A Journal of the Gesellschaft Deutscher Chemiker

Angewandte Chemie

GDCh

International Edition

www.angewandte.org

Accepted Article

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To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.201708892
Angew. Chem. 10.1002/ange.201708892

Link to VoR: http://dx.doi.org/10.1002/anie.201708892
http://dx.doi.org/10.1002/ange.201708892

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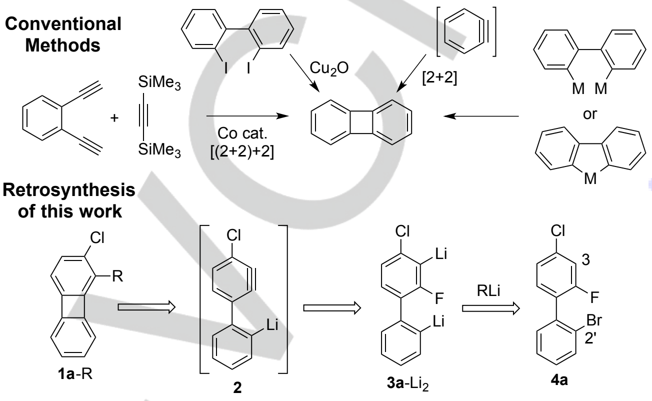
Synthesis of Biphenylenes and Their Higher Homologues by Cyclization of *In-situ* Generated Aryne Derivatives**

Sheng-Li Wang[a], Ming-Lun Pan[a], Wei-Siang Su[a], Yao-Ting Wu*[a]

Dedicated to Prof. Armin de Meijere on the occasion of his 78th birthday

Abstract: This investigation demonstrates that a series of biphenylenes can be easily prepared from their corresponding halobiphenyls by the cyclization of *in-situ* generated 2',3'-didehydro-2-lithiobiphenyls at low temperature. Two remarkable advantages of this synthetic method include 1) the lack of any need for transition metal catalysts or reagents in the cyclization, and 2) the obtaining of C-1 functionalized products by treating the reaction intermediate 1-lithiobiphenylene with an electrophilic reagent. π-Extended derivatives, such as benzobiphenylenes, dibenzobiphenylene, linear/angular [3]phenylenes and biphenyleno[2,3-*b*]biphenylenes, were synthesized similarly using suitable biaryls or teraryls.

Biphenylene is a tricyclic arene with lessened aromaticity.[1] A remarkable example is tris(benzocyclobutadieno)benzene,[2] whose central six-membered ring contains essentially localized single and double bonds, being a cyclohexatriene rather than a benzene. The presence of the four-membered rings in biphenylene and its higher homologues, [*n*]phenylenes, causes these compounds to be novel σ- and π-activated polyarenes, endowing them with many interesting physical properties and chemical reactivities. Given their unique characteristics, some of them have potential for use as molecular magnetic and/or electronic materials.[1]



Scheme 1. Synthesis of biphenylenes.

The first synthesis of biphenylene was documented around 75 years ago,[3a] but few other synthetic methods have been developed since. The important methods of these include the copper-mediated Ullman reaction of 2,2'-diiodobiphenyl,[3b] the cyclodimerization of benzyne,[4] the oxidative cyclization of 2,2'-dimetallabiphenyl (M = Li, Zn) or 9-metallafluorene (M = Zn, Hg),[5] and the cobalt-catalyzed cycloaddition of *o*-dialkynylbenzene with an alkyne (the so-called Vollhardt reaction),[6,7] as presented in Scheme 1. Among these synthetic routes, the last two generate the desired product with a high yield and efficiency. The Vollhardt protocol is more promising because it has made a series of [*n*]phenylenes accessible, but some of these have been obtained with low chemical yields, presumably owing to their high inherent strain and/or low stability.[8] An expedient reaction, which is performed at low temperature via a highly reactive intermediate, should resolve these problems, and may provide a means of preparing biphenylene-based graphene materials. A reaction that involves an aryne satisfies the above requirements, and its retro-synthetic analysis is proposed in Scheme 1. The desired product 2-chloro-1-lithiobiphenyl (**1a**-Li) is expected to be formed by the cyclization of 2',3'-didehydro-2-lithiobiphenyl **2**, which is an elimination product of 4-chloro-2-fluoro-2',3-dilithiobiphenyl (**3a**-Li$_2$). Upon treatment with an organolithium reagent, the ideal starting material 2'-bromo-4-chloro-2-fluorobiphenyl (**4a**) can yield the key intermediate **3a**-Li$_2$ This study investigates the scope and limitations of this synthetic protocol.

The reaction conditions for the synthesis of 2-chlorobiphenyl (**1a**) from 2'-bromo-4-chloro-2-fluorobiphenyl (**4a**) were systematically examined, and the results of the synthesis were found to be strongly influenced by the solvent, temperature, and organolithium reagents utilized (Table 1). After a solution of **4a** in THF at −78 °C was treated with *t*BuLi (3 equiv.) and stirred at that temperature for one hour, only a trace of **1a** was obtained upon quenching a small portion of the sample with methanol. Warming to −50 °C for one hour yielded a mixture of 4-chloro-2-fluorobiphenyl (**3a**) and **1a** in a ratio of around 2:3, according to GC-MS analysis (Entry 1 in Table 1). The amount of **1a** could not be increased, even by using more *t*BuLi (6 equiv.; Entry 2 in Table 1) in the reaction. Notably, organolithium reagents *n*BuLi and *t*BuLi gave similar results (Entries 1 and 3 in Table 1). The aforementioned outcomes may demonstrate that the reaction suffers from autometallation[9] as some of the initially generated 2'-lithio-4-chloro-2-fluorobiphenyl is immediately converted to 4-chloro-2-fluoro-3-lithiobiphenyl by the extraction of the most acidic proton at the C-3 position in **4a**. Indeed, this process was verified by quenching the reaction mixture at −78 °C with D$_2$O, forming a mixture of biphenyls [d_1]-**3a** and [d_2]-**3a**. Autometallation is well documented to be inhibited by conducting the reaction in diethyl ether with *n*BuLi, but this condition did not yield a satisfactory result herein, presumably because the proton at the C-3 position in **4a** could not be removed (Entry 4 in Table 1). Reactions carried out in either THF or diethyl ether with excess of *t*BuLi (6 equiv.) gave a byproduct — *t*Bu-substituted biphenyl **5a** (Entries 2 and 5 in Table 1). The selective formation of **1a** was achieved by conducting the reaction using a suitable

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[a] S.-L. Wang, M.-L. Pan, W.-S. Su, Prof. Y.-T. Wu
Department of Chemistry, National Cheng Kung University
No. 1 Ta-Hsueh Rd., 70101 Tainan (Taiwan)
E-mail: ytwuchem@mail.ncku.edu.tw

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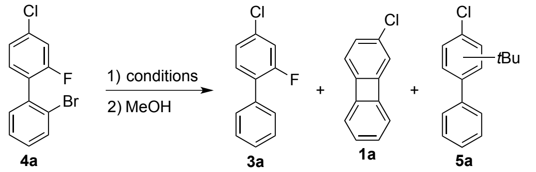
Table 1. Optimization of reaction conditions for preparation of biphenylene **1a**.



4a **3a** **1a** **5a**

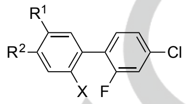
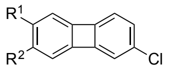
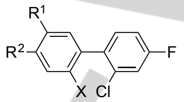
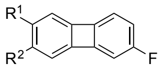
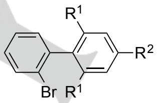
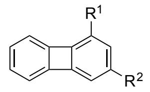
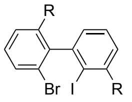
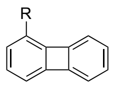
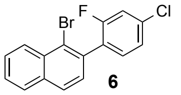
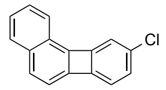
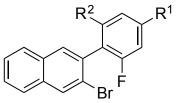
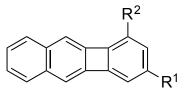
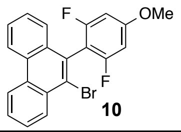
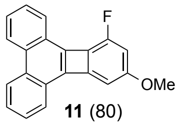
Entry[a]	Solvent (mL)	Base (equiv.)	Temp. (ºC)	Ratio **3a**:**1a**:**5a**
1	THF (15)	*t*BuLi (3.0)	−78 → −50	38:55:7
2	THF (15)	*t*BuLi (6.0)	−78 → −50	32:49:19
3	THF (15)	*n*BuLi (3.0)	−78 → −30	47:53:0
4	Et_2O (15)	*n*BuLi (3.0)	−78 → −50	100:0:0
5	Et_2O (15)	*t*BuLi (5.0)	−78 → −50	34:44:22
6	Et_2O (15)	*t*BuLi (3.0)	−100 → −50	11:80:9
7	Et_2O (15)[b]	*t*BuLi (3.0)	−78 → −50	13:75:12
8	Et_2O (15)[b]	*t*BuLi (3.0)	−100 → −50	7:88:5
9	Et_2O (5)[b,c]	*t*BuLi (3.0)	−100 → −50	0:89:11

[a] A solution of **4a** (1.0 mmol) in a solvent (15 mL) at an initial temperature was treated with an organolithium reagent. After being maintained at this temperature for 1 h, the reaction mixture was warmed to a known temperature, and stirred for 1 h. The ratio of the compounds was determined by GC-MS analysis, the sample for which was pre-treated with methanol or D_2O at the final temperature. [b] Additional toluene (15 mL for Entries 7 and 8; 5 mL for Entry 9) was added at −78 ºC. [c] **1a** was obtained with yields of 86% and 83% on 1- and 5-mmol scales, respectively.

amount of *t*BuLi (3.0 equiv.) at −100 ºC at first and then warming to −50 ºC (Entry 6 in Table 1). The amount of **1a** was also increased by adding the co-solvent toluene to the solution of **3a**-Li_2 at −78 ºC to promote the cyclization. Reducing the amount of solvent used did not significantly alter the result (Entries 7–9 in Table 1). Under the optimal condition, 2-chlorobiphenylene (**1a**) was obtained with yields of 86% and 83% on one- and five-mmole scales, respectively (Entry 9 in Table 1). One advantage of this synthetic protocol is the lack of any need for transition metal catalysts or reagents for the cyclization.

To investigate the scope and limitations of the presented synthetic protocol, a series of biphenyls was prepared by the Suzuki reaction of a haloarene with an arylboronic acid or by the coupling reaction of a lithioarene with an *o*-dihalobenzene (See Supporting Information). The reactivity of biphenyls in the cyclization was studied under the optimal conditions, under which biphenylenes were obtained with moderate to excellent yields (52–95%; Entries 1–13 in Table 2). Although some biphenylenes were easily formed at the optimal temperature (−50 ºC), the cyclization of most examples had to be performed at a higher temperature (−30 ºC) to increase reaction efficiency. For example, the yield for **4h** was improved from 38% to 65% (Entry 8 in Table 2). The reaction conditions used herein are favorable for not only 2-bromobiphenyl but also 2-iodobiphenyl, but better results were obtained with the former (Entries 3 and 8 in Table 2). Simple fluorobiphenylenes such as **1f** and **1n** were not isolated in as large amounts as expected, based on GC-MS analyses, because these compounds easily underwent sublimation at reduced pressure during the solvent evaporation (See below). It has been reported that the generation of 3-fluorobenzyne or 3-chlorobenzyne from 1-chloro-3-fluoro-2-lithiobenzene upon elimination of lithium halide depends on the solvent, and a reaction conducted in diethyl ether or toluene favors the former.[10] However, the results observed herein were not strongly consistent with the aforementioned chemoselectivity. For instance, 2'-bromo-4-chloro-2-fluorobiphenyl **4b** and 2'-bromo-2-chloro-4-fluorobiphenyl **4g** under the same conditions produced 2-chlorobiphenylene **1b** (85%) and 2-fluorobiphenylene **1g** (71%), respectively (Entries 2 and 7 in Table 2). The predominance of 2,3-didehydro-2'-lithiobiphenyl over 3,4-didehydro-2'-lithiobiphenyl was probably caused by the fact that the former can undergo cyclization to yield a stable intermediate 1-lithiobiphenylene. 2'-Bromo-2,4,6-trichlorobiphenyl (**4m**) was observed to be much less reactive than other 2'-bromo-2,4,6-tri-

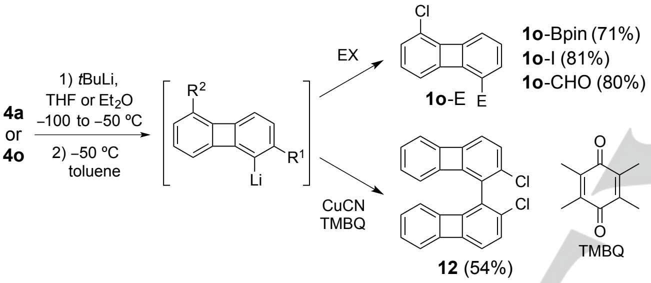
Table 2. Synthesis of biphenylene derivatives.[a]

Entry	Staring material	Final *T* [ºC]	Product (Isolated yield, %)
			
1	**4a** (R^1 = R^2 = H, X = Br)	−50	**1a** (86)
2	**4b** (R^1 = R^2 = Me, X = Br)	−50	**1b** (85)
3	**4c** (R^1 = R^2 = OMe, X = I)	−30	**1c** (65)
4	**4d** (R^1 = H, R^2 = OMe, X = Br)	−50	**1d** (83)
5	**4e** (R^1 = H, R^2 = F, X = Br)	−50	**1e** (79)
			
6	**4f** (R^1 = R^2 = H, X = Br)	−50	**1f** (63, 77[b])
7	**4g** (R^1 = R^2 = Me, X = Br)	−50	**1g** (71)
8	**4h** (R^1 = R^2 = OMe, X = I)	−30	**1h** (65)
			
9	**4i** (R^1 = R^2 = F)	−30	**1i** (83)
10	**4j** (R^1 = F, R^2 = Cl)	−30	**1j** (76)
11	**4k** (R^1 = F, R^2 = OMe)	−50	**1k** (76)
12	**4l** (R^1 = F, R^2 = C≡CPh)	−30	**1l** (95)
13	**4m** (R^1 = R^2 = Cl)	−30	**1m** (52)
			
14	**4n** (R = F)	−30	**1n** (77)
15	**4o** (R = Cl)	−30	**1o** (86)
16	 **6**	−30	 **7** (62)
			
17	**8a** (R^1= Cl, R^2 = H)	−30	**9a** (59)
18	**8b** (R^1 = F, R^2 = OMe)	−30	**9b** (97)
19	 **10**	−30	 **11** (80)

[a] A solution of a biaryl (1.0 mmol) in ether (5 mL) at −100 ºC was treated with *t*BuLi (3.0 equiv.), stirred both at this temperature and −78 ºC for 1 h, and the solution was then diluted by adding toluene (5 mL). The reaction mixture was warmed to a known temperature (Final *T*), and stirred for 1 h, unless otherwise specified. Reactions of biphenyls **4n** and **4o** were initially conducted in THF at −78 ºC with *t*BuLi (4.0 equiv.). [b] Instead of methanol, iodine was added to the reaction mixture to give 2-fluoro-1-iodobiphenylene (**1f**-I).

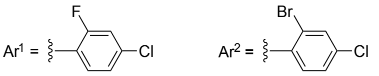
halobiphenyls **4i** and **4j** (Entries 9, 10 and 13 in Table 2). In contrast to the other examples listed in Table 2, the cyclization of 2'-bromo-3-halo-2-iodobiphenyls **4n** and **4o** had to be carried out in THF as the solvent to generate 1-halobiphenylenes **1n** and **1o** (Entries 14 and 15 in Table 2). On the basis of the above results, a suitable precursor for biphenylene is 1,2,2'-trihalo-biphenylenes or 4-substituted 2,2'-dihalobiphenyls, where the substituent is methoxy, halogen or phenylethynyl.

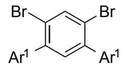
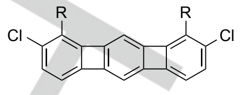
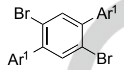
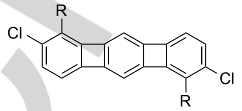
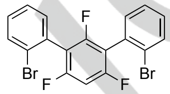
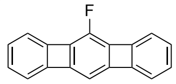
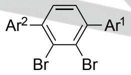
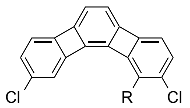
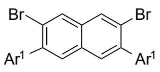
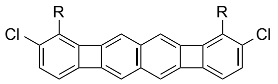
Direct and selective functionalization at the C-1 position of biphenylene is challengeing.[11] The synthetic protocol developed herein provides a advantage that 1-substituted biphenylenes **1o**-E were straightforwardly and efficiently prepared from biphenyl **4o** by treatment with *t*BuLi and subsequently an electrophilic reagent, including isopropoxyboronic acid pinacol ester (*i*PrO-Bpin), iodine or DMF (Scheme 2). 2-Fluoro-1-iodo-biphenylene (**1f**-I) was obtained with a higher yield (77%) than 2-fluoro-biphenylene (**1f**, 63%), supporting the fact of the easy sublimation of simple flouorobiphenyls (Entry 6 in Table 2). Bibiphenylene **12** was obtained by the copper-mediated dimerization of the intermediate 2-chloro-1-lithiobiphenyl (**1a**-Li) using the Lipshutz protocol (Scheme 2).[12] The structures of **1o**-CHO and **12** were ambiguously confirmed by X-ray crystallo-graphy.[13]



Scheme 2. Syntheses of 1-substituted biphenylenes directly from biphenyl **4**.

Table 3. Synthesis of higher homologues of biphenylene[a]



Entry	Staring material	Product (Isolated yield, %)
		
1	**13**	**14** (R = H, 81)
2	**13**	**14**-Bpin (R = Bpin, 60)[b]
		
3	**15**	**16** (R = H, 72)
4	**15**	**16**-Bpin (R = Bpin, 55)[b]
5	 **17**	 **18** (92)[c]
		
6	**19**	**20** (R = H, 60)
7	**19**	**20**-I (R = I, 60)[b]
		
8	**21**	**22** (R= H, 70)
9	**21**	**22**-Bpin (R = Bpin, 64)[b]

[a] A solution of a teraryl (0.5 mmol) in ether (10 mL) at −100 ºC was treated with *t*BuLi (6.0 equiv.), stirred at this temperature and −78 ºC for 1 h and 2 h, respectively. The solution was diluted by adding toluene (5 mL), warmed to −30 ºC, and stirred for additional 2 h, unless otherwise specified. Reactions of terphenyl **19** were initially conducted in THF/toluene at −110 ºC with *t*BuLi (6.0 equiv.), and stirred at this temperature, −50 ºC and −30 ºC for 1 h, 2 h and 2 h, respectively. [b] Instead of methanol, *i*PrO-Bpin or iodine was added to the reaction mixture. [c] The reaction mixture was finally conducted at −20 ºC for 2 h.

π-Extended derivatives benzobiphenylenes **7**/**9** and dibenzobiphenylene **11** were prepared from the corresponding biaryls (Entries 16−19 in Table 2) in a manner similar to that described above. The higher homologues of biphenylenes, such as linear [3]phenylenes **14**/**16**/**18**, angular [3]phenylenes **20**, and biphenyleno[2,3-*b*]biphenylene **22**, were also regioselectively generated from teraryls using different cyclization sequences (Table 3). Compounds **14**/**16** and **22** were easily obtained from **13**/**15** and **21**, respectively, by two independent cyclization processes, like those used in the formation of simple biphenylene **1**, whereas 5-fluoro[3]phenylene (**18**) was prepared from 1,3-diaryl-2,4,6-trifluorobenzene (**17**) via a 1,2,3-tridehydro-benzene equivalent in which the two triple bonds had to be formed successively. Therefore, this reaction had to be performed at a higher temperature and for longer (−20 ºC for two hours). The reaction conditions and mechanism of the formation of angular [3]phenylene **20** differ from those of others reported herein. After being treated with *t*BuLi, the *o*-dibromoaryl moiety in **19** should be regarded as a benzyne, rather than an *o*-dilithiobenzene.[14] This reaction route was strongly favored by using THF as the solvent, and **20** and its 1-iodo-substituted derivative **20**-I were both obtained with yields of 60%. Although the MS spectra for **14**, **16** and **22** are consistent with the proposed structures, the low solubility of these compounds in common organic solvents restricted verification of their structures using NMR spectroscopy. Their boronic esters **14**-Bpin, **16**-Bpin and **22**-Bpin with better solubility resolved this issue (Entries 2, 4 and 9 in Table 3).

In summary, biphenylene and its derivatives can be easily and efficiently obtained at low temperature by the organolithium-mediated cyclization of halobiaryls or haloterphenyls via an aryne intermediate. Biphenylene-based cycloarenes are currently being prepared using this synthetic protocol.

Acknowledgements

This work was supported by the Ministry of Science and Technology of Taiwan (104-2113-M-006-013-MY3). We thank Prof. Sue-Lein Wang and Ms. Pei-Lin Chen (National Tsing Hua University, Taiwan) for the X-ray structure analyses.

Keywords: Biphenylene • Aryne • Organolithium

[1] For selected reviews on biphenylenes, see: a) S. Toyota, *Science of Synthesis*, **2010**, *45b*, 855; b) O. Š. Miljanič, K. P. C. Vollhardt, In *Carbon-Rich Compounds: From Molecules to Materials* (Eds. M. M. Haley, R. R. Tykwinski), Wiley-VCH: Weinheim, **2006**, pp. 140; c) F.

Toda, P. Garratt, *Chem. Rev.* **1992**, *92*, 1685; d) M. K. Sheperd, *Cyclobutarenes: The Chemistry of Benzocyclobutene, Biphenylene, and Related Compounds*, Elsevier, New York, **1991**.

[2] Z R. Diercks, K. P. C. Vollhardt, *J. Am. Chem. Soc.* **1986**, *108*, 3150.

[3] a) W. C. Lothrop, *J. Am. Chem. Soc.* **1941**, *63*, 1187. For a review, see: b) T. D. Nelson, R. D. Crouch, *Organic Reactions* **2004**, *63*, 265.

[4] For selected examples, see: a) F. Schlütter, T. Nishiuchi, V. Enkelmann, K. Müllen, *Angew. Chem.* **2014**, *126*, 1564; *Angew. Chem. Int. Ed.* **2014**, *53*, 1538; b) J. Lu, J. Zhang, X. Shen, D. M. Ho, R. A. Pascal, Jr., *J. Am. Chem. Soc.* **2002**, *124*, 8035; c) C.-D. Campbell, C. W. Rees, *J. Chem. Soc. C* **1969**, 742.

[5] a) M. Iyoda, S. M. H. Kabi, A. Vorashinga, Y. Kuwatani, M. Yoshidi, *Tetrahedron Lett.* **1998**, *39*, 5393; b) G. Wittig, W. Herwig, *Chem. Ber.* **1954**, *87*, 1511; c) T. Schaub, U. Radius, *Tetrahedron Lett.* **2005**, *46*, 8195; d) S. M. H. Kabir, M. Hasegawa, Y. Kuwatani, M. Yoshida, H. Matsuyama, M. Iyoda, *J. Chem. Soc., Perkin Trans. 1* **2001**, 159.

[6] a) B. C. Berris,; Y.-H. Lai, K. P. C. Vollhardt, *J. Chem. Soc., Chem. Commun.* **1982**, 953; b) B. C. Berris, G. H. Hovakeemian, Y.-H. Lai, H. Mestdagh, K. P. C. Vollhardt, *J. Am. Chem. Soc.* **1985**, *107*, 5670.

[7] For other synthetic approaches reported recently, see: a) Z. Jin, Y. C. Teo, N. G. Zulaybar, M. D. Smith, Y. Xia, *J. Am. Chem. Soc.* **2017**, *139*, 1806; b) S. P. Luppino, T. M. Swager, *Synlett* **2017**, *28*, 323; c) S. Nobusue, A. Shimizu, K. Hori, I. Hisaki, M. Miyata, Y. Tobe, *Angew. Chem.* **2013**, *125*, 4278; *Angew. Chem. Int. Ed.* **2013**, *52*, 4184; d) A. Fukazawa, H. Oshima, Y. Shiota, S. Takahashi, K. Yoshizawa, S. Yamaguchi, *J. Am. Chem. Soc.* **2013**, *135*, 1731.

[8] a) Bharat, R. Bhola, T. Bally, A. Valente, M. K. Cyrański, Ł. Dobrzycki, S. M. Spain, P. Rempała, M. R. Chin, B. T. King, *Angew. Chem.* **2010**, *122*, 409; *Angew. Chem. Int. Ed.* **2010**, *49*, 399; b) D. Bruns, H. Miura, K. P. C. Vollhardt, *Org. Lett.* **2003**, *5*, 549.

[9] a) A. J. Bridges, W. C. Patt, T. M. Stickney, *J. Org. Chem.* **1990**, *55*, 773; b) P. L. Coe, A. J. Waring, T. D. Yarwood, *J. Chem. Soc. Perkin Trans. 1*, **1995**, 2729.

[10] a) J. W. Coe, M. C. Wirtz, C. G. Bashore, J. Candler, *Org. Lett.* **2004**, *6*, 1589; b) A. Ramírez, J. Candler, C. G. Bashore, M. C. Wirtz, J. W. Coe, D. B. Collum, *J. Am. Chem. Soc.* **2004**, *126*, 14700; c) U. N. Rao, J. Maguire, E. Biehl, *ARKIVOC* **2004**, 88.

[11] a) H. Kidokoro, M. Sato, S. Ebine, *Bull. Chem. Soc. Jpn.* **1982**, *55*, 3204; b) H. Kidokoro, Y. Saito, M. Sato, S. Ebine, S. Sato, T. Hata, C. Tamura, *Bull. Chem. Soc. Jpn.* **1983**, *56*, 1192; c) A. J. Boulton, J. B. Chadwick, C. R. Harrison, J. F. W. McOmie, *J. Chem. Soc. C* **1968**, 328.

[12] a) B. H. Lipshutz, R. S. Wilhelm, D. M. Floyd, *J. Am. Chem. Soc.* **1981**, *103*, 7672; b) M. Yoshihiro, M. Wu, M. J. Rahman, M. Iyoda, *Chem. Commun.* **2005**, 411.

[13] X-ray crystallographic data for **1o**-CHO (CCDC-1558656) and **12** (1558655) can be obtained from the Cambridge Crystallographic Data Centre via https://www.ccdc.cam.ac.uk/structures.

[14] a) K. Durka, S. Luliński, M. Dąbrowski, J. Serwatowski, *Eur. J. Org. Chem.* **2014**, 4562; b) H. Hart, C.-Y. Lai, G. Nwokogu, S. Shamouilian, A. Teuerstein, C. Zlotogorski, *J. Am. Chem. Soc.* **1980**, *102*, 6649.

10.1002/anie.201708892

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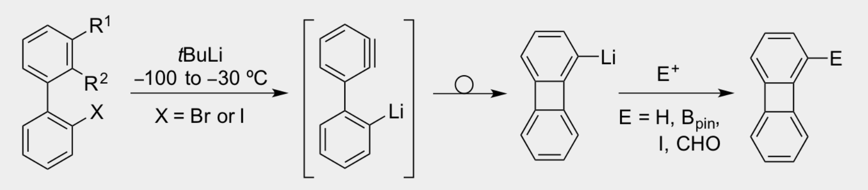

Biphenylene can be easily and efficiently obtained at low temperature by the organolithium-mediated cyclization of halobiphenyl via an aryne intermediate. This synthetic protocol provides an advantage for the direct and controlled functionalization at the C-1 position.

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