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Highly efficient heterogeneous synthesis of benzofurans under aqueous condition



Shi-Xin Sun, Jun-Jie Wang, Zi-Jun Xu, Lu-Ya Cao, Zi-Fa Shi*, Hao-Li Zhang*

State Key Laboratory of Applied Organic Chemistry (SKLAOC), College of Chemistry and Chemical Engineering, Lanzhou University, 222 Tianshui South Road, Lanzhou 730000, China

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ABSTRACT

Highly efficient organic reactions in water are important for designing environmental-friendly and low cost synthetic processes. Herein, we demonstrate an intermediate-in-water strategy for the heterogeneous synthesis of benzofurans in aqueous media. The cyclization reaction of 2-(phenylethynyl)phenol to 2-phenylbenzofuran cannot proceed in pure water. However, this reaction can be efficiently promoted by the formation of sparingly soluble intermediate in the presence of alkaline. Quantitative conversion of a variety of substrates to benzofuran derivatives has been achieved in the absence of noble metal catalyst. Other remarkable features including easy-isolation and purification of product, along with wide range of functional group tolerance render the methodology promising in the realm of green-synthesis.

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1. Introduction

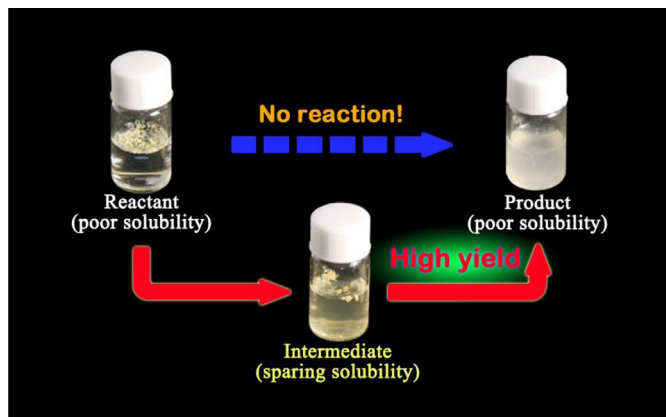
Highly efficient heterogeneous synthesis, especially in aqueous media, is attracting great attention in recent years, because of the increasing environmental awareness of the synthetic organic chemistry community.¹ Water is considered to be an ideal reaction media for heterogeneous reactions due to its many superior properties, such as nonflammable, non-toxic nature, and readily available at low cost,² providing opportunities for clean processing and pollution prevention in organic synthesis process. Chemical reactions in aqueous environment are not new for organic chemists,^{1c,3} and many organic reactions have been carried out in aqueous conditions, including Diels–Alder cycloadditions,⁴ Claisen rearrangements,⁵ Sonogashira reaction,^{3e} and C–H activation reactions.^{3h} However, several issues still hinder the wide use of water as reaction media in synthetic chemistry, such as insolubility to many compounds, high polarity, elevated surface tension, strong hydrogen bonding potential and high vapor pressure.⁶ The relatively poor solubility of most organic compounds in aqueous media results in the separation of reactant and solvent, which means that the reaction must occur in heterogeneous condition.

Previous investigations have classified the heterogeneous reactions to be either ‘on water’ or ‘in water’, which is distinguished by the solubility of the reactants. Sharpless⁷ and Fokin⁸ have described the successful ‘on water’ heterogeneous reactions as the cases where the reactants are insoluble in water but the reaction

may be promoted by water.⁹ By using the similar concept, the heterogeneous reactions involving water soluble reactants can then be classified as ‘in water’ reactions.¹⁰ It should be noted that there is no clear definition to distinguish ‘on water’ or ‘in water’ reactions, and the boundary can be blur for reactions with sparingly soluble reactants.¹¹ For ‘on water’ reactions, the biggest concern is the low reactivity due to the insolubility of reactants. Certain strategies can be employed to improve the solubility, such as modifying the substrates or using organic cosolvents.⁸ However, these strategies tend to diminish the advantages of low cost, simplicity, ease of workup and product isolation that water has over traditional solvents. Physical means, like stirring, shaking, ultrasonication,¹² and using biphasic fluidic platform¹³ are also used in heterogeneous reactions, in which the efficiency varies in different situations.

In an ideal heterogeneous reaction, the product has zero solubility in water and is formed in quantitative yield, so that it can be isolated through simple separation methods, like filtration.¹¹ Herein, as a ‘proof of concept’, we propose an intermediate-in-water strategy, which shows characteristics of high reaction rate under heterogeneous condition and easy product collection. Scheme 1 illustrates the features of this strategy. Firstly, it is applied to a reaction when both the reactant and product are insoluble in aqueous phase, and no reaction could proceed under heterogeneous condition. Secondly, trace of the reactant can be transformed into an intermediate, which has a sparingly solubility in water. Thirdly, the slightly dissolved intermediate is converted into the product with high efficiency. Finally, all the reactants are converted to product and separates out from water due to its insolubility. Herein, we demonstrate the proposed strategy by using a cyclization reaction for 2-phenylbenzofuran synthesis as an example.

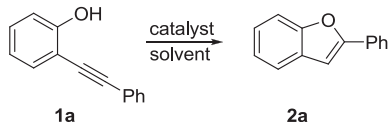
* Corresponding authors. E-mail addresses: shizf@lzu.edu.cn (Z.-F. Shi), haoli.zhang@lzu.edu.cn (H.-L. Zhang).



Scheme 1. Schematic illustration of an ideal intermediate-in-water process, in which both of the reactant and product are insoluble, but the intermediate has sparing solubility allowing the reaction to take place.

2. Results and discussion

Benzofurans carrying functional groups are a ubiquitous organic frame found in nature.¹⁴ Recently, they have received much attention in organic electronics as fluorescence materials.¹⁵ Considerable efforts have been directed toward the development of new and efficient methodologies for the synthesis of benzofuran derivatives.^{15a,16} A diverse array of transition-metal catalysts, such as organometallic complexes¹⁷ and nanoparticles,¹⁸ could effectively improve the transformation ability of the reactant. However, the use of metal catalysts also presents some serious problems, including purification difficulty and increased cost.¹⁹ Consequently, developing of efficient and transition-metal-free process^{19b} for the assembly of benzofuran structures is of great importance. Here, we studied the heterogeneous synthesis of benzofurans from 2-(phenylethynyl)phenol under aqueous condition without using transition metal catalyst (Scheme 2).



Scheme 2. The cyclization reaction of 2-(phenylethynyl)phenol (**1a**) to 2-phenylbenzofuran (**2a**).

Butler has classified reactions taking place in aqueous condition with the reactant concentration below 0.01 mM as ‘on water’ reactions but the boundary is blur.¹¹ The solubilities of the reactant **1a** and product **2a** were characterized by UV–vis spectroscopy (Fig. 1) (more details are available in the Supplementary data, Fig. S1). Both the reactant and product exhibit extremely low solubility (below 0.002 mM) in water. After ultrasonication in K₂CO₃ solution, the UV–vis spectra suggest that small amount of reactant has been dissolved in the aqueous solution, though the concentrations were still very low. For instance, the concentration of the dissolved reactant was below 0.014 mM in 5 mM K₂CO₃ solution. Further increasing of the alkaline concentration could only affect the solubility of the reactant slightly (Supplementary data, Table S1). Because of the poor solubilities of the reactant and product in water, this reaction coincides perfectly with the characteristics of the intermediate-in-water strategy.

Initially, the conversion of **1a** to **2a** was tested under various solvent conditions, and the results are shown in Table 1. As the reactant is well soluble in organic solvents, toluene, xylene were firstly tested. No reaction took place in toluene or xylene, which is

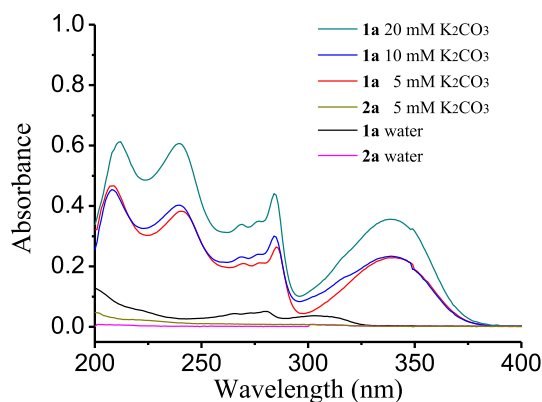


Fig. 1. The UV–vis absorbance spectra of the compound **1a** and **2a** in different solutions. For UV–vis test were prepared by ultrasonication followed by filtration.

Table 1

The cyclization of **1a** in different solutions

Entry ^a	Solvent	Base	Temp (°C)	Time (h)	Yield (%) ^d
1 ^b	Toluene	K ₂ CO ₃	100	15	N. P.
2 ^b	Xylene	K ₂ CO ₃	100	15	N. P.
3	H ₂ O	K ₂ CO ₃	rt	15	N. P.
4	H ₂ O	None	100	15	Trace
5 ^b	H ₂ O	K ₂ CO ₃	100	15	86
6 ^c	H ₂ O	K ₂ CO ₃	100	1	86
7 ^c	H ₂ O	K ₂ CO ₃	90	1	70

^a 2-(Phenylethynyl)phenol (0.5 mmol), solution (5 mL), K₂CO₃ (0.025 mmol).

^b Reaction occurred in oil bath.

^c Microwave irradiation was applied to the mixture in a hermetic polytetrafluoroethylene bottle for a total time of 1 h.

^d Yield of isolated product.

consistent with previous reports that metal catalyst is required in nonpolar solvents.^{18b,c} The reactant showed extremely low reactivity in pure water, and the reaction did not occur at room temperature after long reaction time (15 h). Even under heating, with long time stirring or sonication, the resulted product was too little to be isolated, hence the reaction is not practically viable. Such low reactivity is attributed to the low solubility and no deprotonation of the reactant in water, which is consistent with the above UV–vis results. However, the reaction can be significantly accelerated in alkaline aqueous solution. In the presence of K₂CO₃ (5 mol %), the reaction gave product **2a** in 86% yield under stirring and reflux condition (entry 5). Moreover, higher yield and faster reaction rate can be achieved under microwave irradiation. In the presence of K₂CO₃ (5 mol %) in water, under microwave condition at 100 °C in a sealed polytetrafluoroethylene bottle, nearly all the reactants were converted to the corresponding product in 1 h, as determined by thin layer chromatography (TLC). It is worth mentioning that under aqueous condition, the insoluble product can be readily collected from the water suspension through simple filtration. After purified by column chromatograph, the isolated yield is higher than 86% (entry 6). When a lower temperature was used, i.e., 90 °C, the yield decreased to 70%.

As illustrated in Table 1, K₂CO₃ could efficiently catalyze the cyclization reaction in aqueous media under microwave condition. We then tested various inorganic compounds for their potential catalytic properties (Table 2). When the cyclization reaction performed in pure water or KCl solution, only trace product could be extracted after microwave irradiation. No product was observed under acidic conditions. The conversion efficiency was dramatically increased when alkalines were added to the water solution. In order to optimize the reaction condition, different alkalines were studied. The NaOH and KOH, gave moderate yields (64% and 78%,

Table 2
Optimization of catalysts

Entry ^a	Catalyst (5 mol %)	pH	Yield (%)
1 ^b	None	6.61	Trace
2	KCl	6.61	Trace
3	H ₂ SO ₄	2.10	N. P.
4	HNO ₃	2.23	N. P.
5	NaOH	10.99	64
6	KOH	11.02	78
7	Na ₂ CO ₃	9.92	82
8	Cs ₂ CO ₃	10.31	86
9	K ₂ CO ₃	9.97	86
10 ^c	KOH+KCl	11.03	86
11 ^d	K ₂ CO ₃	10.30	86

^a Microwave irradiation was applied to the mixture of 2-(phenylethynyl)phenol (0.5 mmol) and deionized water (5 mL) in a hermetic polytetrafluoroethylene bottle for a total time of 1 h.

^b Only deionized water.

^c KOH (0.025 mmol) and KCl (0.025 mmol), deionized water (5 mL).

^d The purity of K₂CO₃ is 99.997%.

respectively). The yields were higher than 80% when carbonates were used in the reactions (Na₂CO₃, 82%; Cs₂CO₃, 86%; K₂CO₃, 86%). The comparison between the hydroxy alkaline (entry 5, 6) and the carbonates (entry 7–10) suggests that the carbonates exhibited better catalytic efficiency when the mole ratio was same. Entry 10 and 11 shows that a mixed solution containing 5 mM KOH and 5 mM KCl gave identical yield as 5 mM K₂CO₃, which appears to suggest that the K⁺ concentration plays a role to the catalytic efficiency compared to the pH of the solution. Thus, the cyclization reaction needs an alkaline environment for the solubility and deprotonation of the substrates, and the carbonates are efficient catalysts.

Two tests were employed to rule out the possibility that the reaction was catalyzed by noble metal impurity presented in the solution. First, the utility of K₂CO₃ of normal purity (99.0%) and high purity (99.997%, Alfa Aesar) did not show different yield (entry 9 and 11). Second, both the reaction mixtures and the alkaline solutions were analyzed through inductively coupled plasma atomic emission spectroscopy (ICP-AES), and no transition metal, such as palladium or platinum, was detected (the detection limit of the apparatus was 0.5–1.0 ppm). The above results indicate that potassium carbonate can be used as a highly efficient and low cost catalyst for the heterogeneous synthesis of benzofurans.

In order to realize easy isolation and purification of the product, it is imperative that the heterogeneous reaction should proceed with very high yield. To achieve a complete conversion, we optimized the reaction conditions (Table 3). In the presence of 2%

Table 3
Microwave promoted cyclization of **1a** in the presence of difference quantity of K₂CO₃

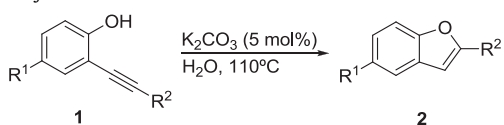
Entry ^a	K ₂ CO ₃ (mol %)	Temp (°C)	Time	Yield (%)
1	2	100	1 h	50
2	2	100	2 h	73
3	2	110	2 h	85
4	5	100	1 h	86
5	5	100	2 h	92
6	5	110	2 h	98
7	10	100	1 h	86
8	10	100	2 h	93
9	10	110	110 min	98
10	20	110	40 min	98
11	100	110	20 min	98
12	200	110	18 min	98

^a Microwave irradiation was applied to the mixture of 2-(phenylethynyl)phenol (0.5 mmol), K₂CO₃, and deionized water (5 mL) in a hermetic polytetrafluoroethylene bottle.

K₂CO₃, the reactions carried out at 100 °C gave isolated yield of 50% and 73% for the reaction times of 1 and 2 h, respectively. Using a higher temperature of 110 °C, 2 h reaction gave a higher yield of 85%, indicating that relatively high temperature and long time are necessary to improve the conversion of the reactant. Further increasing the concentration of K₂CO₃ to 5%, 10%, 20%, 100%, 200% (entries 6, 9, 10, 11, 12), reaction times of 120 min, 110 min, 40 min, 20 min, 18 min, respectively, were required to reach a 98% yield. The results show a clear trend of acceleration of the heterogeneous reaction with the increase of K₂CO₃ concentration. For economic consideration, condition of 5% of K₂CO₃ with 2 h reaction time was selected as the ideal condition for further studies.

As shown above, the cyclization reaction of **1a** shows quantitative conversion under microwave condition in diluted K₂CO₃ solution. We further examined the scope and limitation of substrates. Nineteen 2-(phenylethynyl)phenol derivatives bearing different substituents have been tested for the reactions in aqueous media, and the results are summarized in Table 4. A wide range of functional groups is tolerated in the reaction, and 11 substrates give conversion yield above 80%. The advantage of heterogeneous reaction is that the product can be easily separated from reaction mixture. More importantly, the complete conversion indicates that there was almost no substrate doping in the solidified mixture, and therefore simple filtration gave very pure products. Two substrates, **17** and **18**, give moderate yield, in which the products can be purified through recrystallization. When the methyl, tertiary butyl, and chlorine groups were introduced in the *p*-phenol site, the yield decreases. Six substrates gave relatively low yields, below 44%, and the products need to be purified through column chromatograph. The low conversion yields are attributed to their low solubility in K₂CO₃ solution, which have been confirmed by the UV–vis measurement (Supplementary data, Fig. S2). We also used conventional heating to study the reactions of characteristic compounds **1a**, **1b**, **1d**, **1h**, **1i**, **1p**, and **1q** under aqueous condition. The yields are lower

Table 4
Scope of the cyclization of **1**

			
Entry	R ¹	R ²	Yield ^a (%)
1	H	C ₆ H ₅	2a , 98 (86 ^b)
2	H	2-Thienyl	2b , 87 (80 ^b)
3	H	4-MeC ₆ H ₅	2c , 90
4	H	4-FC ₆ H ₅	2d , 92 (83 ^b)
5	H	4-ClC ₆ H ₅	2e , 90
6	H	4-BrC ₆ H ₅	2f , 84
7	H	3-MeC ₆ H ₅	2g , 81
8	H	3-FC ₆ H ₅	2h , 98 (90 ^b)
9	H	3-ClC ₆ H ₅	2i , 98
10	H	3-BrC ₆ H ₅	2j , 97
11	H	<i>n</i> -Bu	2k , 29
12	Me	C ₆ H ₅	2l , 94 (82 ^b)
13	Me	4-MeC ₆ H ₅	2m , 43
14	<i>t</i> -Bu	C ₆ H ₅	2n , 34
15	<i>t</i> -Bu	4-MeC ₆ H ₅	2o , 20
16	<i>t</i> -Bu	4-ClC ₆ H ₅	2p , 32 (25 ^b , 32 ^c)
17	Cl	C ₆ H ₅	2q , 65 (49 ^b)
18	Cl	4-MeC ₆ H ₅	2r , 70
19	Cl	4-ClC ₆ H ₅	2s , 44

^a Microwave irradiation was applied to the mixture of reactant (0.5 mmol), K₂CO₃ (0.025 mmol), and deionized water (5 mL) in a hermetic polytetrafluoroethylene bottle for a total time of 2 h.

^b The reaction mixture of reactant (0.5 mmol), K₂CO₃ (0.025 mmol), and deionized water (5 mL) was heated to reflux for 40 h.

^c Microwave irradiation was applied to the mixture of reactant (0.5 mmol), K₂CO₃ (0.025 mmol), Bu₄NBr (0.05 mmol), and deionized water (5 mL) in a hermetic polytetrafluoroethylene bottle for a total time of 2 h.

after 40 h than those by microwave irradiation. Meanwhile, we attempted to add the phase transfer catalyst (PTC) to improve the yield of **1p** in the heterogeneous reactions. The result shows that there is little effect on the reaction.

Because of the high conversion rate and the insolubility of the product, simple filtration isolation makes it possible to reuse the catalysts and the reaction solutions. Fig. 2(a) shows that after removal of the product by filtration, the reaction media containing 0.020 M K_2CO_3 can be recovered and reused without significant loss of activity after six times catalytic activity. At very low catalyst concentration, the recycle of the reaction media is somehow hindered by the loss of K_2CO_3 content due to the adsorption by the solid product. For example, the catalytic activity of 0.005 M K_2CO_3 solution shows clear reduction after the fourth cycles due to the reduction of base concentration (Fig. 2(b)), which was evidenced by a change of pH value from 10.0 to 7.9. Adding small amount of K_2CO_3 to adjust the pH value back to 10.0 recovered catalytic activity of the solution, and the yield risen to 98% again.

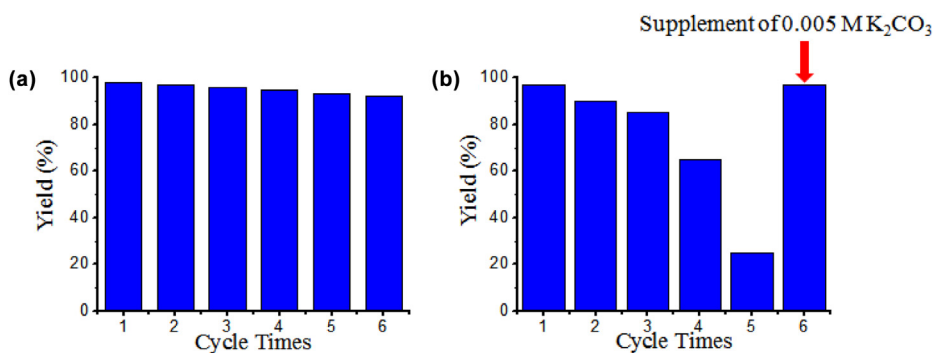


Fig. 2. Reusability of the K_2CO_3 solution. (a) The K_2CO_3 concentration was 0.020 M (0.2 equiv). (b) The initial K_2CO_3 concentration was 0.005 M (0.05 equiv), but the yield reduces with times. The K_2CO_3 concentration was readjusted back to 0.005 M in the sixth cycle.

To investigate the reaction mechanism, the reactions were monitored by in situ infrared (IR) spectroscopy²⁰ under different conditions. Fig. 3(a) and (b) shows the IR spectra of the reaction mixture in pure water, along with the rising of temperature from room temperature to reflux condition. In pure water, no obvious IR peak corresponding to the reactant can be observed at room temperature, suggesting that little reactant was dissolved. At reflux temperature (e.g., after 50 min), the spectra show features of the reactant, indicating that the reactant was slightly dissolved in hot water. However, both the 2D and 3D IR plots show no observable spectral change in a period of 400 min, confirming that no reaction took place in pure water.

Fig. 3(c) shows the IR spectra of the reaction mixture in the presence of 0.1 M K_2CO_3 solution at different temperatures. At room temperature, all the peaks of the IR spectra were very weak, suggesting very low solubility of the reactant even in basic solution. After 50 min, when the system temperature was elevated to reflux condition, much stronger IR absorption starts to emerge, indicating increased solubility at high temperature. At reflux condition, the IR intensity of the basic reaction mixture is about three times higher than that of the pure water reaction mixture, indicating that more soluble species was generated in basic solution. Compared with the spectra of the reactant (Fig. 3(a)) in water, the spectra in Fig. 3(c) show two new and prominent peaks at 1350 and 1303 cm^{-1} , respectively, which can be assigned to the stretching and torsional vibrations of phenolate species.²¹ These two new peaks reveal that trace of **1a** was converted to 2-(phenylethynyl)phenolate (**I**) in the hot alkaline solution. Such trace phenolate intermediate allowed the cyclization reaction to take place. The intensity of the spectra remained nearly unchanged during the reaction period of 50–300 min, indicating that the concentration of the soluble

phenolate intermediate remained constant. After 300 min, the IR spectra absorption gradually decreases with the further progress of the reaction, suggesting the depletion of the reactant and the phenolate intermediate. At the end of the reaction, the spectra became very weak again due to the low solubility of the **2a** product.

Based on the In-situ IR study, the reaction mechanism of the heterogeneous reaction is depicted in Fig. 3(e). In hot and basic aqueous solution, trace of **1a** was converted to **I**, which is sparingly soluble in water, hence can be detected by the IR spectroscopy. The phenolate moieties then attack the acetylenyl group to undergo an intramolecular cyclization process and give the final **2a** compound. Though the IR spectra indicate that only trace amount of the sparingly soluble intermediate is generated during the reaction, the reaction can be still driven towards the forward direction of the equation because the product is insoluble in aqueous reaction mixture and quickly separated from the solution. Finally, all the **1a** reactant was converted into **2a** product, and the heterogeneous reaction occurs in high yield.

3. Conclusion

We have demonstrated the highly efficient and green synthesis of benzofurans under aqueous condition through an intermediate-in-water heterogeneous reaction strategy. The very low solubility of both the reactant and product lead the reaction unavailable in water. However, in high temperature alkaline solutions, sparingly soluble phenolate intermediate could be generated, which enable the heterogeneous reaction to take place with a very high conversion yield. This heterogeneous reaction exhibits many attractive features, including the easy collection and purification of product, wide range of functional group tolerance, thus rendering the methodology as a highly eco-friendly alternative to the existing methods. Further works including expanding the scope of this intermediate-in-water reaction strategy to other structural unites are undergoing.

4. Experimental section

4.1. Benzofuran derivatives

All of the 2-phenylbenzofuran derivatives were prepared by the following method.

Microwave irradiated the mixture of 2-(phenylethynyl)phenol derivatives (0.5 mmol), deionized water (5 mL), and K_2CO_3 (0.025 mmol) in a hermetic polytetrafluoroethylene bottle at 110 °C. Microwave irradiation was applied once the reaction temperature under 110 °C for the total time of 2 h. The solid product obtained through filtration of result product should leave from pure water. The liquid product was purified by flash chromatography in ethyl acetate/petroleum to afford the analytically pure sample.

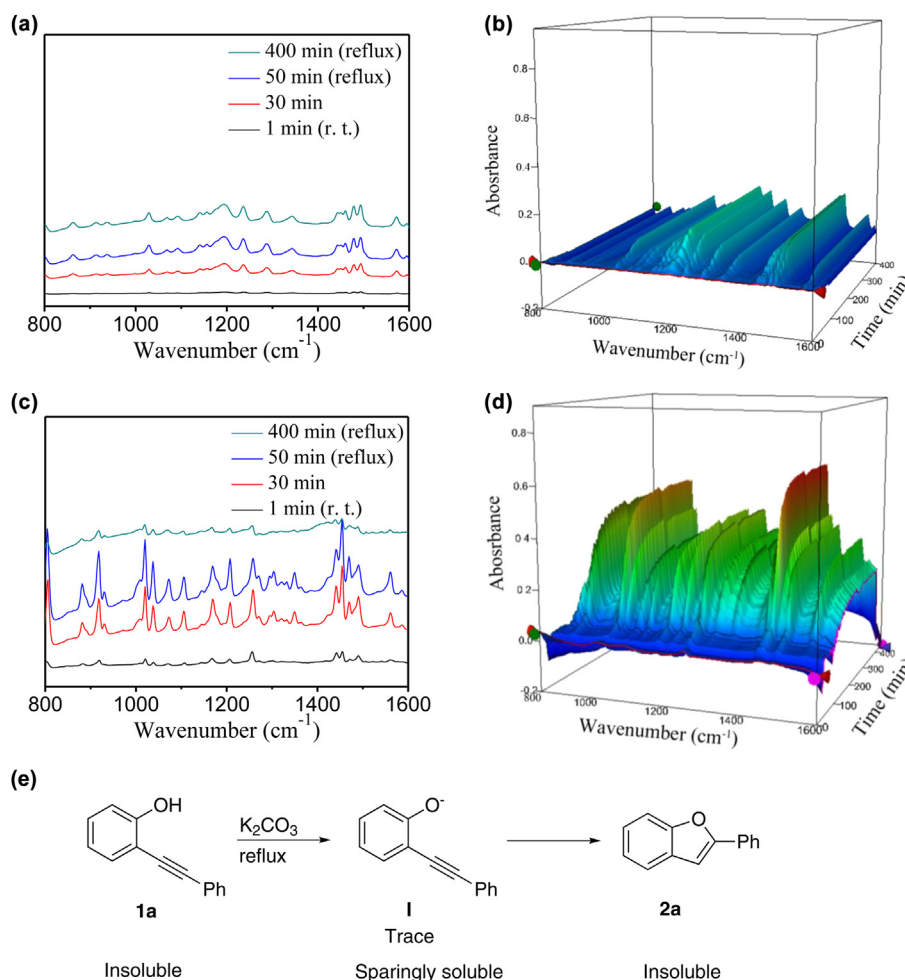


Fig. 3. In situ IR spectra were recorded to determine the mechanistic course of the cyclization reaction. (a) 2D and (b) 3D plots of IR spectra in pure water; (c) 2D and (d) 3D plots of IR spectra in 0.1 M (1 equiv) K_2CO_3 solution; (e) hypothesized reaction mechanism.

The following compounds were prepared by the method above:

4.1.1. 2-Phenylbenzofuran (2a). White solid (92 mg, 95%); 1H NMR (400 MHz) δ : 7.87 (d, $J=7.2$ Hz, 2H), 7.59 (d, $J=7.2$ Hz, 1H), 7.52 (d, $J=8.0$ Hz, 1H), 7.45 (t, $J=7.2$ Hz, 2H), 7.35 (t, $J=7.2$ Hz, 1H), 7.29 (t, $J=7.6$ Hz, 1H), 7.23 (t, $J=7.2$ Hz, 1H), 7.03 (s, 1H); ^{13}C NMR (100 MHz) δ : 155.9, 154.9, 130.5, 129.2, 128.8, 128.5, 124.9, 124.3, 122.9, 120.9, 111.2, 101.3; MS (EI) m/z (%): 194 (M^+ , 100). The spectroscopic data match the previously reported in the literature.²²

4.1.2. 2-(Thiophen-2-yl)benzofuran (2b). White solid (87 mg, 87%); 1H NMR (400 MHz) δ : 7.56–7.51 (m, 1H), 7.50–7.45 (m, 2H), 7.34–7.31 (m, 1H), 7.29–7.24 (m, 1H), 7.24–7.19 (m, 1H), 7.09 (dd, $^1J=4.8$ Hz, $^2J=3.6$ Hz, 1H), 6.86 (s, 1H); ^{13}C NMR (100 MHz) δ : 154.6, 151.3, 133.3, 129.1, 127.9, 125.8, 124.6, 124.3, 123.0, 120.7, 111.0, 101.1; MS (EI) m/z (%): 200 (M^+ , 100).

4.1.3. 2-p-Tolylbenzofuran (2c). White solid (94 mg, 90%); 1H NMR (400 MHz) δ : 7.75 (d, $J=7.2$ Hz, 2H), 7.55 (d, $J=7.2$ Hz, 1H), 7.50 (d, $J=7.6$ Hz, 1H), 7.28–7.23 (m, 3H), 7.21 (t, $J=7.6$ Hz, 1H), 6.96 (s, 1H), 2.39 (s, 3H); ^{13}C NMR (100 MHz) δ : 156.2, 154.8, 138.6, 129.5, 129.3, 127.7, 124.9, 124.0, 122.8, 120.7, 111.1, 100.5, 21.4; MS (EI) m/z (%): 208 (M^+ , 100), 207 (33). The spectroscopic data match the previously reported in the literature.²³

4.1.4. 2-(4-Fluorophenyl)benzofuran (2d). White solid (98 mg, 92%); 1H NMR (400 MHz) δ : 7.86–7.80 (m, 2H), 7.57 (d, $J=7.6$ Hz,

1H), 7.51 (d, $J=8.4$ Hz, 1H), 7.30–7.25 (m, 1H), 7.25–7.20 (m, 1H), 7.17–7.10 (m, 2H), 6.94 (s, 1H); ^{13}C NMR (100 MHz) δ : 164.1, 161.6, 155.0, 154.8, 129.2, 126.8, 126.7, 124.3, 123.0, 120.9, 116.0, 115.8, 111.1, 101.0; MS (EI) m/z (%): 212 (M^+ , 100). The spectroscopic data match the previously reported in the literature.¹⁷ⁱ

4.1.5. 2-(4-Chlorophenyl)benzofuran (2e). White solid (103 mg, 90%); 1H NMR (400 MHz) δ : 7.81–7.77 (m, 2H), 7.57 (d, $J=7.6$ Hz, 1H), 7.51 (d, $J=8.4$ Hz, 1H), 7.43–7.39 (m, 2H), 7.32–7.27 (m, 1H), 7.25–7.10 (m, 1H), 7.00 (s, 1H); ^{13}C NMR (100 MHz) δ : 154.9, 154.8, 134.3, 129.1, 129.0, 128.9, 126.1, 124.6, 123.1, 121.0, 111.2, 101.7; MS (EI) m/z (%): 230 (33), 228 (M^+ , 100). The spectroscopic data match the previously reported in the literature.¹⁷ⁱ

4.1.6. 2-(4-Bromophenyl)benzofuran (2f). White solid (115 mg, 84%); 1H NMR (400 MHz) δ : 7.65 (d, $J=8.8$ Hz, 2H), 7.54–7.46 (m, 4H), 7.29–7.24 (m, 1H), 7.22–7.18 (m, 1H), 6.93 (s, 1H); ^{13}C NMR (100 MHz) δ : 154.9, 154.8, 132.0, 129.4, 129.0, 126.4, 124.6, 123.1, 122.5, 121.0, 111.2, 101.8; MS (EI) m/z (%): 274 (93), 272 (M^+ , 100). The spectroscopic data match the previously reported in the literature.²⁴

4.1.7. 2-m-Tolylbenzofuran (2g). White solid (84 mg, 81%); 1H NMR (400 MHz) δ : 7.67 (s, 1H), 7.63 (d, $J=8.0$ Hz, 1H), 7.54 (d, $J=8.0$ Hz, 1H), 7.50 (d, $J=8.0$ Hz, 1H), 7.31–7.26 (m, 1H), 7.25–7.17 (m, 2H), 7.14–7.10 (m, 1H), 6.95 (s, 1H), 2.38 (s, 3H); ^{13}C NMR (100 MHz) δ : 156.1, 154.9, 138.4, 130.4, 129.4, 129.3, 128.7, 125.5, 124.1, 122.9,

122.1, 120.8, 111.1, 101.1, 21.5; MS (EI) m/z (%): 208 (M^+ , 100). The spectroscopic data match the previously reported in the literature.²⁵

4.1.8. 2-(3-Fluorophenyl)benzofuran (2h). White solid (104 mg, 98%); ^1H NMR (400 MHz) δ : 7.58–7.46 (m, 4H), 7.32 (q, $^1J=8.0$ Hz, $^2J=6.0$ Hz, 1H), 7.26 (t, $J=7.2$ Hz, 1H), 7.20 (t, $J=7.2$ Hz, 1H), 6.99 (t, $J=8.4$ Hz, 1H), 6.94 (s, 1H); ^{13}C NMR (100 MHz) δ : 164.3, 161.9, 154.9, 154.5, 154.4, 132.5, 132.4, 130.3, 130.2, 128.9, 124.7, 123.0, 121.1, 120.5, 120.4, 115.3, 115.1, 111.8, 111.6, 111.2, 102.3; MS (EI) m/z (%): 212 (M^+ , 100), 183 (47). The spectroscopic data match the previously reported in the literature.²⁶

4.1.9. 2-(3-Chlorophenyl)benzofuran (2i). White solid (112 mg, 98%); ^1H NMR (400 MHz) δ : 7.78 (s, 1H), 7.64–7.60 (m, 1H), 7.51 (d, $J=7.6$ Hz, 1H), 7.46 (d, $J=8.4$ Hz, 1H), 7.27–7.22 (m, 3H), 7.19 (t, $J=7.2$ Hz, 1H), 6.91 (s, 1H); ^{13}C NMR (100 MHz) δ : 154.9, 154.3, 134.9, 132.2, 130.0, 128.9, 128.4, 124.9, 124.7, 123.1, 122.9, 121.1, 111.2, 102.4; MS (EI) m/z (%): 230 (34), 228 (M^+ , 100). The spectroscopic data match the previously reported in the literature.²⁷

4.1.10. 2-(3-Bromophenyl)benzofuran (2j). White solid (132 mg, 97%); ^1H NMR (400 MHz) δ : 7.94 (s, 1H), 7.67 (d, $J=7.6$ Hz, 1H), 7.52 (d, $J=7.6$ Hz, 1H), 7.47 (d, $J=8.0$ Hz, 1H), 7.39 (d, $J=8.0$ Hz, 1H), 7.26 (t, $J=7.6$ Hz, 1H), 7.23–7.17 (m, 2H), 6.92 (s, 1H); ^{13}C NMR (100 MHz) δ : 155.0, 154.2, 132.4, 131.3, 130.3, 128.9, 127.8, 124.8, 123.4, 123.1, 123.0, 121.1, 111.3, 102.4; MS (EI) m/z (%): 274 (88), 272 (M^+ , 100). The spectroscopic data match the previously reported in the literature.²⁸

4.1.11. 2-Butylbenzofuran (2k). Colorless oil (25 mg, 29%); ^1H NMR (400 MHz) δ : 7.46 (d, $J=7.6$ Hz, 1H), 7.40 (d, $J=7.6$ Hz, 1H), 7.20–7.16 (m, 2H), 6.37 (s, 1H), 2.77 (t, $J=7.6$ Hz, 2H), 1.77–1.69 (m, 3H), 1.45–1.39 (m, 3H), 0.96 (t, $J=7.6$ Hz, 3H); ^{13}C NMR (100 MHz) δ : 159.7, 154.6, 129.0, 123.0, 122.3, 120.1, 110.7, 101.7, 29.8, 28.1, 22.3, 13.8; MS (EI) m/z (%): 174 (M^+ , 30), 132 (34), 131 (100). The spectroscopic data match the previously reported in the literature.²⁹

4.1.12. 5-Methyl-2-phenylbenzofuran (2l). White solid (98 mg, 94%); ^1H NMR (400 MHz) δ : 7.85 (d, $J=8.0$ Hz, 2H), 7.43 (t, $J=7.6$ Hz, 2H), 7.40–7.31 (m, 3H), 7.09 (t, $J=8.4$ Hz, 1H), 6.95 (s, 1H), 2.44 (s, 3H); ^{13}C NMR (100 MHz) δ : 156.0, 153.3, 132.3, 130.6, 129.3, 128.7, 128.4, 125.5, 124.8, 120.7, 110.6, 101.1, 21.3; MS (EI) m/z (%): 208 (M^+ , 100), 207 (54). The spectroscopic data match the previously reported in the literature.³⁰

4.1.13. 5-Methyl-2-p-tolylbenzofuran (2m). White solid (48 mg, 43%); ^1H NMR (400 MHz) δ : 7.74 (d, $J=8.0$ Hz, 2H), 7.38 (t, $J=7.6$ Hz, 1H), 7.34 (s, 1H), 7.23 (s, 2H), 7.07 (d, $J=8.4$ Hz, 1H), 6.89 (s, 1H), 2.44 (s, 3H), 2.39 (s, 3H); ^{13}C NMR (100 MHz) δ : 156.3, 153.2, 138.4, 132.2, 129.4, 127.9, 125.2, 124.8, 120.6, 110.6, 100.3, 22.7, 21.4; MS (EI) m/z (%): 222 (M^+ , 100), 221 (34). The spectroscopic data match the previously reported in the literature.^{17b}

4.1.14. 5-tert-Butyl-2-phenylbenzofuran (2n). White solid (43 mg, 34%); ^1H NMR (400 MHz) δ : 7.85 (d, $J=7.6$ Hz, 2H), 7.58 (d, $J=1.6$ Hz,

1H), 7.46–7.41 (m, 3H), 7.36–7.31 (m, 2H), 7.07 (d, $J=8.4$ Hz, 1H), 6.99 (s, 1H), 1.39 (s, 9H); ^{13}C NMR (100 MHz) δ : 156.0, 153.2, 146.0, 130.7, 128.9, 128.7, 128.4, 124.9, 122.2, 117.1, 110.4, 101.5, 34.7, 31.8; MS (EI) m/z (%): 250 (M^+ , 31), 235 (58), 44 (100). The spectroscopic data match the previously reported in the literature.¹⁷¹

4.1.15. 5-tert-Butyl-2-p-tolylbenzofuran (2o). White solid (27 mg, 20%); ^1H NMR (400 MHz) δ : 7.74 (d, $J=7.6$ Hz, 2H), 7.56 (d, $J=1.6$ Hz, 1H), 7.42 (d, 1H), 7.30 (dd, $^1J=8.4$ Hz, $^2J=1.6$ Hz, 1H), 7.24 (d, $J=7.2$ Hz, 2H), 6.93 (s, 1H), 2.39 (s, 3H), 1.39 (s, 9H); ^{13}C NMR (100 MHz) δ : 156.3, 153.0, 145.9, 138.4, 129.4, 129.0, 128.0, 124.8, 122.0, 116.9, 110.3, 100.7, 34.7, 31.9, 21.4; MS (EI) m/z (%): 264 (M^+ , 37), 249 (54), 44 (100). The spectroscopic data match the previously reported in the literature.³¹

4.1.16. 5-tert-Butyl-2-(4-chlorophenyl)benzofuran (2p). White solid (45 mg, 32%); ^1H NMR (400 MHz) δ : 7.75 (d, $J=7.2$ Hz, 2H), 7.57 (d, $J=1.6$ Hz, 1H), 7.43–7.33 (m, 4H), 6.95 (s, 1H), 1.38 (s, 9H); ^{13}C NMR (100 MHz) δ : 154.9, 153.2, 146.2, 134.1, 129.2, 129.0, 128.8, 126.0, 122.6, 117.2, 110.5, 101.9, 34.7, 31.8; MS (EI) m/z (%): 284 (M^+ , 49), 269 (100). The spectroscopic data match the previously reported in the literature.³¹

4.1.17. 5-Chloro-2-phenylbenzofuran (2q). White solid (74 mg, 65%); ^1H NMR (400 MHz) δ : 7.83 (d, $J=7.6$ Hz, 2H), 7.52 (d, $J=2.0$ Hz, 1H), 7.46–7.34 (m, 4H), 7.24–7.20 (m, 1H), 6.93 (s, 1H); ^{13}C NMR (100 MHz) δ : 157.4, 153.2, 130.6, 129.9, 128.9, 128.8, 128.5, 125.0, 124.4, 120.4, 112.1, 100.8; MS (EI) m/z (%): 230 (32), 228 (M^+ , 100). The spectroscopic data match the previously reported in the literature.³⁰

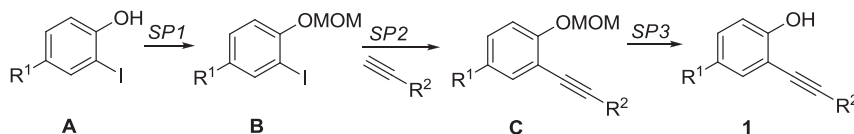
4.1.18. 5-Chloro-2-p-tolylbenzofuran (2r). White solid (85 mg, 70%); ^1H NMR (400 MHz) δ : 7.72 (d, $J=8.4$ Hz, 2H), 7.50 (d, $J=2.0$ Hz, 1H), 7.40 (d, $J=8.4$ Hz, 1H), 7.25–7.20 (m, 3H), 6.87 (s, 1H), 2.39 (s, 3H); ^{13}C NMR (100 MHz) δ : 157.7, 153.1, 139.1, 130.7, 129.5, 128.4, 127.2, 125.0, 124.0, 120.2, 112.0, 100.0, 21.4; MS (EI) m/z (%): 244 (32), 242 (M^+ , 100). The spectroscopic data match the previously reported in the literature.³¹

4.1.19. 5-Chloro-2-(4-chlorophenyl)benzofuran (2s). White solid (58 mg, 44%); ^1H NMR (400 MHz) δ : 7.75 (d, $J=8.8$ Hz, 2H), 7.52 (d, $J=2.0$ Hz, 1H), 7.41 (d, $J=8.4$ Hz, 3H), 7.25–7.21 (m, 1H), 6.92 (s, 1H); ^{13}C NMR (100 MHz) δ : 156.2, 153.3, 134.8, 133.7, 130.4, 129.1, 128.5, 126.3, 124.7, 120.5, 112.1, 101.2; MS (EI) m/z (%): 264 (60), 262 (M^+ , 100). The spectroscopic data match the previously reported in the literature.³¹

4.2. Starting materials

All of the 2-(phenylethynyl)phenol derivatives were prepared according to Scheme 3 using a modified variant of the method reported by Takahashi.³²

4.2.1. MOMCl protection (SP1). MOMCl (12.0 mmol) was added to a mixture of **A** (6.0 mmol) and NaH (24.0 mmol) in DMF (20 mL)



Scheme 3.

with ice-cooling. The mixture was stirred at room temperature until the phenol was consumed, after which the mixture was

diluted with water (15 mL) and ether (100 mL). The layers were separated and the organic phase was washed with abundant water before being dried over Na₂SO₄, filtered, and the solvent was removed under reduced pressure to afford compound **B** as a yellow oil.³³

4.2.2. Sonagashira reaction (SP2). Pd(PPh₃)₂Cl₂ (5 mol %) and CuI (5 mol %) were added to a solution of alkyne (1.1 equiv) and compound **B** (1.0 equiv) in THF and triethylamine mixture solution. The resulting mixture was stirred at 50 °C until the reaction was complete as determined by TLC. On completion, the mixture was allowed to cool to room temperature. Removal of solvent under reduced pressure afforded a residue, which was purified by flash chromatography in ethyl acetate/petroleum ether to afford the compound **C**.

4.2.3. MOM deprotection (SP3). HCl (6 M) was added to a solution of the MOM protected compound **C** in CH₃OH solution and the mixture was stirred at reflux temperature until deprotection was complete. Dilution with water and ethylether and extraction of the aqueous layer with ethylether was followed by washing of the combined organic phases with brine, drying over Na₂SO₄, and removing the solvent under reduced pressure to afford a residue, which can be purified by flash chromatography in ethyl acetate/petroleum to afford the reactants.^{17f}

The following compounds were prepared by this method:

4.2.4. 2-(Phenylethynyl)phenol (1a). Yellow solid (2.59 g, 97%); ¹H NMR (400 MHz, CDCl₃): δ: 7.56–7.53 (m, 2H), 7.43 (dd, ¹J=8.0 Hz, ²J=1.6 Hz, 1H), 7.39–7.37 (m, 3H), 7.30–7.27 (m, 1H), 6.98 (d, ¹J=8.4 Hz, 1H), 6.92 (t, ¹J=7.6 Hz, 1H), 5.83 (s, 1H); ¹³C NMR (100 MHz) δ: 156.5, 131.6, 130.5, 128.8, 128.5, 122.4, 120.4, 114.7, 109.6, 96.4, 83.0; MS (EI) *m/z* (%): 194 (M⁺, 100). The spectroscopic data match the previously reported in the literature.³⁴

4.2.5. 2-(Thiophen-2-ylethynyl)phenol (1b). Yellow solid (801 mg, 85%); ¹H NMR (400 MHz) δ: 7.41 (d, ¹J=7.6 Hz, 1H), 7.33–7.25 (m, 3H), 7.03 (t, ¹J=4.4 Hz, 1H), 6.98 (d, ¹J=8.4 Hz, 1H), 6.91 (t, ¹J=7.6 Hz, 1H), 5.77 (s, 1H); ¹³C NMR (100 MHz) δ: 156.5, 132.5, 131.7, 130.7, 128.0, 127.2, 122.3, 120.5, 114.9, 109.3, 89.3, 86.7; MS (EI) *m/z* (%): 200 (M⁺, 100). The spectroscopic data match the previously reported in the literature.³⁵

4.2.6. 2-(p-Tolylethynyl)phenol (1c). Yellow solid (410 mg, 91%); ¹H NMR (400 MHz) δ: 7.45–7.40 (m, 3H), 7.29–7.24 (m, 1H), 7.18 (d, ¹J=8.0 Hz, 2H), 6.98 (d, ¹J=7.6 Hz, 1H), 6.91 (t, ¹J=7.6 Hz, 1H), 5.84 (s, 1H), 2.39 (s, 3H); ¹³C NMR (100 MHz) δ: 156.5, 139.2, 131.7, 131.6, 130.4, 129.3, 120.5, 119.4, 114.7, 109.9, 96.7, 82.4, 21.6; MS (EI) *m/z* (%): 208 (M⁺, 100), 207 (51). The spectroscopic data match the previously reported in the literature.³⁶

4.2.7. 2-((4-Fluorophenyl)ethynyl)phenol (1d). Yellow solid (312 mg, 90%); ¹H NMR (400 MHz) δ: 7.55–7.51 (m, 2H), 7.41 (dd, ¹J=7.6 Hz, ²J=1.6 Hz, 1H), 7.30–7.26 (m, 1H), 7.08 (t, ¹J=8.4 Hz, 2H), 6.98 (d, ¹J=8.0 Hz, 1H), 6.91 (t, ¹J=8.4 Hz, 1H), 5.77 (s, 1H); ¹³C NMR (100 MHz) δ: 164.1, 161.6, 156.5, 133.6, 133.5, 131.7, 130.6, 120.5, 118.5, 118.4, 116.0, 115.7, 114.8, 109.4, 95.2, 82.8; MS (EI) *m/z* (%): 212 (M⁺, 100). The spectroscopic data match the previously reported in the literature.³⁷

4.2.8. 2-((4-Chlorophenyl)ethynyl)phenol (1e). Yellow solid (211 mg, 88%); ¹H NMR (400 MHz) δ: 7.49–7.45 (m, 2H), 7.42 (dd, ¹J=7.6 Hz, ²J=1.6 Hz, 1H), 7.35 (d, ¹J=8.8 Hz, 2H), 7.31–7.26 (m, 1H), 6.98 (d, ¹J=8.0 Hz, 1H), 6.92 (t, ¹J=7.6 Hz, 1H), 5.75 (s, 1H); ¹³C NMR (100 MHz) δ: 156.5, 134.9, 132.8, 131.7, 130.7, 128.9, 120.9, 120.5, 114.8, 109.3, 95.1, 84.0; MS (EI) *m/z* (%): 228 (M⁺, 100); Anal. Calcd for C₁₄H₉OCl: C

(73.53), H (3.97); Found: C (73.43), H (3.99); HRMS (ESI) *m/z* calcd for C₁₄H₉OClNaO [M+Na]⁺ 251.0234, found: 251.0236. The spectroscopic data match the previously reported in the literature.³⁵

4.2.9. 2-((4-Bromophenyl)ethynyl)phenol (1f). Yellow solid (203 mg, 84%); ¹H NMR (400 MHz) δ: 7.53–7.48 (m, 2H), 7.43–7.36 (m, 3H), 7.31–7.25 (m, 1H), 6.98 (d, ¹J=8.4 Hz, 1H), 6.92 (t, ¹J=7.6 Hz, 1H), 5.76 (s, 1H); ¹³C NMR (100 MHz) δ: 156.5, 133.8, 133.0, 131.8, 131.7, 130.8, 123.1, 121.4, 120.5, 114.9, 109.3, 95.2, 84.3; MS (EI) *m/z* (%): 274 (92), 272 (M⁺, 93), 165 (100). The spectroscopic data match the previously reported in the literature.³⁸

4.2.10. 2-(m-Tolylethynyl)phenol (1g). Colorless oil (264 mg, 90%); ¹H NMR (400 MHz) δ: 7.41 (dd, ¹J=8.0 Hz, ²J=1.6 Hz, 1H), 7.37–7.33 (m, 2H), 7.29–7.24 (m, 2H), 7.18 (d, ¹J=7.6 Hz, 1H), 6.97 (d, ¹J=8.0 Hz, 1H), 6.91 (t, ¹J=7.6 Hz, ²J=1.2 Hz, 1H), 5.84 (s, 1H), 2.36 (s, 3H); ¹³C NMR (100 MHz) δ: 156.5, 138.2, 132.2, 131.6, 130.4, 129.7, 128.7, 128.4, 122.2, 120.4, 114.7, 109.7, 96.6, 82.6; MS (EI) *m/z* (%): 208 (M⁺, 100). HRMS (c ESI) *m/z* calcd for C₁₅H₁₂O [M]⁺ 208.0883, found: 208.0896.

4.2.11. 2-((3-Fluorophenyl)ethynyl)phenol (1h). Yellow solid (277 mg, 91%); ¹H NMR (400 MHz) δ: 7.42 (dd, ¹J=7.6 Hz, ²J=1.6 Hz, 1H), 7.36–7.27 (m, 3H), 7.25–7.22 (m, 1H), 7.12–7.06 (m, 1H), 6.99 (dd, ¹J=8.4 Hz, ²J=0.4 Hz, 1H), 6.93 (dd, ¹J=7.6 Hz, ²J=0.8 Hz, 1H), 5.75 (s, 1H); ¹³C NMR (100 MHz) δ: 163.6, 161.2, 156.6, 131.8, 130.8, 130.2, 130.1, 127.5, 127.4, 124.3, 124.2, 120.5, 118.5, 118.3, 116.3, 116.1, 114.9, 109.1, 95.0, 94.9, 84.0; MS (EI) *m/z* (%): 212 (M⁺, 100). The spectroscopic data match the previously reported in the literature.^{17j}

4.2.12. 2-((3-Chlorophenyl)ethynyl)phenol (1i). Yellow solid (205 mg, 90%), mp 96–98 °C; ¹H NMR (400 MHz) δ: 7.54–7.52 (m, 1H), 7.45–7.40 (m, 2H), 7.36–7.26 (m, 3H), 6.98 (d, ¹J=8.4 Hz, 1H), 6.92 (t, ¹J=8.0 Hz, 1H), 5.74 (s, 1H); ¹³C NMR (100 MHz) δ: 156.6, 134.4, 131.8, 131.4, 130.9, 129.7, 129.6, 124.1, 120.5, 114.9, 109.1, 94.8, 84.3; MS (EI) *m/z* (%): 230 (32), 228 (M⁺, 100); Anal. Calcd for C₁₄H₉OCl: C (73.53), H (3.97); Found: C (73.55), H (3.98). HRMS (c ESI) *m/z* calcd for C₁₄H₉OCl [M]⁺ 228.0336, found: 228.0350.

4.2.13. 2-((3-Bromophenyl)ethynyl)phenol (1j). Yellow solid (193 mg, 87%); ¹H NMR (400 MHz) δ: 7.71–7.69 (m, 1H), 7.54–7.45 (m, 2H), 7.41 (dd, ¹J=7.6 Hz, ²J=1.6 Hz, 1H), 7.32–7.26 (m, 1H), 7.25–7.22 (m, 1H), 6.98 (d, ¹J=7.6 Hz, 1H), 6.92 (t, ¹J=7.6 Hz, 1H), 5.73 (s, 1H); ¹³C NMR (100 MHz) δ: 156.6, 134.3, 131.9, 131.8, 130.9, 130.1, 129.9, 124.4, 122.3, 120.5, 114.9, 109.1, 94.6, 84.5; MS (EI) *m/z* (%): 274 (88), 272 (M⁺, 92), 165 (100). The spectroscopic data match the previously reported in the literature.²⁶

4.2.14. 2-(Hex-1-ynyl)phenol (1k). Colorless oil (176 mg, 70%); ¹H NMR (400 MHz) δ: 7.31 (dd, ¹J=7.6 Hz, ²J=1.6 Hz, 1H), 7.19–7.16 (m, 1H), 6.92 (d, ¹J=8.4 Hz, 1H), 6.86–6.81 (m, 1H), 5.81 (s, 1H), 2.48 (t, ¹J=6.8 Hz, 2H), 1.65–1.58 (m, 2H), 1.53–1.43 (m, 2H), 0.96 (t, ¹J=7.2 Hz, 3H); ¹³C NMR (100 MHz) δ: 156.5, 131.4, 129.6, 120.1, 114.3, 110.2, 98.0, 74.5, 30.8, 22.0, 19.3, 13.6; MS (EI) *m/z* (%): 174 (M⁺, 100), 131 (55). The spectroscopic data match the previously reported in the literature.³⁵

4.2.15. 4-Methyl-2-(phenylethynyl)phenol (1l). Yellow solid (211 mg, 87%); ¹H NMR (400 MHz) δ: 7.53–7.51 (m, 2H), 7.38–7.35 (m, 3H), 7.26–7.23 (m, 1H), 7.07 (dd, ¹J=7.6 Hz, ²J=2.0 Hz, 1H), 6.87 (d, ¹J=8.4 Hz, 1H), 5.66 (s, 1H), 2.28 (s, 3H); ¹³C NMR (100 MHz) δ: 154.4, 131.7, 131.6, 131.3, 129.6, 128.7, 128.5, 122.5, 114.5, 109.2, 96.0, 83.3, 20.3; MS (EI) *m/z* (%): 208 (M⁺, 100), 207 (67). The spectroscopic data match the previously reported in the literature.³⁵

4.2.16. 4-Methyl-2-(p-tolylethynyl)phenol (1m). Yellow solid (173 mg, 81%); ¹H NMR (400 MHz) δ: 7.42 (d, ¹J=8.0 Hz, 2H), 7.22 (s,

1H), 7.17 (d, $J=8.0$ Hz, 2H), 7.06 (dd, $^1J=8.4$ Hz, $^2J=1.6$ Hz, 1H), 6.87 (d, $J=8.4$ Hz, 1H), 5.67 (s, 1H), 2.38 (s, 3H), 2.27 (s, 3H); ^{13}C NMR (100 MHz) δ : 154.3, 143.2, 131.6, 128.7, 128.5, 128.3, 127.8, 122.5, 114.3, 108.8, 95.8, 83.6, 34.1, 31.4; MS (EI) m/z (%): 222 (M^+ , 100), 221 (57). The spectroscopic data match the previously reported in the literature.³⁹

4.2.17. 4-tert-Butyl-2-(phenylethynyl)phenol (1n). Colorless oil (152 mg, 83%); ^1H NMR (400 MHz) δ : 7.55–7.53 (m, 2H), 7.43 (d, $J=3.2$ Hz, 1H), 7.38–7.35 (m, 3H), 7.30 (dd, $^1J=8.8$ Hz, $^2J=2.4$ Hz, 1H), 6.91 (d, $J=8.8$ Hz, 1H), 5.69 (s, 1H), 1.30 (s, 9H); ^{13}C NMR (100 MHz) δ : 154.3, 139.0, 131.6, 131.5, 131.1, 129.6, 129.2, 119.4, 114.4, 109.4, 96.3, 82.6, 21.5, 20.4; MS (EI) m/z (%): 250 (M^+ , 52), 235 (100). The spectroscopic data match the previously reported in the literature.⁴⁰

4.2.18. 4-tert-Butyl-2-(p-tolylethynyl)phenol (1o). Colorless oil (148 mg, 79%); ^1H NMR (400 MHz) δ : 7.45–7.41 (m, 3H), 7.29 (dd, $^1J=8.8$ Hz, $^2J=2.4$ Hz, 1H), 7.17 (d, $J=8.0$ Hz, 2H), 6.91 (d, $J=7.6$ Hz, 1H), 5.69 (s, 1H), 2.38 (s, 3H), 1.30 (s, 9H); ^{13}C NMR (100 MHz) δ : 154.2, 143.2, 139.0, 131.5, 129.2, 128.2, 127.6, 119.4, 114.2, 109.0, 96.0, 82.9, 34.1, 31.4, 21.5; MS (EI) m/z (%): 264 (M^+ , 48), 249 (100); Anal. Calcd for $\text{C}_{19}\text{H}_{20}\text{O}$: C (86.32), H (7.63); Found: C (86.29), H (7.61); HRMS (ESI) m/z calcd for $\text{C}_{19}\text{H}_{20}\text{NaO}$ [$\text{M}+\text{Na}$] $^+$ 287.1406, found: 287.1408.

4.2.19. 4-tert-Butyl-2-((4-chlorophenyl)ethynyl)phenol (1p). Yellow solid (131 mg, 75%), mp 98–100 °C; ^1H NMR (400 MHz) δ : 7.50–7.47 (m, 2H), 7.46 (dd, $^1J=7.2$ Hz, $^2J=2.0$ Hz, 1H), 7.37–7.31 (m, 3H), 6.94 (d, $J=8.4$ Hz, 1H), 5.74 (s, 1H), 1.33 (s, 9H); ^{13}C NMR (100 MHz) δ : 154.3, 143.3, 134.7, 132.7, 128.8, 128.4, 128.0, 121.0, 114.4, 108.5, 94.4, 84.8, 34.1, 31.3; MS (EI) m/z (%): 284 (M^+ , 44), 271 (32), 269 (100); Anal. Calcd for $\text{C}_{18}\text{H}_{17}\text{OCl}$: C (75.92), H (6.02); Found: C (75.89), H (5.99); HRMS (ESI) m/z calcd for $\text{C}_{18}\text{H}_{17}\text{ClNaO}$ [$\text{M}+\text{Na}$] $^+$ 307.0860, found: 307.0862.

4.2.20. 4-Chloro-2-(phenylethynyl)phenol (1q). Yellow solid (167 mg, 85%); ^1H NMR (400 MHz) δ : 7.55–7.52 (m, 2H), 7.40–7.36 (m, 4H), 7.22 (dd, $^1J=8.8$ Hz, $^2J=2.8$ Hz, 1H), 6.92 (d, $J=8.4$ Hz, 1H), 5.79 (s, 1H); ^{13}C NMR (100 MHz) δ : 155.2, 131.7, 130.9, 130.4, 129.2, 128.6, 125.1, 121.9, 116.0, 111.1, 97.3, 81.8; MS (EI) m/z (%): 230 (32), 228 (M^+ , 100). The spectroscopic data match the previously reported in the literature.³⁵

4.2.21. 4-Chloro-2-(p-tolylethynyl)phenol (1r). Yellow solid (151 mg, 83%); ^1H NMR (400 MHz) δ : 7.42 (d, $J=8.0$ Hz, 2H), 7.38 (d, $J=2.8$ Hz, 1H), 7.22–7.17 (m, 3H), 6.91 (d, $J=8.4$ Hz, 1H), 5.79 (s, 1H), 2.39 (s, 3H); ^{13}C NMR (100 MHz) δ : 155.1, 139.5, 131.6, 130.8, 130.2, 129.3, 125.0, 118.8, 116.0, 111.3, 97.6, 81.2, 21.6; MS (EI) m/z (%): 244 (32), 242 (M^+ , 100), 241 (43). The spectroscopic data match the previously reported in the literature.³⁹

4.2.22. 4-Chloro-2-((4-chlorophenyl)ethynyl)phenol (1s). Yellow solid (131 mg, 77%); ^1H NMR (400 MHz) δ : 7.48–7.44 (m, 2H), 7.39–7.35 (m, 3H), 7.23 (dd, $^1J=8.4$ Hz, $^2J=2.8$ Hz, 1H), 6.92 (d, $J=8.8$ Hz, 1H), 5.72 (s, 1H); ^{13}C NMR (100 MHz) δ : 155.2, 135.4, 132.9, 131.0, 130.7, 129.0, 125.2, 120.4, 116.2, 110.8, 96.0, 82.8; MS (EI) m/z (%): 264 (63), 262 (M^+ , 100), 199 (72). The spectroscopic data match the previously reported in the literature.⁴¹

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Supplementary data

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References and notes

- (a) Poliakov, M.; Licence, P. *Nature* **2007**, *450*, 810–812; (b) Constable, D. J. C.; Dunn, P. J.; Hayler, J. D.; Humphrey, G. R.; Leazer, J. J. L.; Linderman, R. J.; Lorenz, K.; Manley, J.; Pearlman, B. A.; Wells, A.; Zaks, A.; Zhang, T. Y. *Green Chem.* **2007**, *9*, 411–420; (c) Dallinger, D.; Kappe, C. O. *Chem. Rev.* **2007**, *107*, 2563–2591.
- Bryant, R. G.; Johnson, M. A.; Rossky, P. J. *Acc. Chem. Res.* **2012**, *45*, 1–2.
- (a) Li, C.-J.; Chen, L. *Chem. Soc. Rev.* **2006**, *35*, 68–82; (b) Basle, O.; Li, C.-J. *Green Chem.* **2007**, *9*, 1047–1050; (c) Zhu, S.; Yu, S.; Ma, D. *Angew. Chem., Int. Ed.* **2008**, *47*, 545–548; (d) Fang, P.-P.; Jutand, A.; Tian, Z.-Q.; Amatore, C. *Angew. Chem., Int. Ed.* **2011**, *50*, 12184–12188; (e) Khalafi-Nezhad, A.; Panahi, F. *Green Chem.* **2011**, *13*, 2408–2415; (f) Gunasekaran, P.; Balamurugan, K.; Sivakumar, S.; Perumal, S.; Menendez, J. C.; Almansour, A. I. *Green Chem.* **2012**, *14*, 750–757; (g) Murase, T.; Nishijima, Y.; Fujita, M. *J. Am. Chem. Soc.* **2012**, *134*, 162–164; (h) Chen, F.; Min, Q.-Q.; Zhang, X. J. *Org. Chem.* **2012**, *77*, 2992–2998; (i) Chakraborti, A. K.; Rudrawar, S.; Jadhav, K. B.; Kaur, G.; Chankeshwara, S. V. *Green Chem.* **2007**, *9*, 1335–1340; (j) Ho, C.-M.; Zhang, J.-L.; Zhou, C.-Y.; Chan, O.-Y.; Yan, J. J.; Zhang, F.-Y.; Huang, F.-Y.; Che, C.-M. *J. Am. Chem. Soc.* **2010**, *132*, 1886–1894; (k) Zheng, Z.; Perkins, B. L.; Ni, B. J. *Am. Chem. Soc.* **2009**, *132*, 50–51; (l) Shaughnessy, K. H. *Chem. Rev.* **2009**, *109*, 643–710.
- Breslow, R. *Acc. Chem. Res.* **1991**, *24*, 159–164.
- (a) Gajewski, J. J. *Acc. Chem. Res.* **1997**, *30*, 219–225; (b) Acevedo, O.; Armacost, K. J. *Am. Chem. Soc.* **2010**, *132*, 1966–1975.
- Scatena, L. F.; Brown, M. G.; Richmond, G. L. *Science* **2001**, *292*, 908–912.
- Narayan, S.; Muldoon, J.; Finn, M. G.; Fokin, V. V.; Kolb, H. C.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2005**, *44*, 3275–3279.
- Chanda, A.; Fokin, V. V. *Chem. Rev.* **2009**, *109*, 725–748.
- (a) Klijn, J. E.; Engberts, J. B. F. N. *Nature* **2005**, *435*, 746–747; (b) Pirrung, M. C. *Chem.—Eur. J.* **2006**, *12*, 1312–1317; (c) Beattie, J. K.; McErlean, C. S.; Phippen, C. B. *Chem.—Eur. J.* **2010**, *16*, 8972–8974.
- (a) Hailes, H. C. *Org. Process Res. Dev.* **2006**, *11*, 114–120; (b) Lindström, U. M. *Chem. Rev.* **2002**, *102*, 2751–2772; (c) Zhao, Q.; Lam, Y.-h.; Kheirabadi, M.; Xu, C.; Houk, K. N.; Schafmeister, C. E. J. *Org. Chem.* **2012**, *77*, 4784–4792; (d) Ackermann, L.; Wang, L.; Wolfram, R.; Lygin, A. V. *Org. Lett.* **2012**, *14*, 728–731.
- Butler, R. N.; Coyne, A. G. *Chem. Rev.* **2010**, *110*, 6302–6337.
- Pirrung, M. C.; Sarma, K. D.; Wang, J. J. *Org. Chem.* **2008**, *73*, 8723–8730.
- Mellouli, S.; Bousekkine, L.; Theberge, A. B.; Huck, W. T. S. *Angew. Chem., Int. Ed.* **2012**, *51*, 7981–7984.
- (a) Keay, B. A.; Dibble, P. W. *Compr. Heterocycl. Chem. II* **1996**, *2*, 395–436; (b) Gidron, O.; Diskin-Posner, Y.; Bendikov, M. *J. Am. Chem. Soc.* **2010**, *132*, 2148–2150.
- (a) Anderson, S.; Taylor, P. N.; Verschoor, G. L. B. *Chem.—Eur. J.* **2004**, *10*, 518–527; (b) Tsuji, H.; Mitsui, C.; Ilies, L.; Sato, Y.; Nakamura, E. *J. Am. Chem. Soc.* **2007**, *129*, 11902–11903; (c) Tsuji, H.; Mitsui, C.; Sato, Y.; Nakamura, E. *Adv. Mater.* **2009**, *21*, 3776–3779; (d) Mitsui, C.; Soeda, J.; Miwa, K.; Tsuji, H.; Takeya, J.; Nakamura, E. *J. Am. Chem. Soc.* **2012**, *134*, 5448–5451; (e) Bunz, U. H. *Angew. Chem., Int. Ed.* **2010**, *49*, 5037–5040; (f) Shinamura, S.; Osaka, I.; Miyazaki, E.; Nakao, A.; Yamagishi, M.; Takeya, J.; Takimiya, K. *J. Am. Chem. Soc.* **2011**, *133*, 5024–5035; (g) Nakano, M.; Mori, H.; Shinamura, S.; Takimiya, K. *Chem. Mater.* **2012**, *24*, 190–198.
- (a) Larock, R. C.; Harrison, L. W. *J. Am. Chem. Soc.* **1984**, *106*, 4218–4227; (b) Ito, Y.; Aoyama, T.; Shioiri, T. *Synlett* **1997**, 1163–1164; (c) Kundu, N. G.; Pal, M.; Mahanty, J. S.; De, M. J. *Chem. Soc., Perkin Trans. 1* **1997**, 2815–2820; (d) Hiroya, K.; Suzuki, N.; Yasuhara, A.; Egawa, Y.; Kasano, A.; Sakamoto, T. *J. Chem. Soc., Perkin Trans. 1* **2000**, 4339–4346; (e) Dai, W.-M.; Lai, K. W. *Tetrahedron Lett.* **2002**, *43*, 9377–9380.
- (a) Larock, R. C. *J. Organomet. Chem.* **1999**, *576*, 111–124; (b) Kabalka, G. W.; Wang, L.; Pagni, R. M. *Tetrahedron* **2001**, *57*, 8017–8028; (c) Bates, C. G.; Saejung, P.; Murphy, J. M.; Venkataraman, D. *Org. Lett.* **2002**, *4*, 4727–4729; (d) Zeni, G.; Larock, R. C. *Chem. Rev.* **2004**, *104*, 2285–2309; (e) Colobert, F.; Castanet, A.-S.; Abillard, O. *Eur. J. Org. Chem.* **2005**, *2005*, 3334–3341; (f) Fürstner, A.; Davies, P. W. *J. Am. Chem. Soc.* **2005**, *127*, 15024–15025; (g) Liang, Y.; Tang, S.; Zhang, X.-D.; Mao, L.-Q.; Xie, Y.-X.; Li, J.-H. *Org. Lett.* **2006**, *8*, 3017–3020; (h) Nakamura, M.; Ilies, L.; Otsubo, S.; Nakamura, E. *Angew. Chem., Int. Ed.* **2006**, *45*, 944–947; (i) Zhang, Y.; Xin, Z.-J.; Xue, J.-J.; Li, Y. *Chin. J. Chem.* **2008**, *26*, 1461–1464; (j) Isono, N.; Lautens, M. *Org. Lett.* **2009**, *11*, 1329–1331.
- (a) Li, Y.; Liu, J. H.-C.; Witham, C. A.; Huang, W.; Marcus, M. A.; Fakra, S. C.; Alayoglu, P.; Zhu, Z.; Thompson, C. M.; Arjun, A.; Lee, K.; Gross, E.; Toste, F. D.; Somorjai, G. A. *J. Am. Chem. Soc.* **2011**, *133*, 13527–13533; (b) Huang, W.; Liu, J. H.-C.; Alayoglu, P.; Li, Y.; Witham, C. A.; Tsung, C.-K.; Toste, F. D.; Somorjai, G. A. *J. Am. Chem. Soc.* **2010**, *132*, 16771–16773; (c) Witham, C. A.; Huang, W.; Tsung, C.-K.; Kuhn, J. N.; Somorjai, G. A.; Toste, F. D. *Nat. Chem.* **2010**, *2*, 36–41.
- (a) Sun, C.-L.; Li, H.; Yu, D.-G.; Yu, M.; Zhou, X.; Lu, X.-Y.; Huang, K.; Zheng, S.-F.; Li, B.-J.; Shi, Z.-J. *Nat. Chem.* **2010**, *2*, 1044–1049; (b) Leadbeater, N. E. *Nat. Chem.* **2010**, *2*, 1007–1009.

20. (a) Payette, J. N.; Yamamoto, H. *J. Am. Chem. Soc.* **2008**, *130*, 12276–12278; (b) Leadbeater, N. E. *Chem. Commun.* **2010**, 6693–6695.
21. (a) Nonella, M.; Suter, H. U. *J. Phys. Chem. A* **1999**, *103*, 7867–7871; (b) Popov, A.; Kondratieva, E.; Gilson, J.-P.; Mariey, L.; Traver, A.; Maugé, F. *Catal. Today* **2011**, *172*, 132–135; (c) McDonald, W. J.; Einarsson, O. I. *J. Phys. Chem. A* **2008**, *112*, 11400–11413.
22. Cano, R.; Yus, M.; Ramón, D. J. *Tetrahedron* **2012**, *68*, 1393–1400.
23. Chen, C.-y.; Dormer, P. G. *J. Org. Chem.* **2005**, *70*, 6964–6967.
24. Miyata, O.; Takeda, N.; Naito, T. *Org. Lett.* **2004**, *6*, 1761–1763.
25. Csékei, M.; Novák, Z.; Kotschy, A. *Tetrahedron* **2008**, *64*, 8992–8996.
26. Boyer, A.; Isono, N.; Lackner, S.; Lautens, M. *Tetrahedron* **2010**, *66*, 6468–6482.
27. Rao, M. L. N.; Awasthi, D. K.; Talode, J. B. *Tetrahedron Lett.* **2012**, *53*, 2662–2666.
28. Takeda, N.; Miyata, O.; Naito, T. *Eur. J. Org. Chem.* **2007**, *2007*, 1491–1509.
29. Nakamura, M.; Ilies, L.; Otsubo, S.; Nakamura, E. *Org. Lett.* **2006**, *8*, 2803–2805.
30. Liu, J.; Chen, W.; Ji, Y.; Wang, L. *Adv. Synth. Catal.* **2012**, *354*, 1585–1592.
31. Kim, Y.-W.; Choi, H.-D.; Seo, P.-J.; Son, B.-W. *J. Korean Chem. Soc.* **2001**, *45*, 391–394.
32. Yoneda, E.; Sugioaka, T.; Hirao, K.; Zhang, S.-W.; Takahashi, S. *J. Chem. Soc., Perkin Trans. 1* **1998**, 477–484.
33. Labrosse, J.-R.; Poncet, C.; Lhoste, P.; Sinou, D. *Tetrahedron: Asymmetry* **1999**, *10*, 1069–1078.
34. Kondo, Y.; Shiga, F.; Murata, N.; Sakamoto, T.; Yamanaka, H. *Tetrahedron* **1994**, *50*, 11803–11812.
35. Liu, J.; Liu, Y. *Org. Lett.* **2012**, *14*, 4742–4745.
36. Álvarez, R.; Martínez, C.; Madich, Y.; Denis, J. G.; Aurrecoechea, J. M.; de Lera, A. R. *Chem.—Eur. J.* **2012**, *18*, 13894–13896.
37. Auzias, M. G.; Neuburger, M.; Wegner, H. A. *Synlett* **2010**, 2443–2448.
38. Wang, H.; Han, X.; Lu, X. *Synlett* **2011**, 2590–2594.
39. Luo, Y.; Wu, J. *Org. Lett.* **2011**, *13*, 5858–5861.
40. Eicher, T.; Schneider, V. *Synthesis* **1989**, *1989*, 372–378.
41. Wang, H.; Luo, Y.; Zhu, B.; Wu, J. *Chem. Commun.* **2012**, 5581–5583.