Electrophilic Carbocyclization of Aryl Propargylic Alcohols: A Facile Synthesis of Diiodinated Carbocycles and Heterocycles
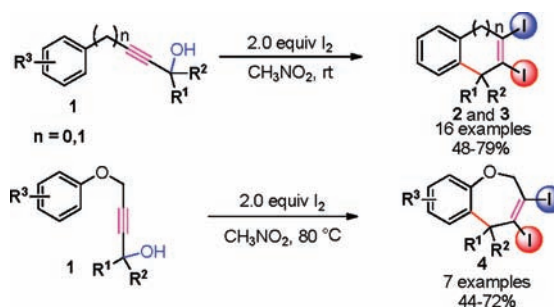
Hai-Tao Zhu, Ke-Gong Ji, Fang Yang, Li-Jing Wang, Shu-Chun Zhao, Shaukat Ali, Xue-Yuan Liu, and Yong-Min Liang*

State Key Laboratory of Applied Organic Chemistry, Lanzhou University, and State Key Laboratory of Solid Lubrication, Lanzhou Institute of Chemical Physics, Chinese Academy of Science, Lanzhou 730000, P.R. China

liangym@lzu.edu.cn

ABSTRACT

Diiodinated carbocycles and oxygen heterocycles can be readily synthesized by electrophilic carbocyclization of aryl propargylic alcohols in moderate to good yields under mild conditions. The resulting diiodide can be further exploited by subsequent oxidizing and coupling reactions. Both the iodine anion and cation generated from I_2 are used effectively. The presence of a trace amount of water is essential for this electrophilic cyclization.

Recently, the intramolecular electrophilic cyclization of nucleophiles, such as oxygen, nitrogen, sulfur, phosphorus, and also sp^2 or sp^3 hybridized carbon, with alkynes has proven to be an effective method for the synthesis of carbocyclic and heterocyclic compounds.[1–11] Many important heterocycles and carbocycles, such as furans,[1] benzo[b]-furans,[2] pyrroles,[3] indoles,[4] isoquinolines,[5] quinolines,[6] benzo[b]thiophenes,[7] phosphaisocoumarins,[8] naphthols,[9]

(1) (a) Kruglov, A. A. *Zh. Obshch. Khim.* **1937**, *7*, 2605. (b) Huang, X.; Fu, W.; Miao, M. *Tetrahedron Lett.* **2008**, *49*, 2359. (c) Zhou, H.; Yao, J.; Liu, G. *Tetrahedron Lett.* **2008**, *49*, 226. (d) Liu, Y.; Zhou, S. *Org. Lett.* **2005**, *7*, 4609. (e) Bew, S. P.; Knight, D. W. *J. Chem. Soc., Chem. Commun.* **1996**, 1007. (f) El-Taeb, G. M. M.; Evans, A. B.; Knight, D. W.; Jones, S. *Tetrahedron Lett.* **2001**, *42*, 5945. (g) Sniady, A.; Wheeler, K. A.; Dembinski, R. *Org. Lett.* **2005**, *7*, 1769. (h) Liu, Y.-H.; Song, F.-J.; Cong, L. Q. *J. Org. Chem.* **2005**, *70*, 6999.

(2) (a) Banwell, M. G.; Flynn, B. L.; Wills, A. C.; Hamel, E. *Aust. J. Chem.* **1999**, *52*, 767. (b) Arcadi, A.; Cacchi, S.; Fabrizi, G.; Marinelli, F.; Moro, L. *Synlett* **1999**, 1432. (c) Arcadi, A.; Cacchi, S.; Di Giuseppe, S.; Fabrizi, G.; Marinelli, F. *Org. Lett.* **2002**, *4*, 2409. (d) Yue, D.; Yao, T.; Larock, R. C. *J. Org. Chem.* **2005**, *70*, 10292. (e) Mehta, S.; Waldo, J. P.; Larock, R. C. *J. Org. Chem.* **2009**, *74*, 1141.

(3) (a) Yoshida, M.; Al-Amin, M.; Shishido, K. *Tetrahedron Lett.* **2009**, *50*, 6268. (b) Knight, D. W.; Redfern, A. L.; Gilmore, J. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2874. (c) Knight, D. W.; Redfern, A. L.; Gilmore, J. *J. Chem. Soc., Perkin Trans. 1* **2002**, 622.

(4) (a) Barluenga, J.; Trincado, M.; Rublio, E.; Gonzalez, J. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 2406. (b) Amjad, M.; Knight, D. W. *Tetrahedron Lett.* **2004**, *45*, 539. (c) Yue, D.; Larock, R. C. *Org. Lett.* **2004**, *6*, 1037.

(5) (a) Huang, Q. H.; Hunter, J. A.; Larock, R. C. *Org. Lett.* **2001**, *3*, 2973. (b) Huang, Q. H.; Hunter, J. A.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 3437. (c) Fischer, D.; Tomeba, H.; Pahadi, N. K.; Patil, N. T.; Huo, Z.; Yamamoto, Y. *J. Am. Chem. Soc.* **2008**, *130*, 15720. (d) Yamamoto, Y.; Gridnev, I. D.; Patil, N. T.; Jin, T. *Chem. Commun.* **2009**, 5075. (e) Fischer, D.; Tomeba, H.; Pahadi, N. K.; Patil, N. T.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 4764. (f) Huo, Z.; Tomeba, H.; Yamamoto, Y. *Tetrahedron Lett.* **2008**, *49*, 5531.

naphthalenes,[10] and indenes[11] have been accessed using this protocol. However, the electrophilic carbocyclization with allenes has often been considered to be less attractive due to the lack of efficient control of the regio- and stereoselectivity.[12] Not long ago, Barluenga and co-workers reported an interesting carbocyclization of allenes to halogenated dihydronaphthalene in the presence of electrophiles. But the use of expensive $I(py)_2BF_4$, and the relatively low temperature make this approach a bit limited synthetically.[13]

Scheme 1. Design of an Electrophile-Promoted Domino Process
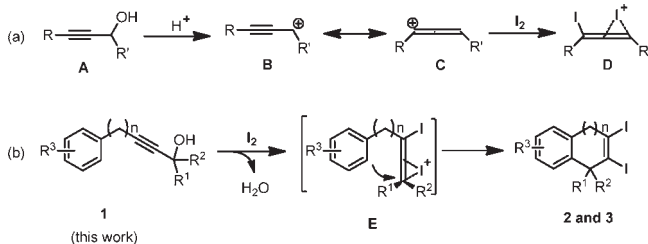
On the basis of our previous work, we have found that in the presence of protons, substrate **A** loses a hydroxyl group to afford the intermediate propargyl carbocations **B**. **B**, in resonance with allene cation **C**, reacts with an iodide anion to give **D**, which can be activated by an iodide cation (Scheme 1a).[14] We envisioned that aryl propargylic alcohols could also undergo the same transformation in the presence of iodine and then can cyclize to give diiodinated carbocycles (Scheme 1 b). Herein, we report an effective method for the synthesis of five- and six-membered carbocyclic rings and seven-membered heterocyclic rings in the presence of I_2.

Our initial study began with 1,3-diphenylprop-2-yn-1-ol (**1a**) (0.3 mmol) and 1.2 equiv of I_2 in wet CH_3NO_2 at room temperature; to our delight, the desired product, 2,3-diiodo-1-phenyl-1H-indene (**2a**), was isolated in 51% yield

(6) (a) Zhang, X.; Campo, M. A.; Yao, T.; Larock, R. C. *Org. Lett.* **2005**, *7*, 763. (b) Zhang, X.; Yao, T.; Campo, M. A.; Larock, R. C. *Tetrahedron* **2010**, *66*, 1177. (c) Huo, Z.; Gridnev, I. D.; Yamamoto, Y. *J. Org. Chem.* **2010**, *75*, 1266.

(7) (a) Flynn, B. L.; Verdier-Pinard, P.; Hamel, E. *Org. Lett.* **2001**, *3*, 651. (b) Yue, D.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 1905. (c) Hessian, K. O.; Flynn, B. L. *Org. Lett.* **2003**, *5*, 4377.

(8) (a) Peng, A. Y.; Ding, Y. X. *Org. Lett.* **2004**, *6*, 1119. (b) Peng, A. Y.; Ding, Y. X. *Tetrahedron* **2005**, *61*, 10303.

(9) (a) Zhang, X.; Sarkar, S.; Larock, R. C. *J. Org. Chem.* **2006**, *71*, 236. (b) Barluenga, J.; Vazque-Villa, H.; Merino, I.; Ballesteros, A.; Gonzalez, J. M. *Chem.—Eur. J.* **2006**, *12*, 5790.

(10) Barluenga, J.; Vazquez-Villa, H.; Ballesteros, A.; Gonzalez, J. M. *Org. Lett.* **2003**, *5*, 4121.

(11) (a) Khan, Z. A.; Wirth, T. *Org. Lett.* **2009**, *11*, 229. (b) Bi, H.-P.; Guo, L.-N.; Duan, X.-H.; Gou, F.-R.; Huang, S.-H.; Liu, X.-Y.; Liang, Y.-M. *Org. Lett.* **2007**, *9*, 397.

(12) (a) Li, J.; Kong, W.; Yu, Y.; Fu, C.; Ma, S. *J. Org. Chem.* **2009**, *74*, 8733. (b) Ma, S. *Acc. Chem. Res.* **2009**, *42*, 1679. (c) Li, W.; Shi, M. *J. Org. Chem.* **2008**, *73*, 6698.

(13) Barluenga, J.; Campos-Gomez, E.; Minatti, A.; Rodriguez, D.; Gonzalez, J. M. *Chem.—Eur. J.* **2009**, *15*, 8946.

(14) (a) Ji, K.-G.; Zhu, H.-T.; Yang, F.; Shaukat, A.; Xia, X.-F.; Yang, Y.-F.; Liu, X.-Y.; Liang, Y.-M. *J. Org. Chem.* **2010**, *75*, 5670. (b) Ji, K.-G.; Shu, X.-Z.; Zhao, S.-C.; Zhu, H.-T.; Niu, Y.-N.; Liu, X.-Y.; Liang, Y.-M. *Org. Lett.* **2009**, *11*, 3206. (c) Ji, K.-G.; Zhu, H.-T.; Yang, F.; Shu, X.-Z.; Zhao, S.-C.; Shaukat, A.; Liu, X.-Y.; Liang, Y.-M. *Chem.—Eur. J.* **2010**, *16*, 6151.

Table 1. Optimization of the Electrophilic Cyclization of 1,3-Diphenylprop-2-yn-1-ol[a]

| entry	solvent	I_2 (equiv)	time (h)	yield (%)[b]
1	CH_3NO_2	1.2	0.5	51
2	CH_3NO_2	1.5	0.5	63
3	CH_3NO_2	2.0	0.5	70
4	CH_3NO_2	3.0	0.5	69
5	CH_3NO_2	2.0	6.0	63
6	CH_2Cl_2	2.0	0.5	52
7	CH_3CN	2.0	0.5	48
8	$ClCH_2CH_2Cl$	2.0	0.5	7
9	1,4-dioxane	2.0	0.5	nr
10	$(CH_3CH_2)_2O$	2.0	0.5	nr

[a] All reactions were run under the following conditions, unless otherwise indicated: 0.3 mmol of **1a** with 2.0 equiv of I_2 in 5 mL of wet CH_3NO_2 at room temperature. [b] nr = no reaction.

after 0.5 h (Table 1, entry 1). On increasing the amount of I_2 to 1.5 equiv, a 63% yield of **2a** was obtained after 0.5 h (Table 1, entry 2). On further increasing the amount of I_2 to 2.0 equiv, a 70% yield of **2a** was obtained (Table 1, entry 3). Increasing the amounts of I_2 to 3.0 equiv gave the slightly decreased yield of 69% (entry 4). Prolonging the reaction time to 6 h decreased the yield to 63% (entry 5). The study of the influence of different reaction media showed that CH_2Cl_2, $ClCH_2CH_2Cl$, and CH_3CN were less effective (entries 6−8), whereas 1,4-dioxane and diethyl ether proved to be ineffective (entries 9 and 10). The optimum reaction conditions thus developed are the following: 1.0 equiv of **1a** and 2.0 equiv I_2 in CH_3NO_2 (5.0 mL) at room temperature.

After having established the optimized conditions for the present reaction, various 1,3-diphenylprop-2-yn-1-ol derivatives **1a−j** were subjected to the above conditions, as depicted in Table 2. Thus, the tandem carbon−carbon bond formations of 1,3-diphenylprop-2-yn-1-ol derivatives **1a−j** proceeded smoothly to provide the corresponding products **2a−j** in moderate to good yields. The reaction could tolerate various substituents on the aromatic R^2 groups. Electron-withdrawing aryl groups showed a bit better result than those with electron-rich groups in this tandem reaction (entries 2−6). Interestingly, substrates like **1h−j** with aliphatic groups also gave the corresponding 2,3-diiodocarbocyclic compounds **2h−j** in moderate yields.

Noteworthily, we also investigated the reaction of 5 mmol of **1a** in the presence of 2.0 equiv of I_2; the desired product 2,3-diiodo-1-phenyl-1H-indene was obtained in 64% yield after 1 h. Furthermore, when using IBr as the electrophilic reagent, substrates 1,3-diphenylprop-2-yn-1-ol (**1a**) and 1-(4-methoxyphenyl)-3-phenylprop-2-yn-1-ol (**1b**) can also afford the desired products 3-bromo-2-iodo-1-phenyl-1H-indene (**5a**) and 3- bromo-2-iodo-1-(4-methoxyphenyl)-1H-indene (**5b**) in 68% and 87% yield, respectively (Scheme 2).

Table 2. Synthesis of 2,3-Diiodophenylindenes **2** from 1,3-Diphenylprop-2-yn-1-ol Derivatives **1** [a]
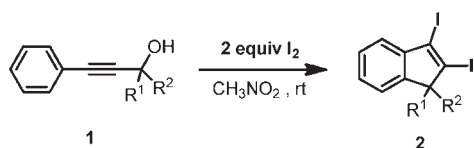
entry	substrate	product	yield(%)[b]
1	R^1 = H, R^2 = Ph	**2a**	70
2	R^1 = H, R^2 = p-MeOC$_6$H$_4$	**2b**	74
3	R^1 = H, R^2 = p-MeC$_6$H$_4$	**2c**	75
4	R^1 = H, R^2 = m-MeC$_6$H$_4$	**2d**	68
5	R^1 = H, R^2 = p-ClC$_6$H$_4$	**2e**	78
6	R^1 = H, R^2 = p-BrC$_6$H$_4$	**2f**	79
7	R^1 = H, R^2 = benzo[1,3]dioxole	**2g**	58
8		**2h**	73[c]
9		**2i**	72[c]
10		**2j**	78[c]

[a] All reactions were run under the following conditions, unless otherwise indicated: 0.3 mmol of **1** with 2.0 equiv of I$_2$ in 5 mL of CH$_3$NO$_2$ at room temperature. [b] Isolated yield. [c] The reaction was carried out at 40 °C.

To explore the scope of this carbocyclization further, we also investigated a range of 1,4-diphenylbut-2-yn-1-ol derivatives **1k−p**. Substrates such as 1,4-diphenylbut-2-yn-1-ol (**1k**) led to the desired product 2,3-diiodo-1-phenyl-1,4-dihydronaphthalene (**3k**) in 78% yield under the optimized condition (Table 3, entry 1). Substituted aryl propargylic acohols **1l−p** were also employed in the reaction, and the corresponding six-membered ring products **3l−p** were isolated in moderate yields.

Seven-membered heterocyclic rings are important intermediates for the synthesis of pharmaceuticals and biologically active molecules.[15] Constructing seven-membered rings through transition metal-catalyzed cyclizations has been accessed.[16] However, successful examples for the preparation of polyoxacyclic ring systems induced by iodine are rarely reported, possibly because of the disadvantageous influence of both entropic and enthalpic factors, as well as both electronic and steric effects. Thus, we designed the reaction of substrate 4- phenoxy-1-phenylbut-2-yn-1-ol (**1q**) in the presence of I$_2$ to construct an important

(15) (a) Rujirawanich, J.; Gallagher, T. *Org. Lett.* **2009**, *11*, 5494. (b) Batchelor, R.; Harvey, J. E.; Northcote, P. T.; Teesdale-Spittle, P.; Hoberg, J. O. *J. Org. Chem.* **2009**, *74*, 7627. (c) Furuta, H.; Hasegawa, Y.; Mori, Y. *Org. Lett.* **2009**, *11*, 4382. (d) Coulter, M. M.; Dornan, P. K.; Dong, V. M. *J. Am. Chem. Soc.* **2009**, *131*, 6932. (e) Hashimoto, T.; Naganawa, Y.; Maruoka, K. *J. Am. Chem. Soc.* **2009**, *131*, 6614.

(16) (a) Shin, S.; Gupta, A. K.; Rhim, C. Y.; Oh, C. H. *Chem. Commun.* **2005**, 4429. (b) Hildebrandt, D.; Huggenberg, W.; Kanthak, M.; Ploger, T.; Muller, I. M.; Dyker, G. *Chem. Commun.* **2006**, 2260. (c) Kim, N.; Kim, Y.; Park, W.; Sung, D.; Gupta, A. K.; Oh, C. H. *Org. Lett.* **2005**, *7*, 5289. (d) Padwa, A.; Fryxell, G. E.; Zhi, L. *J. Am. Chem. Soc.* **1990**, *118*, 3100. (e) Feldman, K. S. *Tetrahedron Lett.* **1983**, *24*, 5585.
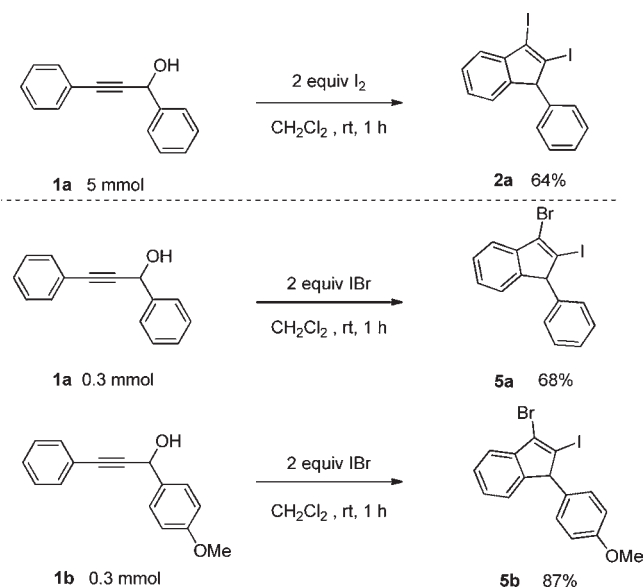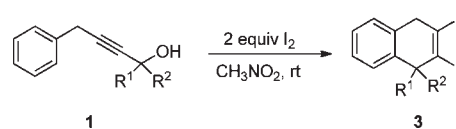
Scheme 2. Synthesis of Funtionalized Indenes

Table 3. Synthesis of 2,3-Diiodophenyldihydronaphthalene **3** from 1,4-Diphenylbut-2-yn-1-ol Derivatives **1**[a]
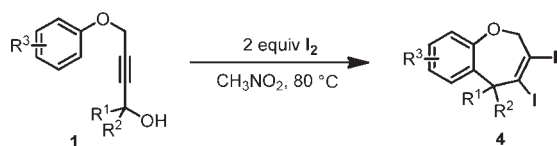
entry	substrate	product	yield (%)[b]
1	R^1 = H, R^2 = Ph	**3k**	78
2	R^1 = H, R^2 = p-MeOC$_6$H$_4$	**3l**	57
3	R^1 = H, R^2 = m-MeOC$_6$H$_4$	**3m**	48
4	R^1 = H, R^2 = o-MeOC$_6$H$_4$	**3n**	61
5	R^1 = H, R^2 = benzo[1,3]dioxole	**3o**	75
6	R^1 = H, R^2 = p-ClC$_6$H$_4$	**3p**	52

[a] All reactions were run under the following conditions, unless otherwise indicated: 0.3 mmol of 1 with 2.0 equiv of I$_2$ in 5 mL CH$_3$NO$_2$ at room temperature. [b] Isolated yield.

polycyclic structure. To our delight, the desired product 3,4-diiodo-5-phenyl-2,5-dihydrobenzo[*b*]oxepine (**4q**) was obtained in 57% yield at 80 °C (Table 4, entry 1). The molecular structure of the representative product **4q** was determined by X-ray crystallography (Figure 1). Substituted phenoxyl substrates **1r** and **1s** led to desired products **4r** and **4s** in 58% and 72% yield, respectively. Substrates such as **1u**, **1v**, and **1w**, having *p*-chloro, *p*-methoxyphenyl, and *p*-bromo substituents, produced 44%, 62%, and 54% yields of seven-membered diiodinated oxacyclic compounds, respectively.

Our study has also shown that the dihydronaphthalene **3k** can be oxidized to 2,3-diiodo-1-phenylnaphthalene (**5k**) by 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) in

Table 4. Synthesis of 3,4-Diiodophenyldihydrobenzo[*b*]-oxepines **4** from 4-Phenoxy-1-phenylbut-2-yn-1-ol Derivatives **1**[*a*]

entry	substrate (R^1, R^2, R^3)	product	yield(%)[*b*]
1	H, Ph, H	**4q**	57
2	H, Ph, *p*-MeO	**4r**	58
3	H, Ph, *p*-Me	**4s**	72
4		**4t**	52
5	H, *p*-ClC$_6$H$_4$, H	**4u**	62
6	H, *p*-MeOC$_6$H$_4$, H	**4v**	54
7	H, *p*-BrC$_6$H$_4$, H	**4w**	44

[*a*] All reactions were run under the following conditions, unless otherwise indicated: 0.3 mmol of **1** with 2.0 equiv of I_2 in 5 mL of CH$_3$NO$_2$ at 80 °C. [*b*] Isolated yield.

93% yield after 18 h. A standard feature of this process is the fact that the dihalogenated carbocyclic compounds produced by iodocyclization can be further exploited by using
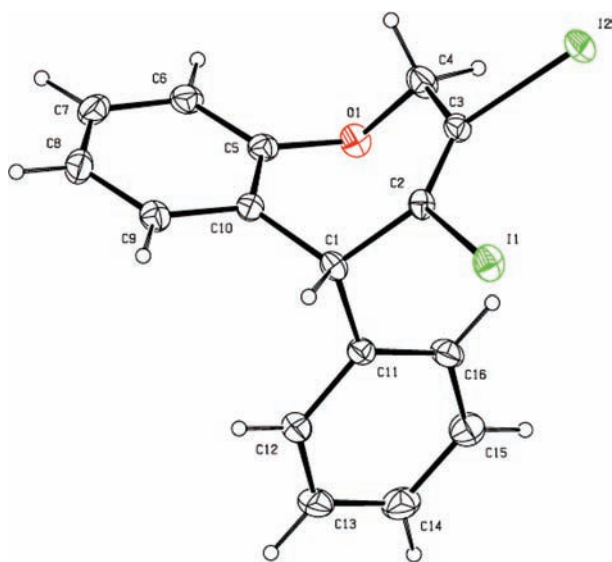

Figure 1. Structure of **4q**.

various palladium-catalyzed processes. For example, the Sonagashira coupling of 2,3-diiodo-1-phenylnaphthalene (**5k**) afforded the corresponding product 2,3-bis((4-methoxyphenyl)ethynyl)-1-phenylnaphthalene (**6k**), which may find utility as fluorescent materials, in 49% yield (Scheme 3).

Scheme 3. Palladium-Catalyzed Sonogashira Coupling Reaction
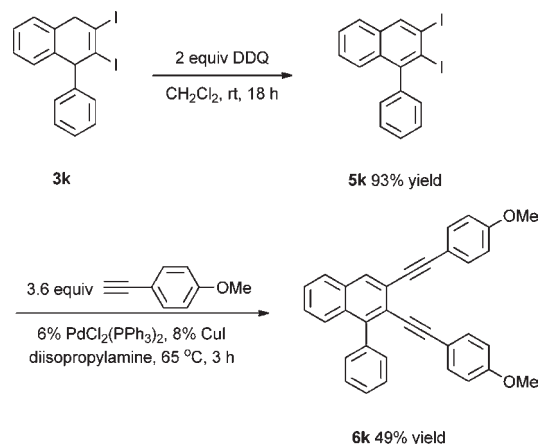
In conclusion, an efficient synthesis of substituted dihalogenated 1*H*-indenes, dihydronaphthalenes, and dihydrobenzo[*b*]oxepines in moderate yields from simple aryl propargylic alcohols under mild reaction conditions has been developed. The dihalogenated moiety can be readily introduced into the carbocycle and heterocycle in a position not easily obtained previously. The resulting diiodinated products can be used to prepare more complex products by using known organopalladium chemistry. In this reaction, both halogen atoms, such as I and Br, are used effectively and trace amounts of water are necessary. Further studies on electrophilic cyclizations of propargylic alcohols are in progress in our laboratory.

Supporting Information Available. Detailed experimental procedure and copies of ^{1}H NMR and ^{13}C NMR spectra of all compounds and X-ray data of **4q** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.