ESI) calcd for $C_{30}H_{25}Cl_2O_5$ $[M+H]^+$: 535.1074, found 535.1082.

diethyl 2-(2-((*Z*)-3-((*Z*)-4-methoxybenzylidene)isobenzofuran-1(3*H*)-ylidene)-1-phenylethylidene) malonate (3m): Red solid; 70% yield (70 mg); mp 143-145 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.76 (d, *J* = 7.6 Hz, 1H), 7.53 (d, *J* = 7.7 Hz, 1H), 7.49-7.38 (m, 7H), 7.24 (s, 1H), 6.73-6.67 (m, 4H), 5.99 (s, 1H), 4.31 (q, *J* = 7.1 Hz, 2H), 3.93 (q, *J* = 7.2 Hz, 2H), 3.81 (s, 3H), 1.33 (t, *J* = 7.1 Hz, 3H), 0.97 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.1, 164.7, 158.4, 157.9, 151.5, 149.2, 139.2, 135.0, 132.8, 130.6, 130.2, 128.9, 128.8, 128.5, 128.2, 126.6, 123.1, 121.2, 119.2, 113.9, 102.0, 96.4, 60.9, 60.9, 55.2, 14.2, 13.7; IR (KBr): 2982, 1701, 1625, 1510, 1210, 1109, 761, 697 cm^{-1}; HRMS (ESI) calcd for $C_{31}H_{29}O_6$ $[M+H]^+$: 497.1959, found 497.1966.

diethyl 2-(2-((1*Z*,3*Z*)-3-(naphthalen-2-ylmethylene)isobenzofuran-1(3*H*)-ylidene)-1-phenylethylidene) malonate (3n): Red solid; 75% yield (77 mg); mp 127-129 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.79-7.72 (m, 3H), 7.63-7.60 (m, 2H), 7.53-7.41 (m, 10H), 7.19 (s, 1H), 6.72 (d, *J* = 8.6 Hz, 1H), 6.22 (s, 1H), 4.29 (q, *J* = 7.1 Hz, 2H), 3.98 (q, *J* = 7.1 Hz, 2H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.00 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.1, 164.7, 157.6, 151.2, 150.8, 139.1, 134.9, 133.2, 133.1, 132.2, 131.8, 130.6, 129.3, 129.1, 128.6, 128.3, 128.2, 128.1, 127.9, 127.5, 126.0, 125.9, 125.8, 123.7, 121.2, 119.6, 102.4, 97.2, 61.0, 61.0, 14.2, 13.7; IR (KBr): 2923, 1720, 1619, 1535, 1443, 1199, 1073, 815, 761 cm^{-1}; HRMS (ESI) calcd for $C_{34}H_{29}O_5$ [M+H]$^+$: 517.2010, found 517.2017.

diethyl (*Z*)-2-(2-(3-methyleneisobenzofuran-1(3*H*)-ylidene)-1-phenylethylidene)malonate (3o): Yellow solid; 81% yield (63 mg); mp 91-92 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.89-7.87 (m, 1H), 7.84-7.82 (m, 1H), 7.60-7.56 (m, 2H), 7.43-7.37 (m, 3H), 7.25 (d, *J* = 6.5 Hz, 2H), 6.72 (s, 1H), 5.05 (d, *J* = 2.7 Hz, 1H), 4.38 (d, *J* = 2.7 Hz, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 3.87 (q, *J* = 7.1 Hz, 2H), 1.20 (t, *J* = 7.1 Hz, 3H), 0.86 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 175.9, 174.5, 166.7, 166.2, 159.5, 149.0, 143.2, 142.6, 140.4, 138.5, 138.1, 137.9, 133.5, 131.2, 106.4, 95.7, 70.6, 70.5, 23.9, 23.4; IR (KBr): 2976, 1701, 1561, 1230, 1195, 827, 768, 704 cm^{-1}; HRMS (ESI) calcd for $C_{24}H_{23}O_5$ [M+H]$^+$: 319.1540, found 319.1543.

Compound **1a'** and **4** was prepared according to the general procedure for **3**.

3-phenyl-1-(2-(phenylethynyl)phenyl)prop-2-yn-1-one (1a'): Yellow oil; The corresponding yields, see Table 2; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.22 (d, *J* = 7.7 Hz, 1H), 7.71 (d, *J* = 7.1 Hz, 1H), 7.65-7.61 (m, 3H), 7.60-7.56 (m, 2H), 7.52-7.44 (m, 2H), 7.39 (d, *J* = 7.5 Hz, 2H), 7.35-7.33 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 177.5, 138.2, 134.3, 133.0, 132.4, 131.9, 131.5, 130.6, 128.5, 128.2, 127.9, 123.1, 123.0, 120.1, 95.4, 93.3, 88.2, 88.1; IR (KBr): 3059, 2196, 1644, 1491, 1442, 994, 756, 689 cm^{-1}; HRMS (ESI) calcd for $C_{23}H_{15}O$ [M+H]$^+$: 307.1117, found 307.1121.

2-((*Z*)-3-((*Z*)-benzylidene)isobenzofuran-1(3*H*)-ylidene)-1-(4-chlorophenyl)ethan-1-one (4): Yellow solid; 45% yield (32 mg); mp 168-169 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.97 (d, *J* = 8.4 Hz, 2H), 7.91 (d, *J* = 7.7 Hz, 2H), 7.80 (d, *J* = 7.8 Hz, 1H), 7.74 (d, *J* = 7.8 Hz, 1H), 7.62-7.59 (m, 1H), 7.52-7.42 (m, 5H), 7.31-7.28 (m, 1H), 6.62 (s, 1H), 6.38 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 187.6, 162.3, 150.5, 138.4, 138.2, 135.8, 133.7, 132.0, 129.5, 129.5, 129.4, 128.9, 128.8, 127.9, 121.5, 120.0, 105.2, 93.6; IR (KBr): 2953, 1629, 1611, 1465, 1279, 1003, 832, 763, 692 cm^{-1}; HRMS (ESI) calcd for $C_{23}H_{16}ClO_2$ [M+H]$^+$: 359.0833, found 359.0837.

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Keywords: TBAF • cation-π interaction • dihydroisobenzofuran • malonate ester • cyclization reaction

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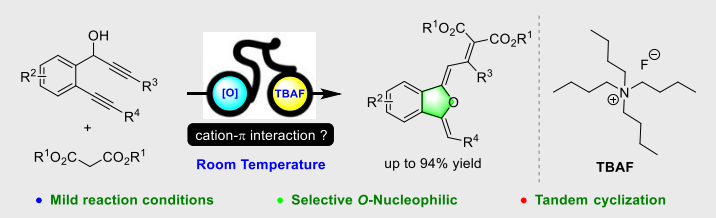

An efficient method has been devised for the synthesis of dihydroisobenzofuran derivatives through the reaction of *in situ* generated ynones with potentially *C*-nucleophilic malonate esters. Both the basicity of fluoride anion and ammonium cation-π interaction with alkyne unit might play a crucial role in the cyclization reaction.

Cation-π interaction

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TBAF-Catalyzed Cyclization Reactions of *o*-(Alkynyl)phenyl Propargyl Alcohols with Malonate Esters: A Possible Cation-π Interaction as The Activation Approach