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Cycloaddition of Arynes with Iodonium Ylides: a Mild and General Route for the Synthesis of Benzofuran Derivatives

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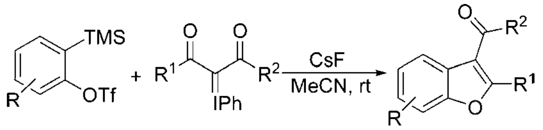
ABSTRACT



A mild and general cycloaddition of arynes with iodonium ylides protocol has been developed for the synthesis of benzofurans. In the presence of CsF, *ortho*-silyl aryltriflates were reacted with iodonium ylides smoothly at room temperature in moderate to good yields.

Benzofuran moieties are widely presented in many naturally occurring and biologically active compounds, which display various pharmacological activities.[1] For this reason, considerable efforts have been devoted to develop efficient methods for their preparation.[2−4] The majority of methods for selectively constructing benzofurans include the transition metal-catalyzed transformations.[2] Although these transformations are efficient and general, two significant drawbacks are usually presented—the requirement of harsh conditions and the cost of the catalytic system.[2]

Caubere and co-workers have reported a new rout to the preparation of benzofurans by the reactions of dihalogenobenzenes with cyclic ketones involving a benzyne process, but harsh conditions including stronger bases ($NaNH_2$ combined with *t*-BuONa) were still required together with low yields.[3] Recently, much attention has been attracted to apply *ortho*-silyl aryltriflates as the benzyne precursors

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(1) (a) Singh, S. N.; Fletcher, R. D.; Fisher, S. G.; Singh, B. N.; Lewis, H. D.; Deedwania, P. C.; Massie, B. M.; Colling, C.; Layyeri, D. *N. Engl. J. Med.* **1995**, *333*, 77. (b) Kálai, T.; Várbiró, G.; Bognár, Z.; Pálfi, A.; Hantó, K.; Bognár, B.; Osz, E.; Sümegi, B.; Hideg, K. *Bioorg. Med. Chem.* **2005**, *13*, 2629. (c) Proksch, P.; Proksch, M.; Towers, G. H. N.; Rodriguez, E. *J. Nat. Prod.* **1983**, *46*, 331. (d) Chakrabarti, J. K.; Eggleton, R. J.; Gallagher, P. T.; Harvey, J.; Hicks, T. A.; Kitchen, E. A.; Smith, C. W. *J. Med. Chem.* **1987**, *30*, 1663. (e) Parodi, F. J.; Fischer, N. H.; Flores, H. E. *J. Nat. Prod.* **1988**, *51*, 594. (f) Durani, N.; Jain, R.; Saeed, A.; Dikshit, D. K.; Durani, S.; Kapil, R. S. *J. Med. Chem.* **1989**, *32*, 1700. (g) Tomaszewski, Z.; Johnson, M. P.; Huang, X.; Nichols, D. E. *J. Med. Chem.* **1992**, *35*, 2061. (h) Jia, Z.; Zhao, Y. *J. Nat. Prod.* **1994**, *57*, 146. (i) Sauter, M.; Adam, W. *Acc. Chem. Res.* **1995**, *28*, 289. (j) Halabalaki, M.; Aligiannis, N.; Papoutsi, Z.; Mitakou, S.; Moutsatsou, P.; Sekeris, C.; Skaltsounis, A.-L. *J. Nat. Prod.* **2000**, *63*, 1672. (k) Bakunova, S. M.; Bakunov, S. A.; Wenzler, T.; Barszcz, T.; Werbovetz, K. A.; Brun, R.; Hall, J. E.; Tidwell, R. R. *J. Med. Chem.* **2007**, *50*, 5807.

(2) For selected reviews and papers on the synthesis of benzofurans by transition metal-catalyzed transformations, see: (a) Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2004**, *104*, 3079. (b) Ziegert, R. E.; Torang, J.; Knepper, K.; Brase, S. *J. Comb. Chem.* **2005**, *7*, 147. (c) Zeni, G.; Larock, R. C. *Chem. Rev.* **2006**, *106*, 4644. (d) Boswell, D. E.; Landis, P. S.; Givens, E. N.; Venuto, P. B. *Ind. Eng. Chem. Prod. Res. Dev.* **1968**, *7*, 215. (e) Kozikowski, A. P.; Ma, D.; Du, L.; Lewin, N. E.; Blumberg, P. M. *J. Am. Chem. Soc.* **1995**, *117*, 6666. (f) Hashmi, A. S. K.; Frost, T. M.; Bats, J. W. *Org. Lett.* **2001**, *3*, 3769. (g) Carril, M.; SanMartin, R.; Tellitu, I.; Dominguez, E. *Org. Lett.* **2006**, *8*, 1467. (h) Zhao, B.; Lu, X. *Org. Lett.* **2006**, *8*, 5987. (i) Gabriele, B.; Mancuso, R.; Salerno, G.; Costa, M. *J. Org. Chem.* **2007**, *72*, 9278. (j) Oppenheimer, J.; Johnson, W. L.; Tracey, M. R.; Hsung, R. P.; Yao, P.-Y.; Liu, R.; Zhao, K. *Org. Lett.* **2007**, *9*, 2361. (k) Nagamochi, M.; Fang, Y.-Q.; Lautens, M. *Org. Lett.* **2007**, *9*, 2955. (l) De Luca, L.; Giacomelli, G.; Nieddu, G. *J. Org. Chem.* **2007**, *72*, 3955. (m) Liao, Y.; Smith, J.; Fathi, R.; Yang, Z. *Org. Lett.* **2005**, *7*, 2707. (n) Bellur, E.; Langer, P. *J. Org. Chem.* **2005**, *70*, 7686. (o) Lu, B.; Wang, B.; Zhang, Y.; Ma, D. *J. Org. Chem.* **2007**, *72*, 5337. (p) Nakamura, I.; Mizushima, Y.; Yamagishi, U.; Yamamoto, Y. *Tetrahedron* **2007**, *63*, 8670.

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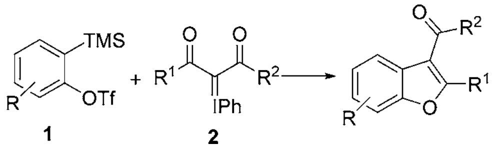
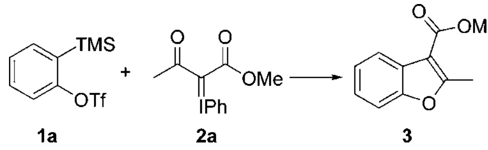
in organic synthesis because *ortho*-silyl aryltriflates could be readily converted into benzynes in situ under mild reaction conditions.[5−7] This prompted us to study the feasibility of synthesizing benzofuran skeletons using *ortho*-silyl aryltriflates under mild conditions.[2] After a series of trials, we were delighted to find that benzofurans could be prepared smoothly by treatment of *ortho*-silyl aryltriflates with iodonium ylides under mild conditions.[8] Herein, we wish to report our primary results of the cycloadditions between arynes and iodonium ylides to synthesize benzofurans (eq 1).



(1)

Initially, the reaction of 2-(trimethylsilyl)phenyl-trifluoromethanesulfonate (**1a**) with methyl 2-phenyliodonio-3-oxobutanoate (**2a**) was chosen as a model to screen the optimal reaction conditions (Table 1). To our delight, treatment of *ortho*-silyl aryltriflate **1a** with iodonium ylide **2a** and CsF in MeCN at room temperature afforded the corresponding benzofuran (**3**) in a 90% yield (entry 1). However, a trace amount of the target product **3** was observed using THF as the medium (entry 2). Two other fluoride-containing bases, TBAF and KF, were subsequently tested, and the results showed that they both were less effective than CsF (entries 3 and 4). It was found that no target product **3** was observed using TBAF (entry 3), and the yield of **3** was reduced to 65% in the presence of KF even with the aid of 18-crown-6 (entry 4). Finally, the reaction temperatures were examined, and it turned out that room temperature gave the best yield (entries 1, 5, and 6). It is noteworthy that high yield is still isolated after 4.5 h when 1.2 mmol of **1a** was reacted with 1 mmol of **2a** and 3 mmol of CsF in MeCN at room temperature (entry 7).

Table 1. Screening Optimal Conditions[a]



entry	base	t (°C)	time (h)	isolated yield (%)
1	CsF	rt	2.5	90
2[b]	CsF	rt	36	<5
3[c]	TBAF	rt	24	0
4[d]	$KF{\cdot}2H_2O$	rt	2.5	65
5	CsF	0	2.5	trace
6	CsF	50	3.5	85
7[e]	CsF	rt	4.5	88

[a] Reaction conditions: **1a** (0.12 mmol), **2a** (0.1 mmol), and base (3 equiv) in MeCN (3 mL) under argon atmosphere. [b] THF (3 mL) instead of MeCN. [c] Messy results were observed, and no target product was determined by GC-MS analysis. [d] 18-Crown-6 (3 equiv) was added. [e] **1a** (1.2 mmol) and **2a** (1 mmol).

With the standard reaction conditions in hand, a variety of arynes and iodonium ylides were surveyed to investigate scope of the cycloaddition reaction (Table 2).[9,10] The results demonstrated that the yield and selectivity were affected by the structures of the two reaction partners to some extent.

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(3) For papers on the synthesis of benzofurans from the reactions of benzynes (from dihalogenobenzenes) with cyclic ketone enolates in the presence of $NaNH_2$ and *t*-BuONa, see: (a) Caubere, P.; Lalloz, L. *J. Org. Chem.* **1975**, *40*, 2853. (b) Caubere, P.; Lalloz, L. *J. Org. Chem.* **1975**, *40*, 2859. (c) Bachelet, J.-P.; Caubere, P. *J. Org. Chem.* **1982**, *47*, 234. (d) Inukay, Y.; Sonoda, T.; Kabayashi, H. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 2657.

(4) For selected recent papers on the synthesis of benzofurans by other methods, see: (a) Miyata, O.; Takeda, N.; Naito, T. *Org. Lett.* **2004**, *6*, 1761. (b) Green, M. P.; Pichlmair, S.; Marques, M. M. B.; Martin, H. J.; Diwald, O.; Berger, T.; Mulzer, J. *Org. Lett.* **2004**, *6*, 3131. (c) Fujita, M.; Oshima, M.; Okuno, S.; Sugimura, T.; Okuyama, T. *Org. Lett.* **2006**, *8*, 4113. (d) Cheng, X.; Liu, X. *J. Comb. Chem.* **2007**, *9*, 906. (e) Fakhari, A. R.; Nematollahi, D.; Shamsipur, M.; Makarem, S.; Hosseini, Davarani, S. S.; Alizadeh, A.; Khavasi, H. R. *Tetrahedron* **2007**, *63*, 3894. (f) Wang, S.; Gates, B. D.; Swenton, J. S. *J. Org. Chem.* **1991**, *56*, 1979. (g) Berard, D.; Jean, A.; Canesi, S. *Tetrahedron Lett.* **2007**, *48*, 8238.

(5) (a) Himeshima, Y.; Sonoda, T.; Kobayashi, H. *Chem. Lett.* **1983**, 1211. (b) Himeshima, Y.; Kobayashi, H.; Sonoda, T. *J. Am. Chem. Soc.* **1985**, *107*, 5286. (c) Kessar, S. V. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 4, p 483.

(6) For papers on the reactions of *ortho*-silyl aryltriflates with the active methylene compounds, see: (a) Tambar, U. K.; Stoltz, B. M. *J. Am. Chem. Soc.* **2005**, *127*, 5340. (b) Yoshida, H.; Watanabe, M.; Ohshita, J.; Kunai, A. *Chem. Commun.* **2005**, 3292. (c) Yoshida, H.; Watanabe, M.; Ohshita, J.; Kunai, A. *Tetrahedron Lett.* **2005**, *46*, 6729. (d) Tambar, U. K.; Ebner, D. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2006**, *128*, 11752. (e) Huang, X.; Xue, J. *J. Org. Chem.* **2007**, *72*, 3965. (f) Liu, Z.; Shi, F.; Martinez, P. D. G.; Raminelli, C.; Larock, R. C. *J. Org. Chem.* **2008**, *73*, 219. (g) Ramtohul, Y. K.; Chartrand, A. *Org. Lett.* **2007**, *9*, 1029.

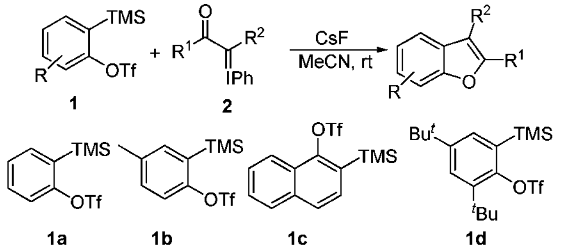
(7) For the other very recent papers on the application of *ortho*-silyl aryltriflates in organic sysnthesis, see: (a) Xie, C.; Zhang, Y. *Org. Lett.* **2007**, *9*, 781. (b) Bhuvaneswari, S.; Jeganmohan, M.; Cheng, C.-H. *Org. Lett.* **2006**, *8*, 5581. (c) Shen, Y.-M.; Grampp, G.; Leesakul, N.; Hu, H.-W.; Xu, J.-H. *Eur. J. Org. Chem.* **2007**, 3718. (d) Yoshida, H.; Morishita, T.; Fukushima, H.; Ohshita, J. i.; Kunai, A. *Org. Lett.* **2007**, *9*, 3367. (e) Beltran-Rodil, S.; Pena, D.; Guitian, E. *Synlett* **2007**, 1308. (f) Xie, C.; Zhang, Y.; Huang, Z.; Xu, P. *J. Org. Chem.* **2007**, *72*, 5431. (g) Yoshida, H.; Mimura, Y.; Ohshita, J.; Kunai, A. *Chem. Commun.* **2007**, 2405. (h) Jin, T.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 3323. (i) Yoshida, H.; Fukushima, H.; Morishita, T.; Ohshita, J.; Kunai, A. *Tetrahedron* **2007**, *63*, 4793. (j) Liu, Z.; Larock, R. C. *Angew. Chem., Int. Ed.* **2007**, *46*, 2535. (k) Yoshida, H.; Watanabe, M.; Morishita, T.; Ohshita, J.; Kunai, A. *Chem. Commun.* **2007**, 1505. (l) Zhao, J.; Larock, R. C. *J. Org. Chem.* **2007**, *72*, 583. (m) Liu, Z.; Larock, R. C. *Tetrahedron* **2007**, *63*, 347. (n) Liu, Z.; Larock, R. C. *J. Org. Chem.* **2007**, *72*, 223. (o) Bhuvaneswari, S.; Jeganmohan, M.; Cheng, C.-H. *Org. Lett.* **2006**, *8*, 5581. (p) Yoshida, H.; Fukushima, H.; Ohshita, J.; Kunai, A. *J. Am. Chem. Soc.* **2006**, *128*, 11040. (q) Henderson, J. L.; Edwards, A. S.; Greaney, M. F. *J. Am. Chem. Soc.* **2006**, *128*, 7426. (r) Raminelli, C.; Liu, Z.; Larock, R. C. *J. Org. Chem.* **2006**, *71*, 4689. (s) Liu, Zhijian;, Larock, Richard, C. *J. Org. Chem.* **2006**, *71*, 3198. (t) Jayanth, T. T.; Jeganmohan, M.; Cheng, M.-J.; Chu, S.-Y.; Cheng, C.-H. *J. Am. Chem. Soc.* **2006**, *128*, 2232.

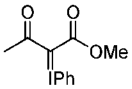
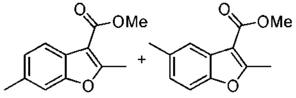
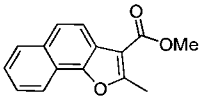
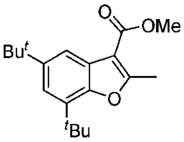
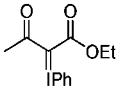
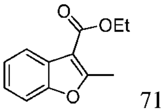
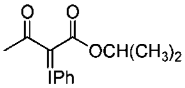
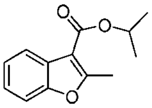
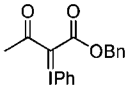
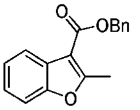
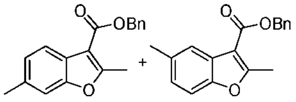
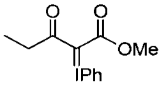
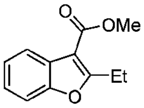
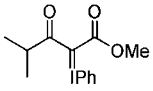
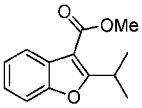
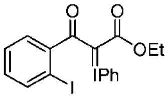
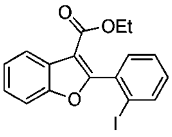
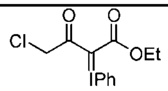
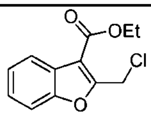
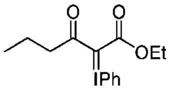
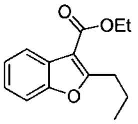
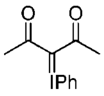
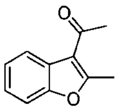
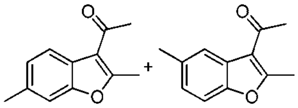
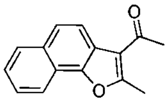
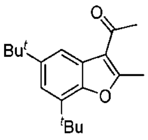
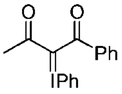
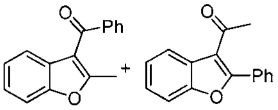
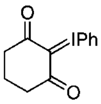
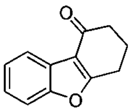
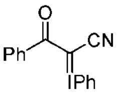
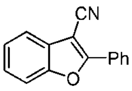
(8) For a papers on the generation of intermediate **A** and **E** from iodonium ylides, see: Moriarty, R. M.; Prakash, O.; Vaild, R. K.; Zhao, L. *J. Am. Chem. Soc.* **1989**, *111*, 6443.

(9) The structure of the isomers of the products **4**, **10**, and **17** was determined according to H−H COSY spectroscopy of **4**, and the authoritative 5-H and/or 8-H shift data of benzofurans in ref 2o. The structure of the isomers of **20** was assigned according to the authoritative ^1H NMR data, see: (a) Sidduri, A.; Rozema, M. J.; Knochel, P. *J. Org. Chem.* **1993**, *58*, 2694. (b) Chatterjea, J. N. *J. Indian Chem. Soc.* **1957**, *34*, 347.

(10) Typical experimental procedure for the cycloaddition reactions of *ortho*-silyl aryltriflates (**1**) and iodonium ylides (**2**). A mixture of *ortho*-silyl aryltriflate **1** (0.12 mmol), iodonium ylide **2** (0.1 mmol), and CsF (3 equiv) in MeCN (3 mL) was stirred at room temperature for the indicated time until complete consumption of starting material as monitored by TLC and GC analysis. Then, the mixture was washed with brine and extracted with diethyl ether. The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was then purified by flash column chromatography to afford the pure product (hexane/ethyl acetate).

Table 2. Cycloadditions of 2-Trimethylsilyltriflates (1) with Iodonium Ylides (2) in the Presence of CsF[a]



entry	1	iodonium ylide	time (h)	product (%)[b]
1	**1b**	 (**2a**)	6	 81 (1:1.3) (**4**)
2	**1c**	(**2a**)	4	 75 (**5**)
3	**1d**	(**2a**)	22	 91 (**6**)
4	**1a**	 (**2b**)	4	 71 (**7**)
5	**1a**	 (**2c**)	4	 85 (**8**)
6	**1a**	 (**2d**)	5	 84 (**9**)
7	**1b**	(**2d**)	4	 68 (1:1.4) (**10**)
8	**1a**	 (**2e**)	5.5	 86 (**11**)
9	**1a**	 (**2f**)	4	 80 (**12**)
10	**1a**	 (**2g**)	15	 32 (**13**)
11	**1a**	 (**2h**)	2.5	 55 (**14**)
12	**1a**	 (**2i**)	4	 78 (**15**)
13	**1a**	 (**2j**)	4.5	 68 (**16**)
14	**1b**	(**2j**)	15	 70 (1:1.2) (**17**)
15	**1c**	(**2j**)	3	 43 (**18**)
16	**1d**	(**2j**)	4	 45 (**19**)
17	**1a**	 (**2k**)	15	 53 (1:1) (**20**)
18	**1a**	 (**2l**)	20	 25 (**21**)
19	**1a**	 (**2m**)	20	 29 (**22**)

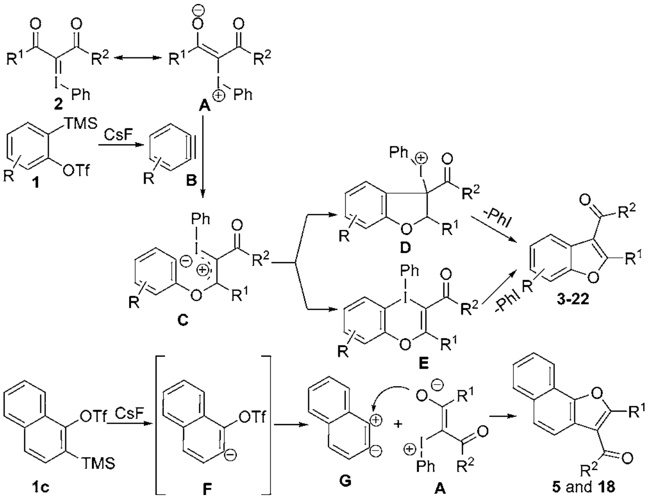
[a] Reaction conditions: **1** (0.12 mmol), **2** (0.1 mmol), and CsF (3 equiv) at room temperature in MeCN (3 mL) under argon atmosphere. [b] Isolated yield. The ratio was given in the parenthesis.

As listed in Table 2, the reactions between the other three *ortho*-silyl aryltriflates, **1b**–**d**, and ylide **2a**, respectively, were also conducted smoothly under the standard conditions (entries 1–3). 4-Methyl-2-(trimethylsilyl)phenyltrifluoromethanesulfonate (**1b**) treated with ylide **2a**, for example, afforded two regioselective products, methyl 2,6-dimethylbenzofuran-3-carboxylate and methyl 2,5-dimethylbenzofuran-3-carboxylate, in a 1:1.3 ratio and an 81% total yield (entry 1).[9] Substrate **1d**, a bulky *ortho*-silyl aryltriflate, also successfully underwent the cycloaddition reaction with ylide **2a** providing high yield (entry 3). Subsequently, a number of 2-phenyliodonio-3-oxobutanoates, **2b**–**i**, were evaluated, and they all were found to be suitable substrates for the reaction with *ortho*-silyl aryltriflates under the standard conditions (entries 4–12). Substrate **2c** bearing a bulky isopropoxy group, for instance, was treated with *ortho*-silyl aryltriflate **1a** and CsF smoothly at room temperature in an 85% yield (entry 5). Substrate **2g** or **2h** containing a halo group was also tolerated well under the same conditions (entries 10 and 11). We were happy to observe that 3-phenyliodonio-2,4-diones, **2j**–**k**, could also react with *ortho*-silyl aryltriflates efficiently in moderate yields (entries 13–18). 3-phenyliodonio-pentane-2,4-dione (**2h**), for example, was treated with ylides **1a**–**d**, respectively, to afford the corresponding products **16**–**19** in 43–70% yields (entries 13–16).[9] Although the yield was low in the reaction of substrate **1a** with ylide **2j**, an interesting tricycles product **21** was constructed (entry 18). Interestingly, the reaction of **1a** with 2-phenyliodonio-3-oxo-3-phenylpropanenitrile (**2k**) was conducted smoothly in a 29% yield under the standard conditions (entry 19).

A working mechanism as outlined in Scheme 1 was proposed for the present reaction on the basis of the previously reported mechanism.[4–8] *ortho*-Silyl aryltriflate **1** can be readily conversed into benzyne **B** in situ with the aid of CsF.[4–7] Subsequently, nucleophilic addition of intermediate **A** with benzyne **B** to yield intermediate **C**, followed by intramolecular cycloaddition of intermediate **C** to afford intermediate **D**[7] or intermediate **E**.[8] Finally, intermediate **D** or intermediate **E** undergoes reductive elimination to generate the desired benzofurans and PhI.

A pathway was also provided to elucidate the reason of the observed high regioselectivities of the products using *ortho*-silyl aryltriflates **2c** and **2d**. Generally, an anion **F** is generated from the cleavage of the C−Si bond, and a cation **G** from the cleavage of the C−O bond, which results in the high regioselectivity in the reactions of ylides with **2c** or **2d**. Compared the selectivity using substrate **2b**, the properties of **2c** and **2d**, such as the steric effect and electron effect, are affected the regioselectivity to some extent. Study of the accurate mechanism is in progress.

Scheme 1. Working Mechanism



In summary, we have developed a mild and general cycloaddition of benzynes with iodonium ylides protocol for the synthesis of benzofurans. In the presence of CsF, *ortho*-silyl aryltriflates successfully underwent the cycloaddition reaction with iodonium ylides at room temperature to afford the corresponding benzofurans in moderate to good yields. Work to probe the detailed mechanism and apply the reaction in organic synthesis is currently underway.

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Supporting Information Available: Analytical data and spectra (^{1}H and ^{13}C NMR) for all the products **3**–**22**; typical procedure for the cycloaddition of *ortho*-silyl aryltriflates with iodonium ylides. This material is available free of charge via the Internet at http://pubs.acs.org.

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