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Phase-Transfer-Catalyzed Intramolecular Cyclization of *ortho*-Alkynyl Phenyl Ether Derivatives for Synthesis of 2,3-Disubstituted Benzo[*b*]furans

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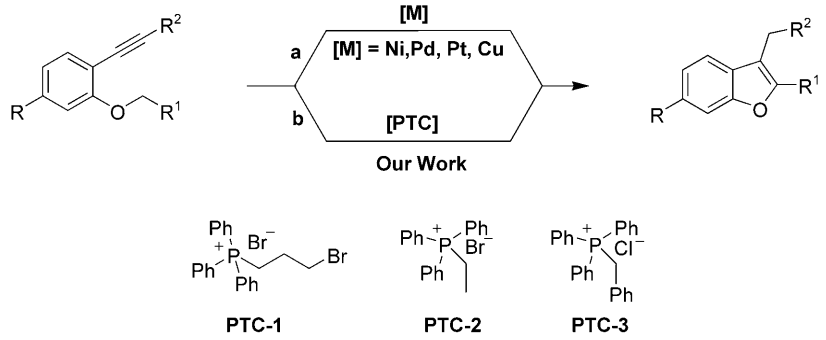
Abstract: A variety of substituted benzo[*b*]furans are readily prepared in good to excellent yields under the mild reaction conditions from *o*-(1-alkynylphenoxy)-1-phenylethanone under phase-transfer catalysis (PTC). This methodology accommodates simple experimental operations, inexpensive and environmentally benign catalysts, metal catalyst-free conditions, facile reagents and the possibility to conduct large-scale preparations. The development of carbon-carbon bond formation processes *via* an overall structural isomerization represents the most atom-economical approach.

Keywords: benzo[*b*]furans; C–C bond formation; cyclization; metal-free conditions; phase-transfer catalysts

The benzo[*b*]furan moiety has attracted widespread interest in view of its presence in natural products, and their biological and pharmacological activities.[1–4] As a result, a number of routes leading to differently substituted benzo[*b*]furans have been described in the literature.[5–26] Transition metal-catalyzed intramolecular cyclization of the corresponding *ortho*-alkynyl phenyl ethers derivatives as a simple and efficient protocol has attracted much attention in recent years (Scheme 1, a).[27–31] However, the direct carbocyclization of *ortho*-alkynyl phenyl ethers under PTC (phase-transfer catalyst) conditions for the synthesis of 2,3-disubstituted benzo[*b*]furan under metal-free conditions has not previously been reported (Scheme 1, b). Compared with other methods phase-transfer catalysis has long been recognized as a versatile methodology for organic synthesis in both industrial and academic laboratories, featuring its simple reaction procedure, safe, inexpensive, environmentally friendly reagents, absence of anhydrous solvents, ease of scale-up, and metal-free conditions.[32–36] To the



Scheme 1. Transition metal-catalyzed or phase-transfer-catalyzed intramolecular cyclization of the corresponding *ortho*-alkynyl phenyl ether derivatives.

best of our knowledge, this report is the first example about the intramolecular cyclization of the corresponding *ortho*-alkynyl phenyl ethers under phase-transfer catalysis.

Initially, we investigated the reaction of 0.20 mmol of 2-[4-methyl-2-(2-phenylethynyl)phenoxy]-1-phenylethanone (**1a**), 5 mol% of PTC-**1** and 1.5 equivalents of K_2CO_3 in DMSO at 60 °C in air. To our delight, the desired product benzo[*b*]furan **2a** was formed in 80% yield after 2 h and the structure was unambiguously secured by an X-ray crystal structure analysis (Figure 1).[37] Encouraged by this result, we further optimized the reaction conditions. Other solvents, such as THF, 1,4-dioxane, and acetonitrile were also tested; acetonitrile gave the best yield of 83% (Table 1, entries 2–4). A subsequent screen of bases revealed that the Cs_2CO_3 was superior to the others (entries 5–12). In the absence of base or PTC condi-

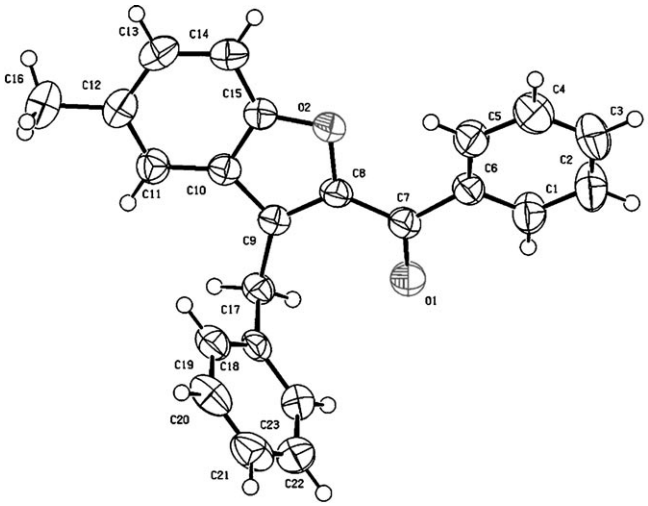
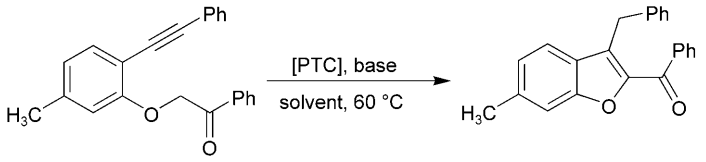


Figure 1. X-ray crystal structure of **2a**.

Table 1. Optimization of the phase-transfer-catalyzed intramolecular cyclization of 2-[4-methyl-2-(2-phenylethynyl)phenoxy]-1-phenylethanone (**1a**).[a]

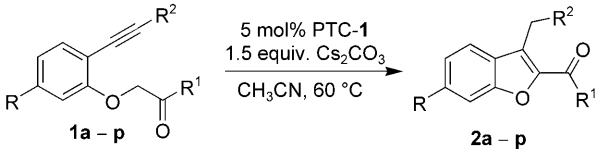


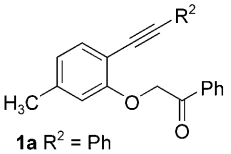
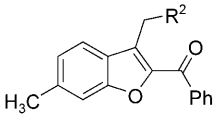
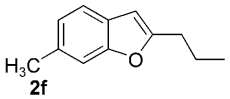
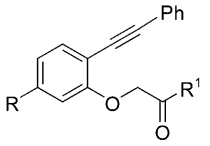
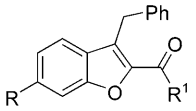
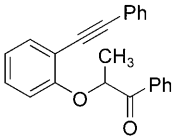
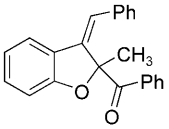
1a **2a**

Entry	[PTC] (mol%)	Base (equiv.)	Solvent	Time [h]	Yield [%][b]
1	PTC-1 (5.0)	K_2CO_3 (1.5)	DMSO	2	80%
2	PTC-1 (5.0)	K_2CO_3 (1.5)	THF	12	10%
3	PTC-1 (5.0)	K_2CO_3 (1.5)	1,4-dioxane	12	trace
4	PTC-1 (5.0)	K_2CO_3 (1.5)	CH_3CN	2	83%
5	PTC-1 (5.0)	Cs_2CO_3 (1.5)	CH_3CN	2	95%
6	PTC-1 (5.0)	–	CH_3CN	12	N.R.[c]
7	–	Cs_2CO_3 (1.5)	CH_3CN	12	N.R.[c]
8	PTC-1 (5.0)	NEt_3 (1.5)	CH_3CN	12	N.R.[c]
9	PTC-1 (5.0)	NaOAc(1.5)	CH_3CN	12	N.R.[c]
10	PTC-1 (5.0)	$NaOCH_3$ (1.5)	CH_3CN	12	N.R.[c]
11	PTC-1 (5.0)	NaO-*t*-Bu (1.5)	CH_3CN	12	N.R.[c]
12	PTC-1 (5.0)	KH (1.5)	CH_3CN	12	N.R.[c]
13	PTC-2 (5.0)	Cs_2CO_3 (1.5)	CH_3CN	2.5	40%
14	PTC-3 (5.0)	Cs_2CO_3 (1.5)	CH_3CN	2	76%
15	TEAB (5.0)	Cs_2CO_3 (1.5)	CH_3CN	2	74%
16	TBAC (5.0)	Cs_2CO_3 (1.5)	CH_3CN	2	64%
17	TEAI (5.0)	Cs_2CO_3 (1.5)	CH_3CN	2	67%
18	TBAF (5.0)	Cs_2CO_3 (1.5)	CH_3CN	2	78%
19	PTC-1 (5.0)	Cs_2CO_3 (1.0)	CH_3CN	4.5	77%

[a] Reactions were carried out on a 0.2 mmol scale in 2.0 mL of solvent in air at 60 °C with 1.0 equiv. of **1a**, 1.5 equiv. of base and 5 mol% equiv. of PTC.
[b] Isolated yield.
[c] N.R. = no reaction.

Table 2. Phase-transfer-catalyzed intramolecular cyclization of acetylenic ketones and ester (**1**).[a]



Entry	Substrate	Product	Yield [%][b]
			
1	**1a** R^2 = Ph	**2a** R^2 = Ph	95
2	**1b** R^2 = *p*-BrC_6H_4	**2b** R^2 = *p*-BrC_6H_4	93
3	**1c** R^2 = *p*-$CH_3OC_6H_4$	**2c** R^2 = *p*-$CH_3OC_6H_4$	81
4	**1d** R^2 = TMS	**2d** R^2 = TMS	98
5	**1e** R^2 = H	**2e** R^2 = H	98
			
6	**1f** R^2 = $CH_3CH_2CH_2$	**2f**	24
7	**1g** R^2 = $HOCH_2$	**2g** R^2 = $HOCH_2$	73
8	**1h** R^2 = $THPOCH_2$	**2h** R^2 = $THPOCH_2$	64
9	**1i** R^2 = $HOCH_3CH$	**2i** R^2 = $HOCH_3CH$	66
10	**1j** R^2 = $HO(CH_3)_2C$	**2j** R^2 = $HO(CH_3)_2C$	75
			
11	**1k** R = CH_3, R^1 = *p*-BrC_6H_4	**2k** R = CH_3, R^1 = *p*-BrC_6H_4	98
12	**1l** R = H, R^1 = Ph	**2l** R = H, R^1 = Ph	99
13	**1m** R = Cl, R^1 = Ph	**2m** R = Cl, R^1 = Ph	99
14	**1n** R = CH_3, R^1 = CH_3	**2n** R = CH_3, R^1 = CH_3	95
15	**1o** R = H, R^1 = ethoxy	**2o** R = H, R^1 = ethoxy	80
			
16	**1p**	**2p**	86

[a] All reactions were carried out under the optimal conditions reported in the text for 2 h.
[b] Isolated yields.
[c] Reactions were carried out for 20 h.

tions, the reaction did not proceed (entries 6 and 7). It should be pointed out that our work is limited to substrates of sufficient acidity. When different PTCs were examined, the results showed that PTC-**2** and PTC-**3** could promote this cyclization, but the desired product **2a** was only obtained with 40% and 76% yields, respectively (entries 13 and 14). Tetraalkylammonium salts, such as Et_4NBr, Bu_4NCl, Et_4NI and Bu_4NF have also been applied to this process, and the yields were not better than with PTC-**1** (entries 15–18). Decreasing the loading of base will lead to lower yields (entry 19). Thus, we chose the following reaction conditions as optimum for all subsequent cyclizations: 0.20 mmol of **1a**, 5 mol% PTC-**1**, and 0.30 mmol Cs_2CO_3 in CH_3CN at 60 °C in air.

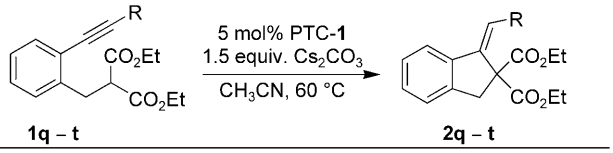
With the optimized conditions in hand, the scope of this reaction was then investigated, and the results are summarized in Table 2. On employing arylacetylenes bearing methoxy and bromide groups on the aromatic ring, cyclization products **2b** and **2c** were obtained in good yields, respectively (Table 2, entries 2 and 3). The results indicated that the presence of an electron-

withdrawing group on the aromatic ring gave a higher yield. When R^2 was the TMS or H, the same product was achieved almost quantitatively and the TMS group happened to undergo desilylation at the same time (entries 4 and 5). Surprisingly, when R^2 was replaced by an alkyl group, the unexpected 5-methyl-2-propylbenzo[*b*]furan (**2f**) was obtained in poor yield (entry 6). On introducing the primary, secondary, tertiary and THP-protected primary aryl alcohols on the terminal alkynes, the desired products were generated in moderate to good yields (entries 7–10). The electronic effect of the R groups on the aromatic ring is not evident in the reaction (enties 11–13). Furthermore, the substituent R^1 was also examined. On replacing the phenyl with methyl and ethoxy at the R^1 position, the reaction proceeded smoothly to give the corresponding cyclization/isomerization products in good to excellent yields, although the substrate **1o** required a longer reaction time (entries 14 and 15). Probably the activity of the α-H the ester is lower than that of a ketone. In light of the structure of products **2a–o**, we believe that introducing a substituent in the α-position of the carbonyl compounds should also work. Hence, we prepared the substrate **1p** and, as we expected, **2p** was obtained in 86% yield (entry 16).

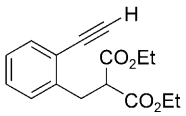
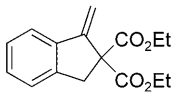
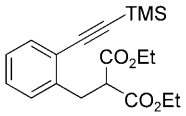
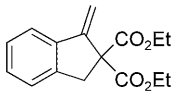
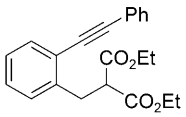
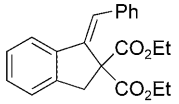
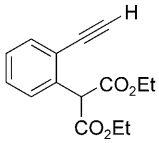
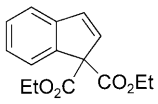
To expand the scope of this reaction, we also investigated the substrates **1q–t**. To our delight, the reaction proceeded smoothly and gave the indane derivatives **2q, 2r** and **2s** in good to excellent yield (Table 3, entries 1–3), only **2t** was obtained in a lower yield (entry 4).

The proposed mechanism for the reaction is showed in Scheme 2. Firstly, there is formation of an *ortho*-alkynylphenylethanone ether ion by deprotonation with the corresponding base, and the cation exchange possibly proceeds *via* phase-transfer catalyst

Table 3. Phase-transfer-catalyzed intramolecular cyclization of acetylenic malonates (**1**).[a]

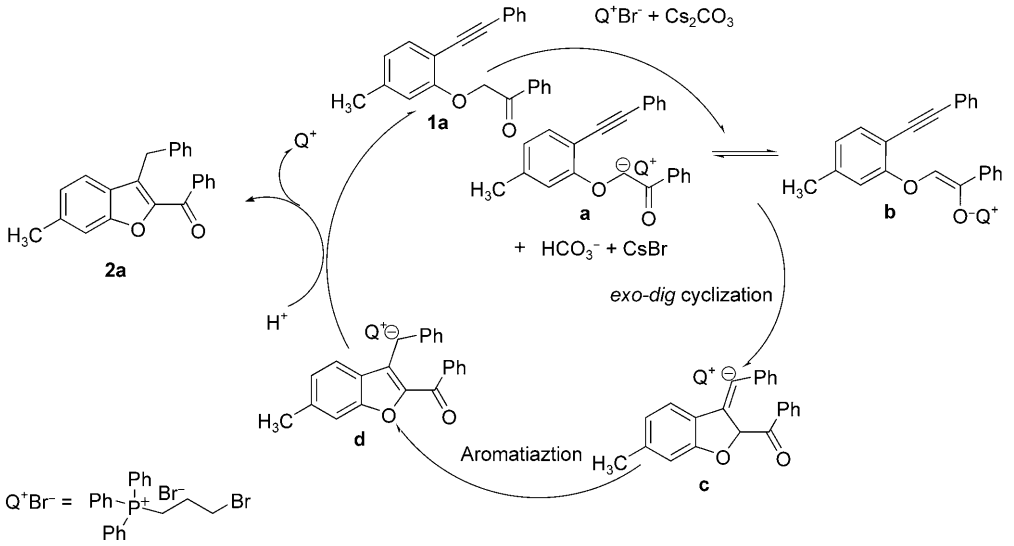


1q – t **2q – t**

Entry	Substrate	Product	Yield [%][b]
1			98
2			75
3			91
4			55

[a] All reactions were carried out under the optimal conditions reported in the text for 2 h.
[b] Isolated yields.
[c] The reaction was carried out for 5 h.

to form the active intermediate **a** or **b**. Subsequently active intermediate **a** or **b** underwent an *exo-dig* model intramolecular cyclization, then aromatic iso-



Scheme 2. Proposed mechanism for the phase-transfer-catalyzed intramolecular cyclization.

merization achieved the intermediate **d**, which, after protonation and release the product of **2a**, realized the catalyst cycling.

In conclusion, we have developed an efficient and versatile route to 2,3-disubstituted benzo[*b*]furans *via* phase-transfer-catalyed and base-mediated cyclization of alkynyl compounds bearing various functional groups under metal-free conditions. A wide range of substrates undergo this process in good to excellent yields. Thus, we believe this reaction will find considerable application in industrial production due to its simple experimental operations, efficient and environmentally friendly catalysts and mild reaction conditions. The scope, mechanism, and synthetic applications of this reaction are currently under investigation.

Experimental Section

Representative Procedure

To a solution of **1a** (65.2 mg, 0.20 mmol) in 2.0 mL of CH_3CN was added Cs_2CO_3 (97.7 mg, 0.30 mmol). The mixture was allowed to stir at room temperature for 1 min and PTC-**1** (4.74 mg, 5 mol%) was added. The resulting mixture was then heated under air at 60 °C. When the reaction was considered complete as determined by TLC analysis, the reaction mixture was allowed to cool to room temperature and quenched with a saturated aqueous solution of ammonium chloride, after which the mixture was extracted with EtOAc. The combined organic extracts were washed with water and saturated brine. The organic layers were dried over Na_2SO_4 and filtered. Solvents were evaporated under reduced pressure. The residue was purified by chromatography on silica gel to afford 2,3-disubstituted benzo[*b*]furan **2a**.

CCDC 734260 contains the supplementary crystallographic data for compound **2a** of this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

Acknowledgements

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References

[1] X. L. Hou, Z. Yang, K. S. Yeung, H. N. C. Wong, in: *Progress in Heterocyclic Chemistry*, (Eds.: G. W. Gribble, J. A. Joule), Elsevier, Oxford, **2008**, Vol. 19, pp 176–207, and previous volumes in the series.

[2] D. J. Sall, D. L. Bailey, J. A. Bastian, J. A. Buben, N. Y. Chirgadze, A. C. Clemens-Smith, M. L. Denney, M. J. Fisher, D. D. Giera, D. S. Gifford-Moore, R. W. Harper, L. M. Johnson, V. J. Klimkowski, T. J. Kohn, H.-S. Lin, J. R. McCowan, A. D. Palkowitz, M. E. Richett, G. F. Smith, D. W. Snyder, K. Takeuchi, J. E. Toth, M. Zhang, *J. Med. Chem.* **2000**, *43*, 649.

[3] B. Carlsson, B. N. Singh, M. Temciuc, S. Nilsson, Y.-L. Li, C. Mellin, J. Malm, *J. Med. Chem.* **2002**, *45*, 623.

[4] B. L. Flynn, E. Hamel, M. K. Jung, *J. Med. Chem.* **2002**, *45*, 2670.

[5] X.-L. Hou, Z. Yang, H. N. C. Wong, *Furans and Benzofurans*, in: *Progress in Heterocyclic Chemistry*, (Eds.: G. W. Gribble, T. L. Gilchrist), Pergamon, Oxford, England, **2002**, Vol. 14, pp 139–179.

[6] M. C. Willis, D. Taylor, A. T. Gillmore, *Org. Lett.* **2004**, *6*, 4755.

[7] C. Chen, P. G. Dormer, *J. Org. Chem.* **2005**, *70*, 6964.

[8] M. Carril, R. SanMartin, I. Tellitu, E. Dominguez, *Org. Lett.* **2006**, *8*, 1467.

[9] Y. Fang, C. Li, *J. Org. Chem.* **2006**, *71*, 6427.

[10] M. C. Willis, D. Taylor, A. T. Gillmore, *Tetrahedron.* **2006**, *62*, 11513.

[11] D. E. Boswell, P. S. Landis, E. N. Givens, P. B. Venuto, *Ind. Eng. Chem. Prod. Res. Dev.* **1968**, *7*, 215.

[12] A. P. Kozikowski, D. Ma, L. Du, N. E. Lewin, P. M. Blumberg, *J. Am. Chem. Soc.* **1995**, *117*, 6666.

[13] A. S. K. Hashmi, T. M. Frost, J. W. Bats, *Org. Lett.* **2001**, *3*, 3769.

[14] F. Alonso, I. P. Beletskaya, M. Yus, *Chem. Rev.* **2004**, *104*, 3079.

[15] Y. Liao, J. Smith, R. Fathi, Z. Yang, *Org. Lett.* **2005**, *7*, 2707.

[16] E. Bellur, P. Langer, *J. Org. Chem.* **2005**, *70*, 7686.

[17] R. E. Ziegert, J. Torang, K. Knepper, S. Brase, *J. Comb. Chem.* **2005**, *7*, 147.

[18] G. Zeni, R. C. Larock, *Chem. Rev.* **2006**, *106*, 4644.

[19] M. Carril, R. SanMartin, I. Tellitu, E. Dominguez, *Org. Lett.* **2006**, *8*, 1467.

[20] B. Zhao, X. Lu, *Org. Lett.* **2006**, *8*, 5987.

[21] B. Gabriele, R. Mancuso, G. Salerno, M. Costa, *J. Org. Chem.* **2007**, *72*, 9278.

[22] J. Oppenheimer, W. L. Johnson, M. R. Tracey, R. P. Hsung, P.-Y. Yao, R. Liu, K. Zhao, *Org. Lett.* **2007**, *9*, 2361.

[23] M. Nagamochi, Y.-Q. Fang, M. Lautens, *Org. Lett.* **2007**, *9*, 2955.

[24] L. De Luca, G. Giacomelli, G. Nieddu, *J. Org. Chem.* **2007**, *72*, 3955.

[25] B. Lu, B. Wang, Y. Zhang, D. Ma, *J. Org. Chem.* **2007**, *72*, 5337.

[26] I. Nakamura, Y. Mizushima, U. Yamagishi, Y. Yamamoto, *Tetrahedron.* **2007**, *63*, 8670.

[27] N. Monteiro, G. Balme, *Synlett* **1998**, *7*, 746.

[28] I. Nakamura, G. B. Bajracharya, H. Wu, K. Oishi, Y. Mizushima, I. D. Gridnev, Y. Yamamoto, *J. Am. Chem. Soc.* **2004**, *126*, 15423.

[29] A. Fürstner, P. W. Davies, *J. Am. Chem. Soc.* **2005**, *127*, 15024.

[30] I. Nakamura, Y. Mizushima, Y. Yamamoto, *J. Am. Chem. Soc.* **2005**, *127*, 15022.

[31] D. Shikanai, H. Murase, T. Hata, H. Urabe, *J. Am. Chem. Soc.* **2009**, *131*, 3166.

[32] E. V. Dehmlow, S. S. Dehmlow, *Phase Transfer Catalysis*, 3rd edn., VCH, Weinheim, Germany, **1993**.

[33] C. M. Starks, C. L. Liotta, M. Halpern, *Phase-Transfer Catalysis*, Chapman & Hall, New York, **1994**.
[34] Y. Sasson, R. Neumann, (Eds.), *Handbook of Phase-Transfer Catalysis*, Blackie Academic & Professional, London, **1997**.
[35] M. E. Halpern, (Ed.), *Phase-Transfer Catalysis*, ACS Symposium Series 659, American Chemical Society, Washington, DC, **1997**.
[36] T. Hashimoto, K. Maruoka, *Chem. Rev.* **2007**, *107*, 5656.
[37] See the Supporting Information for X-ray crystallographic data.

