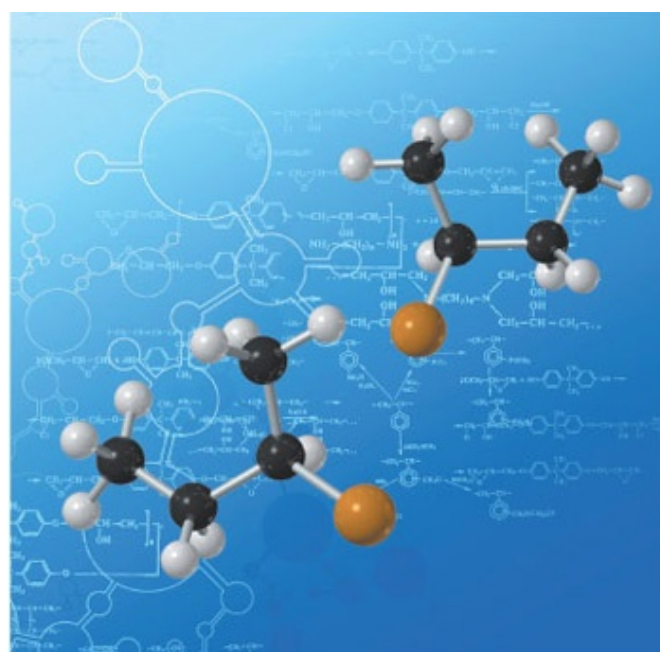This article is part of the

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

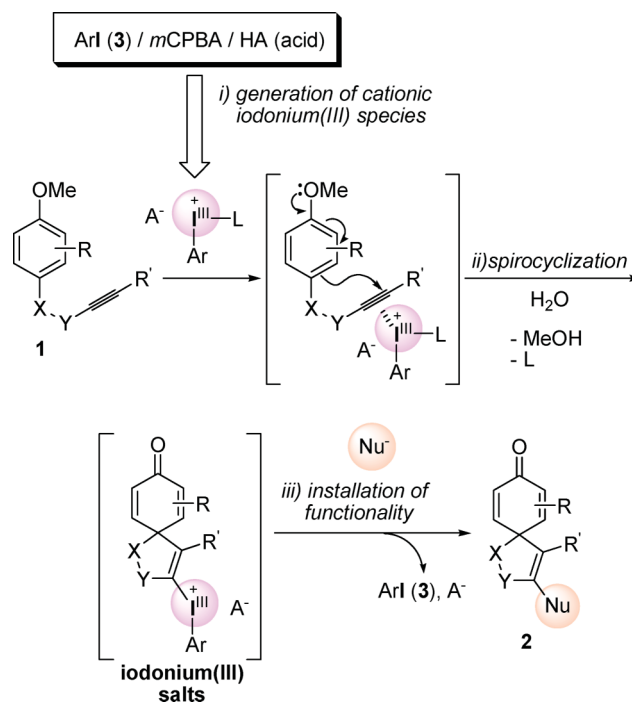## Toshifumi Dohi, Tomofumi Nakae, Yohei Ishikado, Daishi Kato and Yasuyuki Kita*

A very effective spirocyclization procedure for installing nucleophiles (Nu = N₃, NO₂, SCN, SO₂Tol, 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), X₂ (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

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‡ Electronic supplementary information (ESI) available. See DOI: 10.1039/c1ob06199b

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

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 butyl-ammonium azide (Bu₄N⁺N₃⁻) for the aryl alkyne **1a**[4b–d] (eqn 1), which gave an unsatisfactory result regarding the formation of **2a/N₃** 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/N₃** 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.
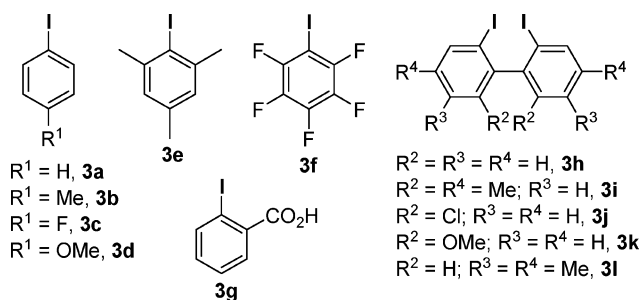

Fig. 1 Screened iodoarenes **3a–l**.

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 R² 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, Bu₄N⁺N₃⁻ (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 (Bu₄N⁺N₃⁻, NaN₃, and TMSN₃), 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/N₃**	37
2	**3b**	**2a/N₃**	66
3	**3c**	**2a/N₃**	67
4	**3d**	**2a/N₃**	n.d.
5	**3e**	**2a/N₃**	n.d.
6	**3f**	**2a/N₃**	n.d.
7	**3g**	**2a/N₃**	n.d.
8	**3h**	**2a/N₃**	92
9	**3h**	**2b/N₃**	99
10	**3i**	**2b/N₃**	82
11	**3j**	**2b/N₃**	33
12	**3k**	**2b/N₃**	n.d.
13	**3l**	**2b/N₃**	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·H₂O (2 equiv.) for 3 h, then treated with Bu₄N⁺N₃⁻ (1.1 equiv.) in chloroform overnight. [b] Isolated yield of the pure product **2a/N₃** or **2b/N₃**. n.d. = not determined (less than 5% yield of **2a/N₃** or **2b/N₃** 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/N₃** (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

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

Entry	Aryl alkyne (**1**)	Spiro product (**2/N₃**)	Yield[b]
	1c-e	**2c-e/N₃**	
1	R[(1)] = OMe, R[(2)] = H, **1c**	R[(1)] = OMe, R[(2)] = H, **2c/N₃**	86%
2	R[(1)] = H, R[(2)] = Cl, **1d**	R[(1)] = H, R[(2)] = Cl, **2d/N₃**	97%
3	R[(1)] = H, R[(2)] = ᵗBu, **1e**	R[(1)] = H, R[(2)] = ᵗBu, **2e/N₃**	88%
4	**1f**	**2f/N₃**	99%
5	**1g**	**2g/N₃**	74%
6	**1h**	**2h/N₃**	60%
7	**1i**	**2i/N₃**	99%
8	**1j**	**2j/N₃**	94%

Table 2 (*Contd.*)

Entry	Aryl alkyne (**1**)	Spiro product (**2/N₃**)	Yield[b]
9	**1k**	**2k/N₃**	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.

Nu = NO₂ (70%), **2b/NO₂** (R' = Ph)
Nu = SCN (95%), **2b/SCN** (R' = Ph)
Nu = SO₂Tol (99%), **2b/SO₂Tol** (R' = Ph)
Nu = Br (90%), **2b/Br** (R' = Ph)
Nu = Br (67%), **2l/Br** (R' = Br)
Nu = Br (80%), **2m/Br**
(R' = Br, aryl = naphthalene)
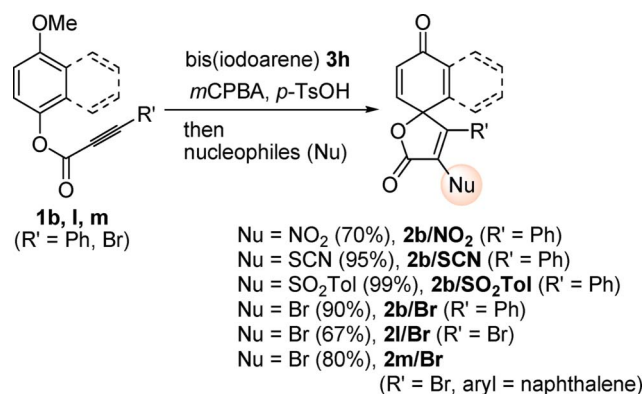
Scheme 2 Introduction of other types of nucleophiles.

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]

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