

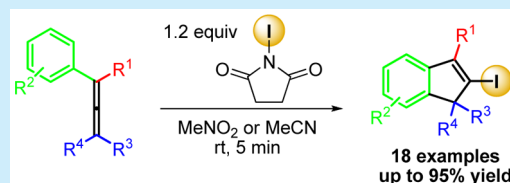
# Synthesis of Polysubstituted 2-Iodoindenes via Iodonium-Induced Cyclization of Aryllallenes

Charlotte Grandclaudon, Véronique Michelet,\* and Patrick Y. Toullec\*,†

PSL Research University, Chimie ParisTech-CNRS, Institut de Recherche de Chimie Paris, F-75005 Paris, France

**S** Supporting Information

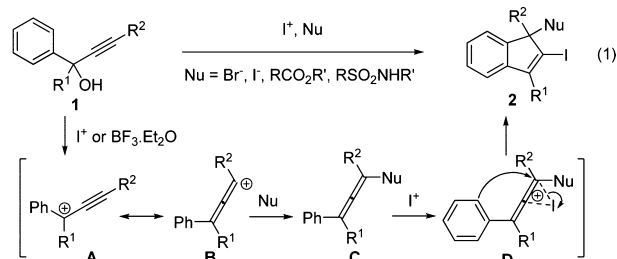
**ABSTRACT:** A new chemoselective iodocarbocyclization of allenyl arenes was developed leading to the formation of 2-iodoindenes. In acetonitrile or nitromethane, electrophilic sources of iodine cations react selectively with the C<sub>2</sub>–C<sub>3</sub> double bond of 1-aryllallenes to give, after *anti* nucleophilic attack of the aromatic ring, 2-iodoindene products in high yields. Variations of the allenic skeletons revealed the high 5-*endo* selectivity and some competitive pathways of cyclization. Postfunctionalization reactions of the carbon–iodine bond, via Pd- and Cu-cross-couplings, gave rise to substituted indenenes in good to excellent yields.



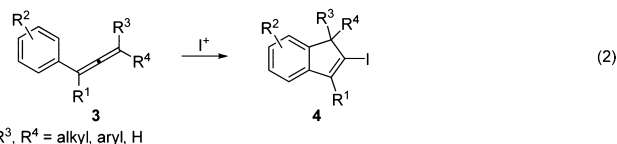
Polysubstituted indene derivatives are an important class of compounds which is found in a number of biologically active molecules.<sup>1</sup> This structural unit also serves as building blocks for the synthesis of optoelectronic devices in material sciences<sup>2</sup> and as ligand precursors in homogeneous catalysis.<sup>3</sup> Considering the interest for this scaffold and the need for synthetic methodologies enabling the introduction of substituent diversity upon postfunctionalization, some effort has been devoted to the synthesis of 2- and 3-haloindenes.<sup>4–7</sup> Among the various routes developed, the strategies based on the electrophilic activation of a C–C unsaturation followed by the intramolecular attack of a carbon nucleophile play a pivotal role as they allow the formation of complex, polysubstituted structures from simple precursors in one step using an efficient and atom-economical protocol.<sup>8</sup> So far, much attention has been paid to methodologies involving the activation of an alkyne function either in the presence of protic<sup>5</sup> or halogen<sup>6</sup> electrophiles delivering the 3-iodoindene isomer. More recently, methodologies involving iodonium-induced activation of propargylic alcohol substrates have offered the opportunity to synthesize functionalized 2-iodoindenyl products via a tandem reaction<sup>7</sup> in the presence of a second nucleophile (Scheme 1, eq 1). The mechanism of such transformations involves the initial formation of a propargylic carbocation **A** upon reaction between an electrophilic iodine reagent or boron trifluoride diethyl etherate and the propargylic alcohol substrate. Isomerization of **A** to the allenyl cation **B** followed by nucleophilic addition of a variety of nucleophiles including halides,<sup>7a,c</sup> esters,<sup>7d</sup> and sulfonamides,<sup>7b,e</sup> delivers the aryllallene **C**. Formation of an iodonium ion **D** upon further reaction of **C** with a second equivalent of cationic iodine atom followed by *anti* 5-*endo* nucleophilic attack of the aryl group gives the functionalized 2-iodoindene **2**. Considering the versatility of the carbocyclization reactions promoted by halogen electrophiles<sup>9</sup> and prior reports in the literature illustrating the possibility to activate allene unsaturations with halogen electrophiles toward *anti* nucleophilic arylation reactions,<sup>10</sup> we decided to investigate the formation of 2-iodoindenes **4** using an unprecedented

## Scheme 1. Approaches to 2-Iodoindenes

Previous works:



This work:





methodology based on the electrophilic iodocarbocyclization of tri- and tetrasubstituted aryllallenes<sup>11</sup> **3** (Scheme 1, eq 2).

Based on these considerations, the iodocarbocyclization of **3a**, which possesses a phenyl substituent, was investigated in the presence of an iodonium source using a variety of conditions. Results are reported in Table 1. Treatment of the allene **3a** with *N*-iodosuccinimide **6a** in dichloromethane at room temperature provided a mixture of the desired cyclized iodoindene **4a** along with the undesired 2-iodo-1,3-diene **5a** in 24% and 72% yields respectively (entry 1). When the reaction was performed in toluene, a lower conversion of **3a** (77%) and the exclusive formation of the diene **5a** were monitored (entry 2). Interestingly, using polar solvents such as nitromethane and acetonitrile, a reversal of selectivity was observed, leading to the formation of the halogenated indene product **4a** in 69% and 74% respectively (entries 3–4). In contrast, the use of DMF as

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Table 1. Optimization of Reaction Conditions<sup>a</sup>

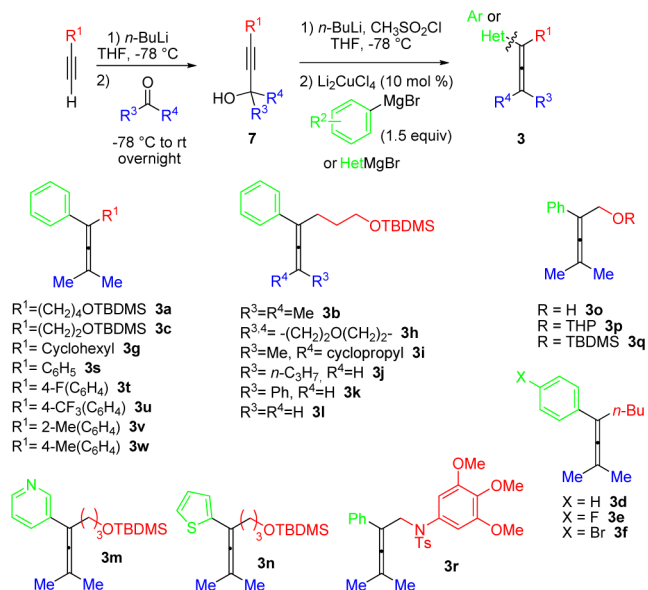
entry	[I <sup>+</sup> ] source	solvent	concn (M)	4a/5a yield <sup>b</sup> (%)
1		CH <sub>2</sub> Cl <sub>2</sub>	0.1	24/72
2 <sup>c</sup>	<b>6a</b>	PhMe	0.1	-/44
3	<b>6a</b>	MeNO <sub>2</sub>	0.1	69/23
4	<b>6a</b>	MeCN	0.1	74/19
5	<b>6a</b>	DMF	0.1	5/58
6 <sup>d</sup>	<b>6a</b>	MeCN	0.1	67/16
7	I <sub>2</sub>	MeNO <sub>2</sub>	0.1	-/ - <sup>e</sup>
8		MeCN	0.1	69/10
9	<b>6a</b>	MeCN	0.05	71/20
10	<b>6a</b>	MeCN	1	73/21
11 <sup>f</sup>	<b>6a</b>	MeCN	0.1	67/22

<sup>a</sup>All reactions were run under the following conditions, unless otherwise indicated: 0.1 mmol of **3a**, 0.12 mmol of the halogen source **6** were placed in a tube with 1 mL of solvent at room temperature for 5 min. The reaction mixture is then treated with 1 mL of aq saturated Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub>. <sup>b</sup>Yields were determined by <sup>1</sup>H NMR using acenaphthene as a standard. <sup>c</sup>77% conversion. <sup>d</sup>Reaction run at -30 °C. <sup>e</sup>Degradation of **3a**. <sup>f</sup>1 equiv instead of 1.2 equiv of **6a** was used.

solvent gave only trace amounts of **4a** and 58% of the diene **5a** (entry 5). Decreasing the temperature had a detrimental effect on the yield of the cyclized product (entry 6). Other sources of electrophilic iodine were also tested: when employing I<sub>2</sub>, only degradation was observed (entry 7), whereas, in the presence of the diiodohydantoin **6b**, a good yield of the iodoindene (**69%**) **4a** was obtained (entry 8). The concentration of the substrate did not show any significant impact on the yield or selectivity of the transformation (entries 9, 10). Finally, diminishing the quantity of halogenating agent **6a** resulted in a slightly lower yield (entry 11).

We prepared a set of variously substituted aryllallenes by a two-step methodology starting from terminal alkynes (Scheme 2). Formation of propargylic alcohols **7** occurred upon nucleophilic attack of the alkynyl lithium intermediates on carbonyl derivatives. Introduction of the aryl substituent was conducted via a Li<sub>2</sub>CuCl<sub>4</sub>-catalyzed SN<sub>2</sub>' attack of aryl or heteroaryl Grignard reagents on the *in situ* formed mesylates derived from **7**.<sup>12</sup> Variation of the allenyl skeleton was envisaged on the 4 positions, starting from R<sup>1</sup>. Alkyl as well as functionalized alkyl groups were tolerated during the starting material preparation process and led to **3a–d**, **3f**, **3g**, and **3o–r** in good yields (see Supporting Information). In order to evaluate the influence of the substitution on the aromatic moiety during the cyclization process, we prepared several diaryl-functionalized allenes **3t–w**, bearing electron-withdrawing and electron-donating groups. Considering the importance of organofluorine and heterocycle compounds in various areas including pharmaceuticals and agrochemicals, we prepared **3e**, **3m**, and **3n** bearing fluoroaryl, pyridinyl, and thiophenyl

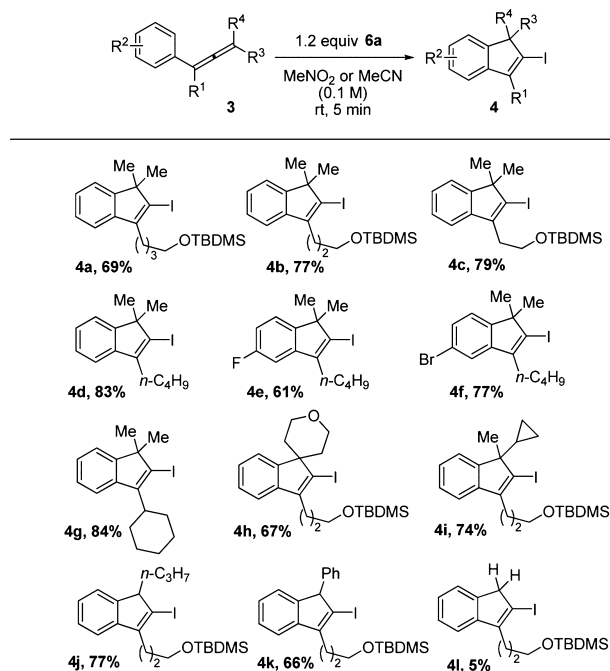
Scheme 2. Synthesis of Aryllallenes 3



groups. Modifications on R<sup>3</sup>/R<sup>4</sup> positions were also performed, as exemplified by the synthesis of **3h–l**.

We then studied the scope of the iodonium-induced carbocyclization under the optimized conditions. The reaction proceeded in good yields for a large spectrum of primary and secondary alkyl substituents on position 1 (Scheme 3, products **4a–f**). The

Scheme 3. Substrate Scope of the Iodonium-Induced Carbocyclization of Aryllallenes 3a–l

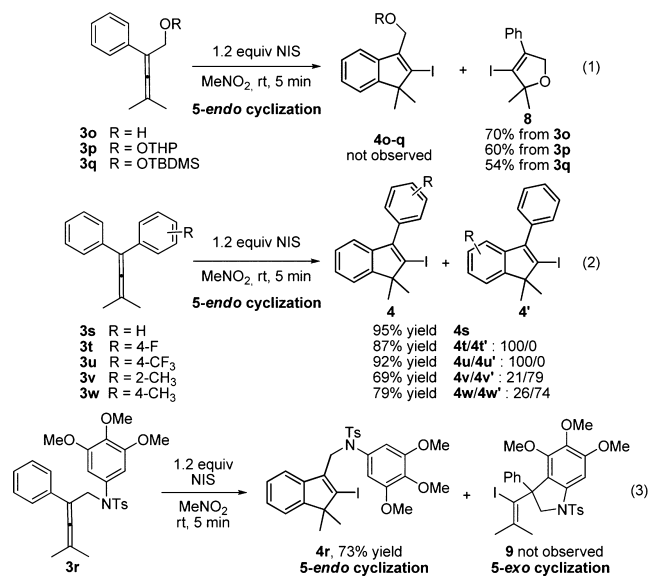


formation of the 2-iodo-1,3-diene byproduct **5** was only observed in the case of substrates **3a**, **3e**, and **3f** (14% and 5% yield for **5e** and **5f** respectively). The presence of an electron-withdrawing halogen atom on the aromatic ring nucleophile had a negative influence on the yield (83%, 77%, and 61% products **4d**, **4f**, and **4e** respectively). Cyclization of allenes bearing an aromatic heterocycle hardly occurred; we

observed only decomposition of substrates **3m** under the reaction conditions, and only traces of **4n** could be monitored in the case of thienylallene **3n**. The variation of the substitution pattern on the 3 position of the allene ( $R^3$  and  $R^4$  groups) was also studied. With a substrate bearing a tetrahydropyranyl substituent instead of the dimethyl group, the reaction provided the spirocycle **4h** in 67% yield. The allene **3i** with a methyl-cyclopropyl combination of substituents was cleanly converted to **4i** in good yield (74%). The reaction also took place for substrates bearing a single substituent on position 3 (alkyl or aryl); the cyclized products **4j** and **4k** were isolated in 77% and 66% yields, respectively. Finally, the terminal allene **3l** was also submitted to the intramolecular iodocyclization conditions. Decomposition was observed in this case, the 2-iodoindene **4l** being isolated with a very low yield.

To further investigate the scope of this reaction, we decided to study the iodocyclization of aryllallene substrates bearing a second nucleophile able to react via a 5-*endo* mode of cyclization. In the case of substrates **3o–q**, exclusive formation of the 3-iododihydrofuran **8**, resulting from the attack of the oxygen nucleophile, occurred in 54–70% yield, whereas the corresponding iodoindenes **4o–q**, resulting from the attack of the phenyl nucleophile, could not be monitored (Scheme 4, eq 1).

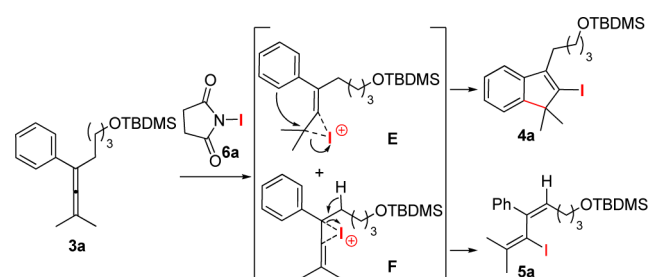
**Scheme 4. Regio- and Chemoselectivity Issues of the Iodocarbocyclization of Aryllallenes 3o–w**



The length of the tether between the allene function and the oxygen nucleophile therefore had a crucial impact on the chemoselectivity, as no product resulting from the attack of the oxygen nucleophile was detected in the case of substrates **3a–c** and **3h–l**. We also challenged the iodonium-induced cyclization on 1,1-diaryllallenes in order to evaluate the importance of the nucleophilicity of the aromatic substituent on the course of the reaction (Scheme 4, eq 2). In the case of the symmetric diphenyl-substituted substrate **3s**, the reaction proceeded with an excellent yield of 95%. For substrates where the phenyl group was placed in competition with an aromatic ring bearing an electron-withdrawing substituent, the chemoselectivity was excellent and only the products **4t** and **4u** resulting from the attack of the phenyl ring was observed. When electron-donating groups were placed in competition with the phenyl, a moderate

regioselectivity in favor of the 2-iodoindenes **4v'** and **4w'** resulting from the attack of the more electron-rich aryl moiety was observed in both cases. Very interestingly, substrate **3r** also cleanly reacted via a 5-*endo* attack of the phenyl nucleophile to give the iodoindene **4r**, whereas the competitive 5-*exo* cyclization of the electron-rich trimethoxyaniline nucleophile to give the iodovinylindoline **9** was not observed (Scheme 4, eq 3). Based on the experimental evidence, we proposed a mechanism for the formation of **4a** and **5a**, involving the initial formation of an iodonium cation upon reaction between the cationic iodine atom and a carbon–carbon double bond of the allene **3a**. Depending on the reaction conditions used, iodonium **E** and **F** may be formed (Scheme 5). *Anti*

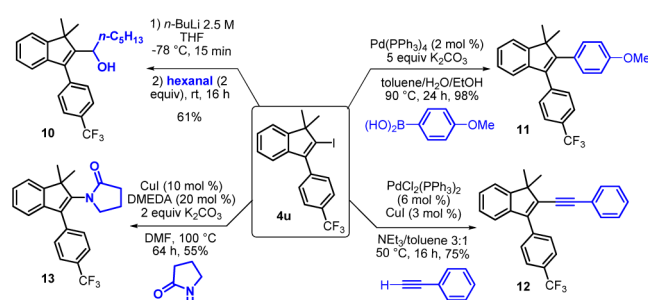
**Scheme 5. Postulated Mechanism**



nucleophilic attack of the phenyl group on iodonium **E** delivers the cyclized 2-iodoindene **4a**, whereas proton elimination from intermediate **F** leads to the formation of diene **5a**. The stereochemistry of **5a** has been confirmed by a 2D NOE NMR experiment.

The benefit of the 2-iodoindene scaffolds was finally demonstrated by conducting relevant postfunctionalization reactions on iododerivative **4u** (Scheme 6).

**Scheme 6. Derivatization of 4u**



Halogen–metal exchange<sup>13</sup> followed by trapping with an aldehyde allowed the formation of the indene **10** bearing an alcohol moiety in 61% yield. Palladium-catalyzed Sonogashira<sup>14</sup> and Suzuki–Miyaura<sup>7c</sup> cross-couplings were performed, and compounds **11** and **12** were isolated in 98% and 75% yields, respectively. A copper-catalyzed C–N coupling<sup>15</sup> involving pyrrolidin-2-one enabled the formation of the indenylamide **13** in 55% yield.

In conclusion, a new and mild protocol for the synthesis of 2-iodoindenes has been developed. In the presence of *N*-iodosuccinimide, the iodonium-induced carbocyclization of a wide set of functionalized allenes proceeded rapidly in good to excellent yields, tolerating a wide range of substituents. Variations of the allenic skeletons revealed the high 5-*endo* selectivity and some competitive pathways of cyclization.

Moreover, 2-iodoindene products can be used as key synthons for the synthesis of substituted derivatives upon functionalization of the reactive C<sub>sp</sub><sup>2</sup>–iodine bond.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03634.

Experimental procedures, characterization data and spectra of new compounds (PDF)

## ■ AUTHOR INFORMATION

### Corresponding Authors

\*veronique.michelet@chimie-paristech.fr

\*patrick.toullec@u-bordeaux.fr

### Present Address

<sup>†</sup>Univ. Bordeaux, Institute of Molecular Sciences, UMR 5255, F-33400 Talence, France.

### Notes

The authors declare no competing financial interest.

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## ■ REFERENCES

- (1) (a) Witak, D. T.; Kakodkar, S. V.; Brunst, G. E.; Baldwin, J. R.; Rahwan, R. G. *J. Med. Chem.* **1978**, *21*, 1313. (b) Korach, K. S.; Metzler, M.; McLachlan, J. A. *J. Biol. Chem.* **1979**, *254*, 8963. (c) Anstead, G. M.; Peterson, C. S.; Pinney, K. G.; Wilson, S. R.; Katzenellenbogen, J. A. *J. Med. Chem.* **1990**, *33*, 2726. (d) Palm, J.; Boegesoe, K. P.; Liljefors, T. *J. Med. Chem.* **1993**, *36*, 2878. (e) Huang, H.-C.; Chamberlain, T. S.; Selbert, K.; Koboldt, C. M.; Isakson, P. C.; Reitz, D. B. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 2377. (f) Hagishita, S.; Yamada, M.; Shirahase, K.; Okada, T.; Murakami, Y.; Ito, Y.; Matsuura, T.; Wada, M.; Kato, T. *J. Med. Chem.* **1996**, *39*, 3636. (g) Gao, H.; Katzenellenbogen, J. A.; Garg, R.; Hansch, C. *Chem. Rev.* **1999**, *99*, 723. (h) Korte, A.; Legros, J.; Bolm, C. *Synlett* **2004**, 2397. (i) Wang, Y.; Mo, S.-Y.; Wang, S.-J.; Li, S.; Yang, Y.-C.; Shi, J.-G. *Org. Lett.* **2005**, *7*, 1675. (j) Clegg, N. J.; Paruthiyil, S.; Leitman, D. C.; Scanlan, T. S. *J. Med. Chem.* **2005**, *48*, 5989. (k) Huffman, J. W.; Padgett, L. W. *Curr. Med. Chem.* **2005**, *12*, 1395. (l) Alcalde, E.; Mesquida, N.; López-Pérez, S.; Frigola, J.; Mercé, R. *J. Med. Chem.* **2009**, *52*, 675.
- (2) (a) Grimsdale, A. C.; Mullen, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 5592. (b) Levi, Z. U.; Tilley, T. D. *J. Am. Chem. Soc.* **2010**, *132*, 11012. (c) Zeng, X.; Ilies, L.; Nakamura, E. *J. Am. Chem. Soc.* **2011**, *133*, 17638.
- (3) (a) Halterman, R. L. *Chem. Rev.* **1992**, *92*, 965. (b) Cadierno, V.; Diez, J.; Pilar Gamasa, M.; Gimeno, J.; Lastra, E. *Coord. Chem. Rev.* **1999**, *193–195*, 147. (c) Alt, H. G.; Köppl, A. *Chem. Rev.* **2000**, *100*, 1205. (d) Zargarian, D. *Coord. Chem. Rev.* **2002**, *233–234*, 157.
- (4) For selected examples, see: (a) Roussel, C.; Rajoharison, H. G.; Bizzari, S. L. *J. Org. Chem.* **1988**, *53*, 683. (b) Ivchenko, N. B.; Ivchenko, P. V.; Nifant'ev, I. E.; Kotov, V. V. *Russ. Chem. Bull.* **2000**, *49*, 942. (c) Tutar, A.; Cakmak, O.; Balci, M. *Tetrahedron* **2001**, *57*, 9759. (d) Zhou, X.; Zhang, H.; Xie, X.; Li, Y. *J. Org. Chem.* **2008**, *73*, 3958. (e) Ye, S.; Gao, K.; Zhou, H.; Yang, X.; Wu, J. *Chem. Commun.* **2009**, *36*, 5406. (f) Zhou, F.; Han, X.; Lu, X. *J. Org. Chem.* **2011**, *76*, 1491. (g) Akbar, S.; Srinivasan, K. *RSC Adv.* **2015**, *5*, 5542.
- (5) Saito, S.; Homma, M.; Gevorgyan, V.; Yamamoto, Y. *Chem. Lett.* **2000**, 722.
- (6) (a) Khan, Z. A.; Wirth, T. *Org. Lett.* **2009**, *11*, 229. (b) Sanz, R.; Martínez, A.; García-García, P.; Fernández-Rodríguez, M. A.; Rashid, M. A.; Rodríguez, F. *Chem. Commun.* **2010**, *46*, 7427.
- (7) (a) Zhu, H.-T.; Ji, K.-G.; Yang, F.; Wang, L.-J.; Zhao, S.-C.; Ali, S.; Liu, X.-Y.; Liang, Y.-M. *Org. Lett.* **2011**, *13*, 684. (b) Zhu, Y.; Yin, G.; Hong, D.; Lu, P.; Wang, Y. *Org. Lett.* **2011**, *13*, 1024. (c) Zhou, C.; Chen, X.; Lu, P.; Wang, Y. *Tetrahedron* **2012**, *68*, 2844. (d) Zhu, H.-T.; Dong, X.; Wang, L.-J.; Zhong, M.-J.; Liu, X.-Y.; Liang, Y.-M. *Chem. Commun.* **2012**, *48*, 10748. (e) Sun, L.; Zhu, Y.; Wang, J.; Lu, P.; Wang, Y. *Org. Lett.* **2015**, *17*, 242.
- (8) (a) Larock, R. C. In *Acetylene Chemistry. Chemistry, Biology, and Material Science*; Diederich, F., Stang, P. J., Tykewinski, R. R., Eds.; Wiley-VCH: New York, 2005; Chapter 2, pp 51–99. (b) *Modern Alkyne Chemistry*, Trost, B. M., Li, C.-J., Eds.; Wiley-VCH: New York, 2015.
- (9) For reviews, see: (a) Rousseau, G.; Homsy, F. *Chem. Soc. Rev.* **1997**, *26*, 453. (b) Yamamoto, Y.; Gridnev, I. D.; Patil, N. T.; Jin, T. *Chem. Commun.* **2009**, *34*, 5075. (c) Godoi, B.; Schumacher, R. F.; Zeni, G. *Chem. Rev.* **2011**, *111*, 2937. (d) Palisse, A.; Kirsch, S. F. *Org. Biomol. Chem.* **2012**, *10*, 8041. (e) Hummel, S.; Kirsch, S. F. *Beilstein J. Org. Chem.* **2011**, *7*, 847.
- (10) For examples of iodoarylation of allenes, see: (a) Barluenga, J.; Campos-Gomez, E.; Minatti, A.; Rodriguez, D.; Gonzalez, J. M. *Chem. - Eur. J.* **2009**, *15*, 8946. (b) Wang, M.; Li, J.; Fu, C.; Ma, S. *Org. Lett.* **2014**, *16*, 4976.
- (11) For a single example of bromocarbocyclization of xanthenyl- and thioxanthenylallenes, see: Abdul-Malik, N. F.; Awad, S. B.; Sakla, A. B. *Helv. Chim. Acta* **1979**, *62*, 1872. No indication of yield for the transformation is given in this publication.
- (12) Fouquet, G.; Schlosser, M. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 82.
- (13) Nowrouzi, F.; Janetzko, J.; Batey, R. A. *Org. Lett.* **2010**, *12*, 5490.
- (14) Barluenga, J.; Palomas, D.; Rubio, E.; González, J. M. *Org. Lett.* **2007**, *9*, 2823.
- (15) Jiang, L.; Job, G. E.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 3667.