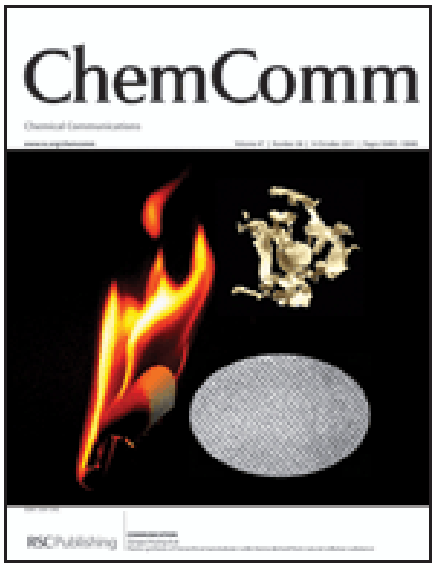

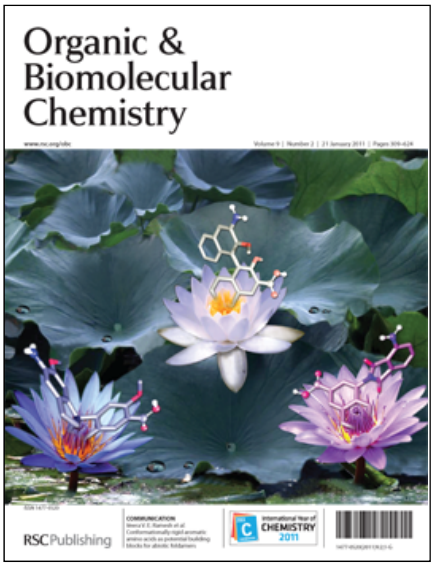

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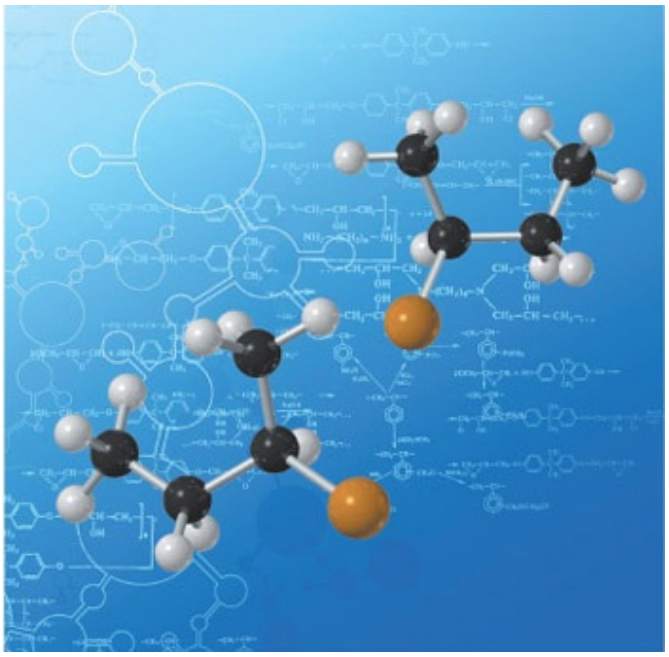

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COMMUNICATION

New synthesis of spirocycles by utilizing *in situ* forming hypervalent iodine species†‡

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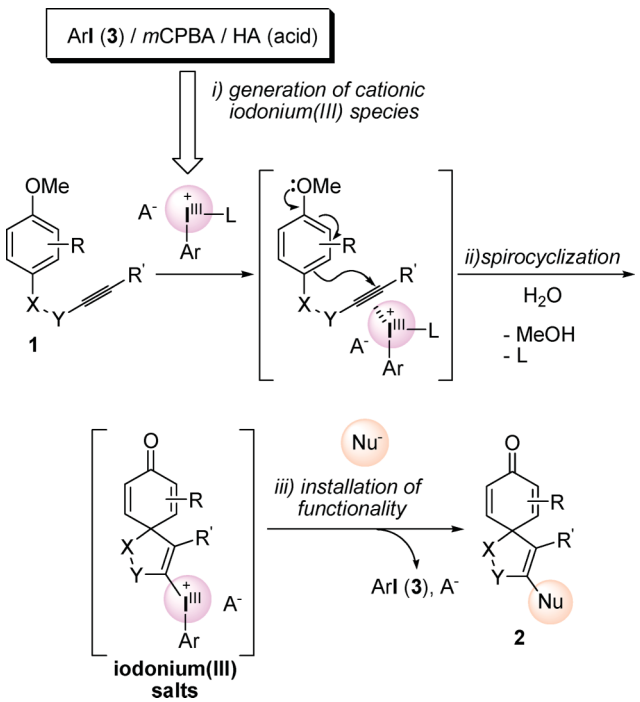
A very effective spirocyclization procedure for installing nucleophiles (Nu = N_3, NO_2, SCN, SO_2Tol, and halogens) *via* iodonium(III) salts has been developed using the combination of iodoarene and *m*CPBA. The high-yielding syntheses of the cyclohexadienone-type spirocyclic compounds 2 having varied functionalities in the skeletons have been achieved from the aryl alkynes 1 with the optimized bis(iodoarene) 3h.

There exists a number of spirocyclic compounds in nature, and these consist of classes that have received significant interest in recent years as the privileged structures of some pharmaceuticals, organic materials for optoelectronics and other applications, chiral ligands and catalysts for synthetic uses, *etc.*[1] Due to their useful biological activities and physical properties in combination with their unique structural aspects, many synthetic chemists inspired by biosynthetic hypotheses devoted themselves to develop valuable routes to these spirocyclic compounds focusing on the spiroannulation processes,[2,3] among which the *ipso*-cyclization of aryl alkynes triggered by electrophiles, such as NBX (where X = I, Br, Cl), X_2 (X = I, Br) and CuX (X = I, Br, SCN) combined with oxidants, has been reported by several groups.[4] These are attractive as one of the expeditious approaches to construct the functionalized spirocyclohexadienone-type structures. These known methods, namely, the electrophilic *ipso*-cyclizations, can indeed furnish the desired spiro carbon–carbon bonds with the accompanying introduction of halogens[4] or thiocyanate (up to 59%)[4d] to the products. However, the limitation of the electrophiles that can be used to induce effective spirocyclizations restricted the kind of functionalities installed in the final spirocyclic skeletons. Herein, this paper describes a very effective and facile method for synthesizing spirocyclic compounds with functionality from aryl alkynes by the continuous involvement of hypervalent iodine chemistry during the course of the reaction.

Our approach to the spirocyclization of aryl alkynes **1** which can permit installation of various functionalities is depicted in Scheme 1. It contains the following three key steps: (i) *in situ* generation of cationic hypervalent iodine species from iodoarene **3** using



Scheme 1 Strategy to functionalized spirocycles **2** from aryl alkynes **1** *via* iodonium salts (L = ligand).

m-chloroperbenzoic acid (*m*CPBA) in the presence of acid (HA),[5] (ii) alkyne activation by the electrophilic iodines[6] for inducing *ipso*-cyclization of aryl alkynes **1** directed by their methoxy group at the aryl ring, forming the spirocyclized iodonium(III) salts, and (iii) final installation of nucleophiles by reductive coupling[7] of the formed salts to produce the functionalized spirocyclic compounds **2**. The introduction of the hypervalent onium salts as intermediates for both the effective spirocyclization and facile attachment of the functionalities is a significant characteristic of the strategy. Only the successful completion of all steps should furnish two new bonds to the alkyne groups of the substrates **1**, forming the spiro carbon–carbon and carbon–nucleophile bonds of the spirocyclic products **2** in good yield. This approach was, in fact, partially realized using the prepared hypervalent iodine reagent, but the yields were sometimes unsatisfactory (for example, 77% yield at best for azidative spirocyclization) except for producing iodinated spirocycles.[8] Further elaboration to the onium salt-mediated approach is possible, thus we present the idea utilizing

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in situ forming hypervalent iodine species and the results of the evaluation of iodoarenes for producing the functionalized spirocycles **2**.

We initially evaluated the synthetic strategy using the simple iodobenzene **3a**, *m*CPBA, *p*-TsOH monohydrate, and butylammonium azide ($Bu_4N^+N_3^-$) for the aryl alkyne **1a**[4b–d] (eqn 1), which gave an unsatisfactory result regarding the formation of **2a**/N_3 having the azide functionality (Table 1, entry 1), despite consumption of the starting **1a**. Other typical iodoarenes **3b–g** (Fig. 1) were also treated using the same procedure, only yielding the desired spirocyclic compound **2a**/N_3 at best with a 67% yield (entries 2–7), even when testing other acids, azide sources, and modified conditions. The NMR observations and TLC monitoring of the reaction mixtures revealed that these iodoarenes **3a–g** had some problems regarding the alkyne activation for the *ipso*-cyclization step (Scheme 1, step (ii) and/or the generation of the hypervalent iodine species by the action of *m*CPBA (step (i)). Thus, further candidates for the spirocyclization of **1a** could not be found in our attempts to use mono-iodoarenes.

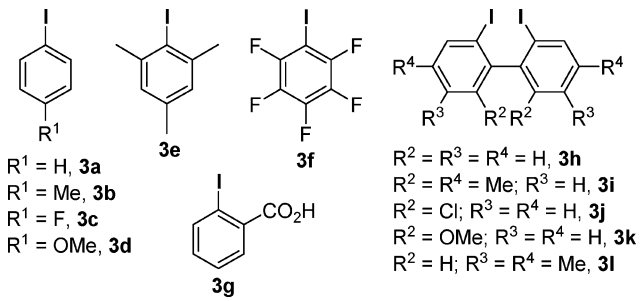
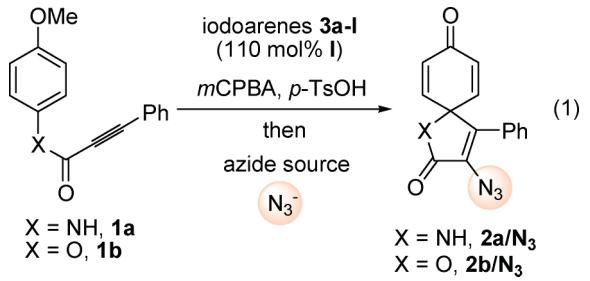


Fig. 1 Screened iodoarenes **3a–l**.

In clear contrast to the mono-iodoarenes **3a–g**, some bis(iodoarene)s having the *ortho*-iodinated biaryl structures showed very promising behavior for the *ipso*-cyclization and iodonium salt-mediated strategy. We could confirm the formal azidative spirocyclization of either **1a** or **1b**[4b–d] leading to the spirocyclic compounds **2a** and **2b** in excellent yields when using the bis(iodoarene) **3h** (entries 8 and 9). The use of 0.55 equiv. of **3h** was possible as both the iodine atoms can participate in the alkyne transformations. The *ortho*-substituents R^2 of the bis **3i–k**,[8,9] which should limit the conformation of the biaryl structures, decreased the reaction efficiency (entries 10–12). Among the screened bis(iodoarene)s **3h–l**, the best result of over 99% product yield was obtained using the bis **3h** for the aryl alkyne **2b** (entry 9).[10] As the generation and formation of the iodonium species and intermediate salts would be facilitated by the aid of fluoroalcohols,[11] the reactions were typically carried out by adding **1b** over 15 min to a pre-mixed trifluoroethanol (TFE) solution including the bis(iodoarene) **3h**, wet *m*CPBA (*ca.* 69% purity, 1.1 equiv.), and *p*-TsOH monohydrate (2 equiv.). After 3 h, $Bu_4N^+N_3^-$ (1.1 equiv.) in chloroform was added dropwise. The ideal conditions for the azidative spirocyclization were thus determined regarding the reagent combination and solvents, though the optimized bis(iodoarene) **3h** could provide flexibility for the possible azide sources ($Bu_4N^+N_3^-$, NaN_3, and $TMSN_3$), acids (methanesulfonic acid, triflic acid, *etc.*), and solvents (hexafluoroisopropanol, acetonitrile, *etc.*) to give similar results.

Table 1 Optimization of the Strategy[a]



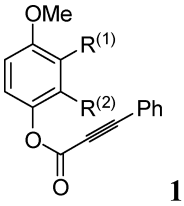
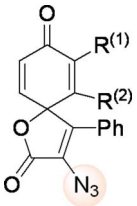
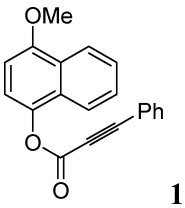
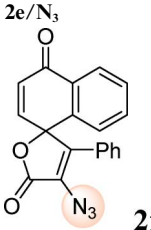
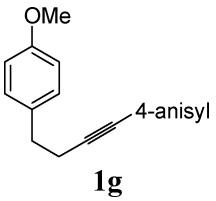
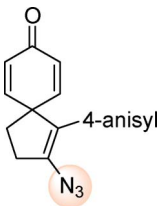
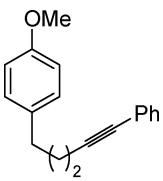
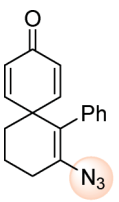
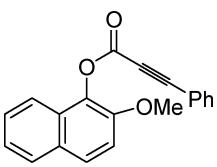
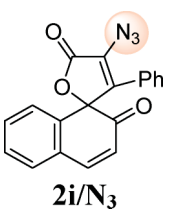
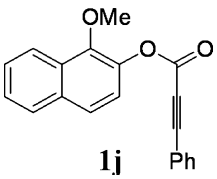
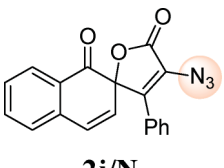
Entry	Iodoarene (**3**)	Product	Yield[b] (%)
1	**3a**	**2a**/N_3	37
2	**3b**	**2a**/N_3	66
3	**3c**	**2a**/N_3	67
4	**3d**	**2a**/N_3	n.d.
5	**3e**	**2a**/N_3	n.d.
6	**3f**	**2a**/N_3	n.d.
7	**3g**	**2a**/N_3	n.d.
8	**3h**	**2a**/N_3	92
9	**3h**	**2b**/N_3	99
10	**3i**	**2b**/N_3	82
11	**3j**	**2b**/N_3	33
12	**3k**	**2b**/N_3	n.d.
13	**3l**	**2b**/N_3	90

[a] Each reaction was performed at room temperature by adding **1a** or **1b** to a pre-mixed trifluoroethanol solution including iodoarene **3a–g** (1.1 equiv. relative to **1a**) or bis(iodoarene) **3h–l** (0.55 equiv. relative to **1a** or **1b**), wet *m*CPBA (1.1 equiv.), and *p*-TsOH·H_2O (2 equiv.) for 3 h, then treated with $Bu_4N^+N_3^-$ (1.1 equiv.) in chloroform overnight. [b] Isolated yield of the pure product **2a**/N_3 or **2b**/N_3. n.d. = not determined (less than 5% yield of **2a**/N_3 or **2b**/N_3 formation).

The optimized iodoarene **3h** obtained by this screening could expand the versatility of the strategy in terms of the range of the nucleophiles and usable substrates **1**.[12] Table 2 includes the results of using an extensive number of ring- and tether-modified aryl alkynes **1c–k** that could verify the generality of the new synthetic method. As well as the construction of five- and six-membered *para*-spirocyclized cyclohexadienones **2a–h**/N_3 (Tables 1 and 2), application to the valuable *ortho*-spirolactone structures that are frequently seen in some natural products[13] is acceptable based on the demonstrations of the aryl alkynes **1i–k** (entries 7–9). In addition to the azide functionality, a series of nitrogen, sulfur, and halogen nucleophiles participated effectively in the spirocyclization of **1b** and its analogues **1l** and **1m** having different alkynes (Scheme 2).[14,15] The yields were dramatically increased when compared to the previous results[8] using the prepared reagent based on the bis(iodoarene) **3i**.

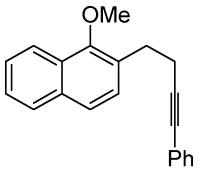
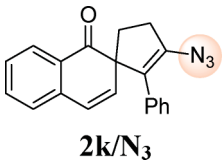
Regarding the iodoarene, the *ortho*-diiodinated biaryl structure should be essential for developing the transformations with good performance. The minor manipulations of the substituents in the bis(iodoarene)s would contribute to not only the *ipso*-cyclization and the formation of the spirocyclized iodonium salts, but also to the final substitution event by the nucleophiles at the alkenyl moieties (see Scheme 1). Although the details of the explanation are still under consideration, the use of **3h** is important to suppress contamination of the iodinated spirocycles that would be formed by cleavage of the reagent C_{aryl}–I(III) bonds in the last step. For example, such a chemoselective issue[16] might be associated with

Table 2 Scope of the substrates **1** in the azidative spirocyclization using the bis(iodoarene) **3h**[a]

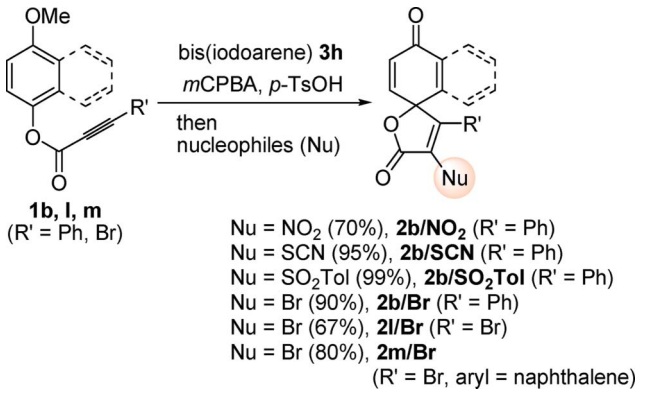
Entry	Aryl alkyne (**1**)	Spiro product (**2**/N_3)	Yield[b]
	 **1c-e**	 **2c-e/N_3**	
1	$R^{(1)}$ = OMe, $R^{(2)}$ = H, **1c**	$R^{(1)}$ = OMe, $R^{(2)}$ = H, **2c**/N_3	86%
2	$R^{(1)}$ = H, $R^{(2)}$ = Cl, **1d**	$R^{(1)}$ = H, $R^{(2)}$ = Cl, **2d**/N_3	97%
3	$R^{(1)}$ = H, $R^{(2)}$ = ^{t}Bu, **1e**	$R^{(1)}$ = H, $R^{(2)}$ = ^{t}Bu, **2e**/N_3	88%
4	 **1f**	 **2f/N_3**	99%
5	 **1g**	 **2g/N_3**	74%
6	 **1h**	 **2h/N_3**	60%
7	 **1i**	 **2i/N_3**	99%
8	 **1j**	 **2j/N_3**	94%

the spirocyclizations especially in the case of the bis(iodoarene) **3j** having the electron-withdrawing group (see Table 1).

Table 2 (*Contd.*)

Entry	Aryl alkyne (**1**)	Spiro product (**2**/N_3)	Yield[b]
9	 **1k**	 **2k/N_3**	99%

[a] Performed using the reagent **3h** and according to the conditions optimized in Table 1. [b] Isolated yield based on the aryl alkyne **1** used.



Scheme 2 Introduction of other types of nucleophiles.

In summary, we have established a new and reliable one-pot procedure for synthesizing the spirocyclic compounds **2** having varied functionalities from the aryl alkynes **1** by utilizing the results of hypervalent iodine chemistry. The fine tuning of the bis(iodoarene) **3h** in this strategy could permit significant increases of the product yield. Thus, this new strategy could provide easy access to a variety of functionalized spirocyclic motifs, which were hardly obtainable by other spirocyclization methods, and might serve as a platform for some functionalized natural products and other useful molecules. The catalytic versions of the new synthetic transformations by the bis(iodoarene) will be described in due course.[17]

Acknowledgements

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Notes and references

1 For utilities and naturally occuring spirocyclic compounds, see the following reviews: (*a*) C. H. Heathcock, S. L. Graham, M. C. Pirrung, F. Plavac and C. T. White, In *The Total Synthesis of Natural Products*, J. Apsimon, ed., Wiley-Interscience, New York, 1983; vol. 5, pp 264-313; (*b*) M. Hesse, *Alkaloide*, Verlag Helvetica Chimica Acta, Zürich, Switzerland, 2000; (*c*) H. Greger, *Planta Med.*, 2006, **72**, 99; (*d*) V. I.

Minkin, *Chem. Rev.*, 2004, **104**, 2751; (*e*) R. Pudzich, T. Fuhrmann-Lieker and J. Salbeck, *Adv. Polym. Sci.*, 2006, **199**, 83; (*f*) T. P. I. Saragi, T. Spehr, A. Siebert, T. Fuhrmann-Lieker and J. Salbeck, *Chem. Rev.*, 2007, **107**, 1011; (*g*) K. Ding, Z. Han and Z. Wang, *Chem.–Asian J.*, 2009, **4**, 32.

2 The updated synthetic reviews: (*a*) S. Kotha, A. C. Deb, K. Lahiri and E. Manivannan, *Synthesis*, 2009, 165; (*b*) S. Rosenberg and R. Leino, *Synthesis*, 2009, 2651; (*c*) S. Rodriguez and P. Wipf, *Synthesis*, 2004, 2767; (*d*) C. Cismas, A. Terec, S. Mager and I. Grosu, *Curr. Org. Chem.*, 2005, **9**, 1287.

3 For the studies in our laboratory using hypervalent iodine reagents, see the selected examples: (*a*) Y. Tamura, T. Yakura, J. Haruta and Y. Kita, *J. Org. Chem.*, 1987, **52**, 3927; (*b*) Y. Kita, H. Tohma, M. Inagaki, K. Hatanaka and T. Yakura, *J. Am. Chem. Soc.*, 1992, **114**, 2175; (*c*) Y. Kita, T. Takada, M. Gyoten, H. Tohma, M. H. Zenk and J. Eichhorn, *J. Org. Chem.*, 1996, **61**, 5857; (*d*) M. Arisawa, N. G. Ramesh, M. Nakajima, H. Tohma and Y. Kita, *J. Org. Chem.*, 2001, **66**, 59; (*e*) H. Tohma and Y. Kita, *Top. Curr. Chem.*, 2003, **224**, 209 and references cited therein.

4 (*a*) T. R. Appel, N. A. M. Yehia, U. Baumeister, H. Hartung, R. Kluge, D. Ströhl and E. Fanghänel, *Eur. J. Org. Chem.*, 2003, 47; (*b*) X. Zhang and R. C. Larock, *J. Am. Chem. Soc.*, 2005, **127**, 12230; (*c*) B.-X. Tang, D.-J. Tang, S. Tang, Q.-F. Yu, Y.-H. Zhang, Y. Liang, P. Zhong and J.-H. Li, *Org. Lett.*, 2008, **10**, 1063; (*d*) B. X. Tang, Q. Yin, R. Y. Tang and J. H. Li, *J. Org. Chem.*, 2008, **73**, 9008 and references therein.

5 (*a*) T. Dohi, A. Maruyama, M. Yoshimura, K. Morimoto, H. Tohma and Y. Kita, *Angew. Chem., Int. Ed.*, 2005, **44**, 6193; (*b*) M. Ochiai, Y. Takeuchi, T. Katayama, T. Sueda and K. Miyamato, *J. Am. Chem. Soc.*, 2005, **127**, 12244; (*c*) R. D. Richardson and T. Wirth, *Angew. Chem., Int. Ed.*, 2006, **45**, 4402; (*d*) E. A. Merritt, V. M. T. Carneiro, L. F. Jr. Silva and B. Olofsson, *J. Org. Chem.*, 2010, **75**, 7416.

6 Formation of alkenylodonium salts by the oxygenations of alkynes: (*a*) G. F. Koser, L. Rebrovic and R. H. Wettach, *J. Org. Chem.*, 1981, **46**, 4324; (*b*) L. Rebrovic and G. F. Koser, *J. Org. Chem.*, 1984, **49**, 4700; (*c*) T. Kitamura, R. Furuki, H. Taniguchi and P. J. Stang, *Tetrahedron Lett.*, 1990, **31**, 703. On the other hand, no general method using hypervalent iodine reagent to furnish carbon–carbon bonds toward alkynes was reported.

7 Reactions of alkenyliodonium salts with nucleophiles: (*a*) M. Ochiai, K. Sumi, Y. Takaoka, M. Kunishima, Y. Nagao, M. Shiro and E. Fujita, *Tetrahedron*, 1988, **44**, 4095; (*b*) J.-M. Chen and X. Huang, *Synlett*, 2004, 552; (*c*) J. Yan, H. Jin and Z. Chen, *J. Chem. Res.*, 2007, 233.

8 Very recently, we reported the isolation of new iodonium salts formed by the spirocyclization, in which the possibility of a similar one-pot synthesis was described for specific cases. The utilization and optimization of the *in situ* generated hypervalent iodine species from iodoarenes were not treated in that study. See: T. Dohi, D. Kato, R. Hyodo, D. Yamashita, M. Shiro and Y. Kita, *Angew. Chem., Int. Ed.*, 2011, **50**, 3784.

9 The bis(iodoarene)s also showed the high catalytic efficiencies in the spirocyclization of the *N*-methoxy aryl amides. See: T. Dohi, N. Takenaga, K.-I. Fukushima, T. Uchiyama, D. Kato, M. Shiro, H. Fujioka and Y. Kita, *Chem. Commun.*, 2010, **46**, 7697.

10 Other regioisomeric bis(iodoarene)s of **3h** were less effective than the 2,2′-derivative in this transformation.

11 The fluoroalcohols can accelerate generation of hypervalent iodine(III) species from iodoarenes and formation of the diaryliodonium salts. See: (*a*) T. Dohi, A. Maruyama, Y. Minamitsuji, N. Takenaga and Y. Kita, *Chem. Commun.*, 2007, 1224; (*b*) T. Dohi, M. Ito, K. Morimoto, Y. Minamitsuji, N. Takenaga and Y. Kita, *Chem. Commun.*, 2007, 4152; (*c*) T. Dohi, N. Yamaoka and Y. Kita, *Tetrahedron*, 2010, **66**, 5775.

12 The use of excess amounts of the nucleophiles (~5 equiv.) was possible in order to avoid introduction of *m*CPBA to the final spirocyclic products, though it was a very minor competitive path.

13 For selected examples of natural product syntheses containing the related *ortho*-spirolactone structures, see: (*a*) K. Watanabe, Y. Iwata, S. Adachi, T. Nishikawa, Y. Yoshida, S. Kameda, M. Ide, Y. Saikawa and M. Nakata, *J. Org. Chem.*, 2010, **75**, 5573; (*b*) D. A. Henderson, P. N. Collier, G. Pave, P. Rzepa, A. J. P. White, J. N. Burrows and A. G. M. Barrett, *J. Org. Chem.*, 2006, **71**, 2434; (*c*) F. Konno, T. Ishikawa, M. Kawahata and K. Yamaguchi, *J. Org. Chem.*, 2006, **71**, 9818; (*d*) C. Cox and S. J. Danishefsky, *Org. Lett.*, 2000, **2**, 3493.

14 The pK_a values of conjugated acids of the nucleophiles are typically lower than 5.

15 Comparable reaction yields were obtained for the substrates **1** in Table 1 in these nucleophiles.

16 (*a*) M. Ochiai, K. Oshima and Y. Masaki, *Chem. Lett.*, 1994, 871; (*b*) M. Ochiai, T. Shu, T. Nagaoka and Y. Kitagawa, *J. Org. Chem.*, 1997, **62**, 2130.

17 For the related bis(iodoarene) catalysts developed by us, see: (*a*) T. Dohi, A. Maruyama, N. Takenaga, K. Senami, Y. Minamitsuji, H. Fujioka, S. Caemmerer and Y. Kita, *Angew. Chem., Int. Ed.*, 2008, **47**, 3787; (*b*) T. Dohi and Y. Kita, *Chem. Commun.*, 2009, 2073.

