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ONE-POT SYNTHESIS OF 9-SPIROFLUORENES VIA TANDEM COPPER-CATALYZED ARYLATIVE CYCLIZATION AND SPIROCYCLIZATION OF BIARYL-SUBSTITUTED ALKYNYL ALCOHOLS

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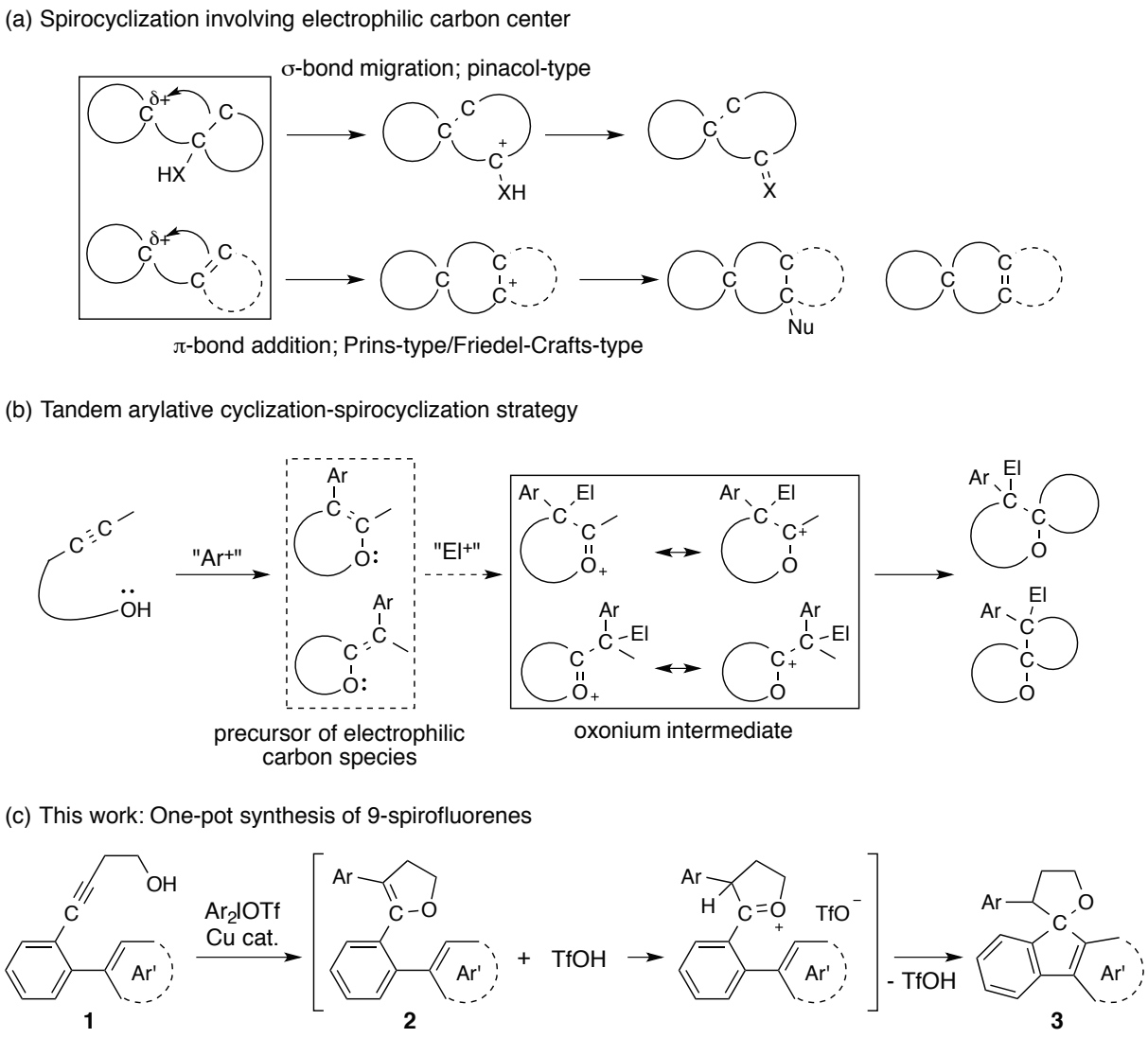
Abstract – A tandem copper-catalyzed arylative cyclization and spirocyclization strategy to access spiro cyclic compounds is described. This method enables the one-pot construction of 9-spirofluorenes from readily available alkynyl alcohols with biaryl-substituents via the copper-catalyzed arylative ring-closing reaction and the Friedel–Crafts reaction.

Spirocycles are prevalent core structures in natural products, bioactive molecules, organic functional materials, and chiral ligands.[1] Therefore, it has attracted the intense attention of organic chemists to synthesize the unique structure of spirocarbocycles.[2] Among the known synthetic methods, elegant examples of transition-metal-catalyzed intramolecular spirocyclizations, such as the dearomatization of functionalized phenols[3] with a tethered electrophilic species, are regarded as efficient and reliable approaches to constructing three-dimensional spirocycles.[4] However, the classical cation-triggered spirocyclization is still one of the most practical approaches and avoids the use of expensive metal catalysts. From a general mechanistic point of view, such a process is initiated by the generation of an electrophilic carbon center (*e.g.*, carbocation) on the pre-spiro center, which triggers two types of the C-C bond formation step: (1) migration of an adjacent C-C bond (pinacol-type)[5] and (2) electrophilic addition to an adjacent C-C π-bond (Prins-type/Friedel–Crafts-type).[6] A variety of methods can be used to generate these electrophilic carbon centers (Scheme 1(a)).

The electrophile-initiated intramolecular heterocyclization of alkynes is a versatile synthetic transformation widely applied to the preparation of various heterocycles.[7] We have recently reported on the arylative ring-closing reactions[8] of 2-alkynylbenzamides, 2-alkynylphenylcarbamates and 2-alkynylphenylureas[9] using the combination of diaryliodonium salts[10] and copper catalysts. Although a

selective arylation and cyclization pattern were observed deriving from the different properties of the substituents and metal catalyst,[9] the starting alkyne was converted into an electron-rich double bond with an aryl substituent. To investigate this promising synthetic strategy, we focused our attention on the arylative product with an electron-rich double bond. If activated by the electrophile, a cyclic vinyl ether obtained from the intramolecular arylative cyclization of an alkynyl alcohol would be a precursor of the electrophilic carbon species. This would lead to a spirocycle possessing an aryl group on the carbon next to the spiro center. We assumed that the acid byproduct formed from the arylative cyclization could activate the resulting vinyl ether by protonation to generate an oxonium intermediate, which then undergoes spirocyclization via either of the two above-mentioned processes[5,6] (Scheme 1(b)).



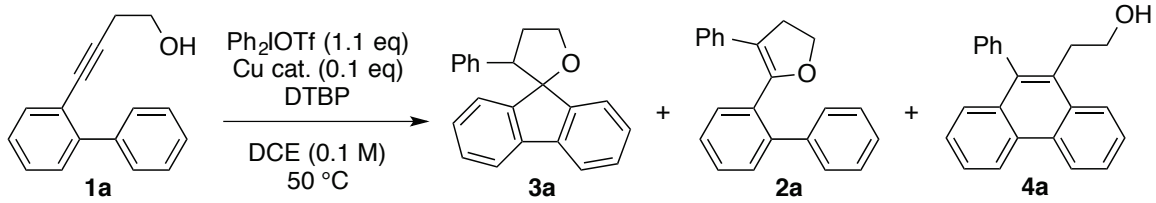
Scheme 1. Tandem arylative cyclization-spirocyclization strategy

To test our hypothesis, we first chose an easily accessible alkynyl alcohol **1** having a biaryl moiety on the alkynyl group, leading to the formation of 9-spirofluorene **3** via dihydrofuran **2**. Surprisingly, there are no

reports on an intramolecular arylative cyclization of simple linear aliphatic alcohols, except for the alkoxy derivatives,[8h] with diaryliodonium salts reported in the literature. Furthermore, some 9-spirofluorenes show important biological activities.[11] Herein, we describe a tandem copper-catalyzed arylative ring-closing reaction and Friedel–Crafts reaction of readily available alkynyl alcohols with diaryliodonium salts for the one-step synthesis of 9-spirofluorenes (Scheme 1(c)).

The reaction of the alkynyl alcohol **1a** with diphenyliodonium triflate (Ph_2IOTf) in the presence of a catalytic amount of $(CuOTf)_2$·toluene in 1,2-dichloroethane (DCE) at 50 °C for 2 h afforded the desired 9-spirofluorene **3a** in 49% isolated yield, together with the phenanthrene derivative **4a** (entry 1, Table 1). The structures of **3a** and **4a** were unambiguously determined by X-ray crystallographic analysis.[12] Addition of 2,6-di-*tert*-butylpyridine (DTBP) improved the yield of **3a** and the best result was obtained when 0.5 equivalent of DTBP was used (entries 2 and 3). Increasing the amount of DTBP was less effective, resulting in either prolonged reaction times or the formation of dihydrofuran **2a** as a major product (entries 4 and 5). Other copper salts and Ph_2IPF_6, instead of Ph_2IOTf, delivered inferior results (entries 6–9). The control experiment proved $(CuOTf)_2$·toluene to be crucial (entry 10).

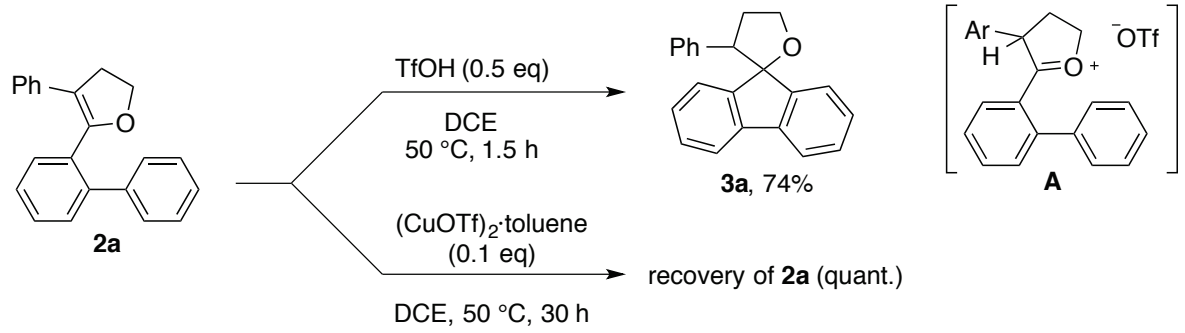
Table 1. Optimization of the reaction conditions[a]



Entry	Cu cat.	DTBP (eq)	Time (h)	Yield[b,c]			
				3a (%)	**2a** (%)	**4a** (%)	**1a** (%)
1	$(CuOTf)_2$·toluene	-	2	49	-	(18)	-
2	$(CuOTf)_2$·toluene	0.3	2.5	65	-	-	-
3	$(CuOTf)_2$·toluene	0.5	3	68	-	-	-
4	$(CuOTf)_2$·toluene	0.8	12	62	-	-	-
5	$(CuOTf)_2$·toluene	1.1	24	-	(72)	-	(28)
6	CuCl	0.5	2	56	-	-	-
7	CuBr	0.5	9	64	-	-	-
8	$Cu(OTf)_2$	0.5	24	-	-	-	(quant.)
9[d]	$(CuOTf)_2$·toluene	0.5	24	-	(60)	-	(14)
10	-	0.5	24	-	-	-	(quant.)

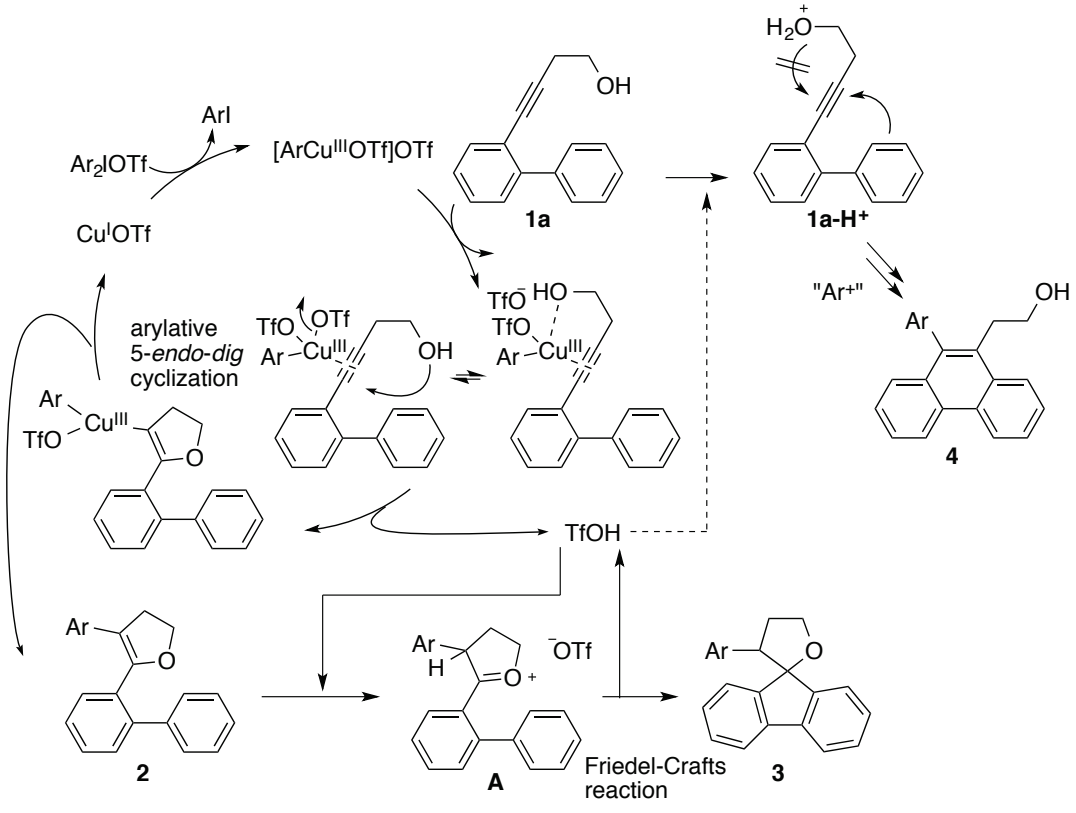
[a]Reactions run on a 0.1 mmol scale. [b]Isolated yields. [c]Determined by ^{1}H NMR analysis of the crude reaction mixtures using 1,2-dichloroethane as an internal standard in parentheses. [d]Ph_2IPF_6 was used instead of Ph_2IOTf.

Treatment of dihydrofuran **2a** with TfOH yielded 9-spirofluorene **3a**, while treatment with $(CuOTf)_2$·toluene resulted in the recovery of **2a**. This suggested that the oxonium **A** formed from a protonation by TfOH would be an intermediate, which underwent the intramolecular Friedel–Crafts reaction to furnish 9-spirofluorene **3** (Scheme 2).



Scheme 2. Conversion of **2a** to **3a**

On the basis of our observations, a plausible mechanism for the formation of 9-spirofluorene **3** from **1a** is shown in Scheme 3. The electrophilic Ar–Cu(III) species generated *in situ* activates the carbon-carbon triple bond[8] and causes an intramolecular 5-*endo-dig* cyclization by a hydroxy group. Reductive elimination of the resulting vinyl-copper(III) species provides the dihydrofuran **2** together with TfOH as a byproduct.

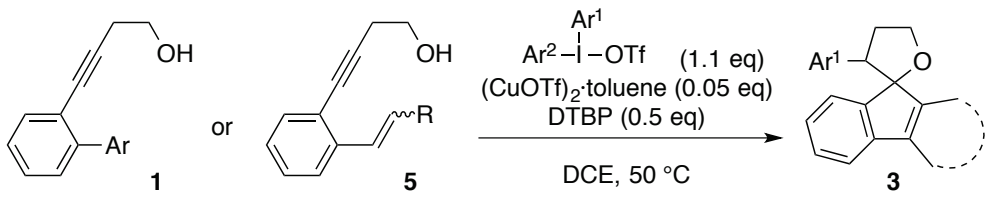


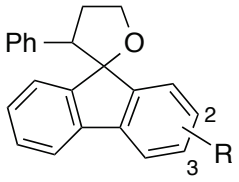
Scheme 3. Plausible reaction mechanism

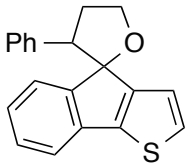
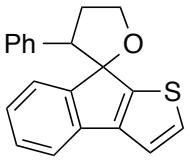
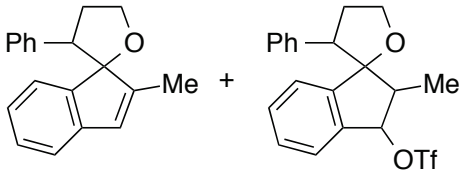
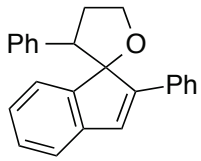
Subsequently, the Friedel–Crafts reaction to **3** occurs via the oxonium intermediate **A** formed from the protonation of **2** by TfOH. Increasing the concentration of TfOH before the complete conversion to **2** would lead to the undesired arylative cyclization to **4** because of the lower nucleophilicity of the protonated hydroxy group.[13] A basic DTBP might prevent the formation of **4** at the beginning of the reaction.

The reactions of various alkynyl alcohols **1** or **5** with the diaryliodonium salt were studied (Table 2). Diaryliodonium salts bearing a methyl group or a fluorine atom on the phenyl ring reacted well (entries 1 and 2). The electronic properties of the *ortho*-aryl group of **1** affected the reactivity. Compounds **1b** and **1c** bearing a methyl group on the phenyl ring provided the corresponding 9-spirofluorenes **3d** and **3e** in almost the same yield as **3a**, albeit as an equal mixture of diastereomers (entries 3 and 4). However, compound **1d** bearing a chloro-substituted phenyl group gave dihydrofuran **2b** as the major product, indicating that the lower electron density of the *ortho*-aryl group hindered the Friedel–Crafts reaction (entry 5). The 2-thienyl-substituted **1e** also participated in the reaction, providing **3f** in moderate yield, while the 3-thienyl derivative **1f** afforded the corresponding **3g** in low yield (entries 6 and 7). The alkenyl-substituted **5a**–**c** delivered inferior results owing to a complex mixture of products (entries 8–10).

Table 2. Substrate scope[a]

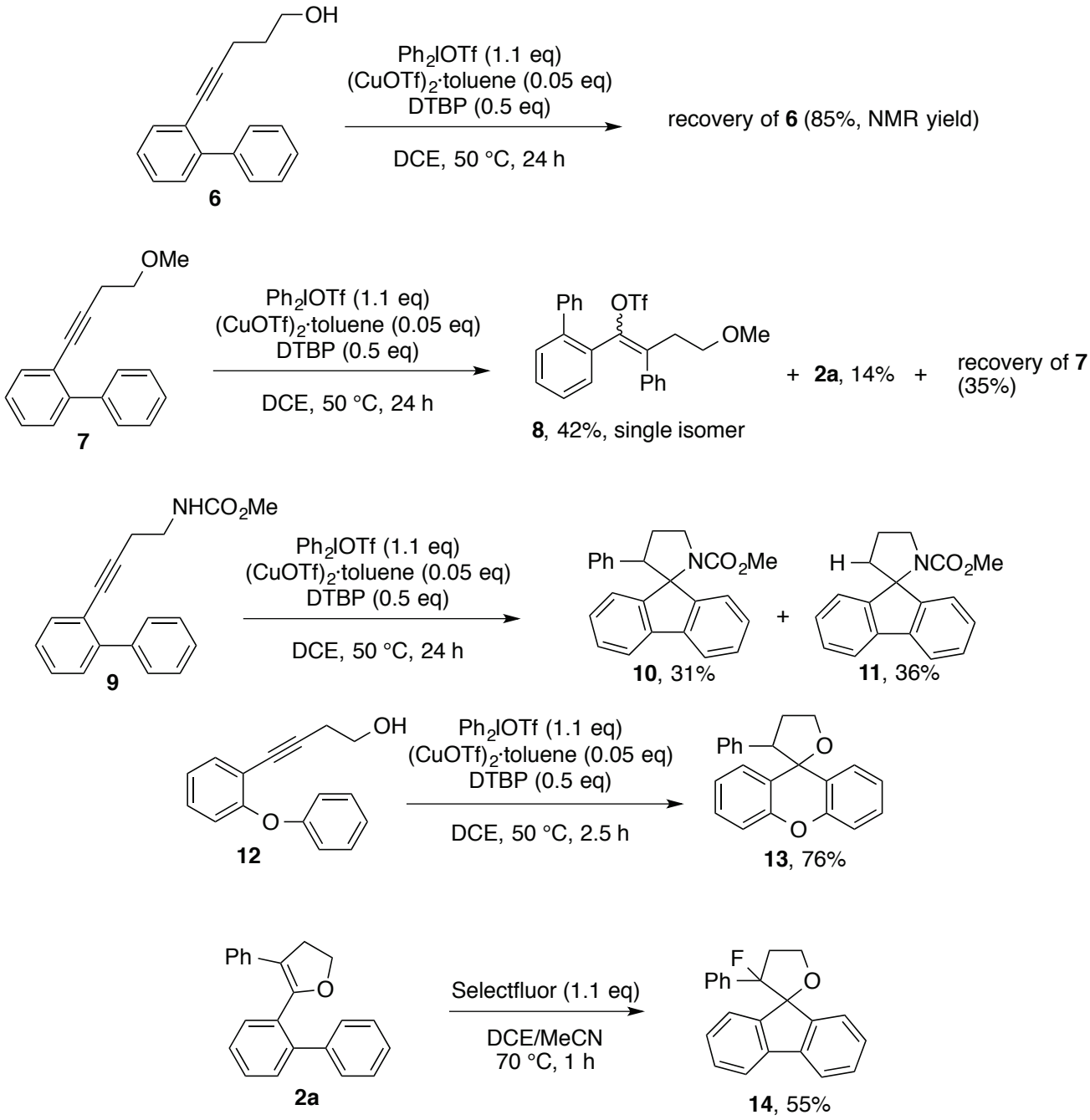


Entry	**1**	[Ar[1]–I–Ar[2]]OTf	Time (h)	Product (%)[b,c]
1	**1a**	[Tol–I–Mes]OTf	4	**3b**, 57
2	**1a**	$(4\text{-}FC_6H_4)_2IOTf$	7	**3c**, 64
3	**1b** (Ar = *p*-MeC_6H_4)	Ph_2IOTf	4	 **3d**: R = 2-Me, 67, d.r. = 54:46
4	**1c** (Ar = *m*-MeC_6H_4)	Ph_2IOTf	1.5	**3e**: R = 3-Me, 66, d.r. = 50:50
5	**1d** (Ar = *p*-ClC_6H_4)	Ph_2IOTf	5	**2b**, 50

6	**1e** (Ar = 2-thienyl)	Ph_2IOTf	4	 **3f**, 46[d], d.r. = 62:38
7	**1f** (Ar = 3-thienyl)	Ph_2IOTf	2.5	 **3g**, 14, d.r. = 75:25
8	**5a** (R = Me, *E*/*Z* = 54:46)	Ph_2IOTf	6.5	 <19% as an inseparable mixture
9	**5b** (R = Ph, *E*/*Z* = 51:49)	Ph_2IOTf	5	 **3h**, 23, single isomer
	5c (R = TMS, *E*)	Ph_2IOTf	24	complex mixture

[a]Reactions run on a 0.1 mmol scale. [b]Isolated yields. [c]Diastereomeric ratios determined by ^1H NMR analysis of the isolated products. [d]Recovery of **1e** (35%).

To evaluate the scope and limitations of the developed reaction sequence, we tested some other types of substrates. The alkynyl alcohol **6** with different alkyl tether lengths led to the recovery of the unchanged starting material. Against expectations for the methoxy derivative **7** based on Chen and Qu's report on the intramolecular arylative cyclization of an alkoxy alkyne with diaryliodonium salts and $Cu(OTf)_2$ as the catalyst,[8h] **7** afforded the arylative alkene **8** as a major product under optimized conditions.[14] The alkynyl carbamate **9** gave the desired 9-spirofluorene **10** together with the non-arylated **11**. The background cyclization that was probably catalyzed by the Cu(I) salt itself, rather than the Ar–Cu(III) species, occurred owing to a more nucleophilic character in the nitrogen atom than the oxygen atom. As expected, 9-spiroxanthene **13** was obtained in 76% yield from the phenoxy-substituted **12**. Treatment of dihydrofuran **2a** with the Selectfluor afforded the fluorinated 9-spirofluorene **14** in moderate yield.



In summary, this work demonstrates a tandem arylative cyclization and spirocyclization to form various 9-spirofluorenes and 9-spiroxanthene by taking advantage of the nature of the arylative cyclization, namely the formation of an electron-rich double bond intermediate and acid byproduct. Current efforts in our group are now focused on expanding the scope of these reactions to other substrates.

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SUPPORTING INFORMATION

Supplementary (synthesis of 9-spirofluorenes, IR, ^{1}H and ^{13}C NMR, MS spectra, etc.) data associated with this article can be found, in the online version, at URL: https://www.heterocycles.jp/newlibrary/downloads/PDFsi/26241/101/2.

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12. CCDC 1916219 (**3a**), and 1916221 (**4a**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.

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