J|A|C|S
ARTICLES

Synthesis of Bicyclic *p*-Diiodobenzenes via Silver-Catalyzed C*sp*-H Iodination and Ruthenium-Catalyzed Cycloaddition

Yoshihiko Yamamoto,*,† Kozo Hattori, and Hisao Nishiyama

Contribution from the Department of Applied Chemistry Graduate School of Engineering, Nagoya University, Chikusa, Nagoya 464-8603, Japan

Received March 8, 2006; E-mail: omyy@apc.titech.ac.jp

Abstract: Highly substituted iodobenzenes were efficiently and regioselectively synthesized from readily available 1,6-diynes via two-step process consisting of silver-catalyzed C*sp*-H iodination and subsequent ruthenium-catalyzed [2 + 2 + 2] cycloaddition of resultant iododiynes. Some of the obtained iodobenzenes were subjected to palladium-catalyzed C−C bond-forming reactions such as Mizoroki−Heck reaction, Sonogashira reaction, and Suzuki−Miyaura coupling, giving highly conjugated molecules.

Introduction

Iodobenzenes are highly valuable intermediates in organic synthesis.[1] They are readily transformed into fine chemicals via catalytic cross-coupling reactions,[2] or tritium-labeled biologically active compounds via catalytic hydrodehalogenation.[3] Moreover, *p*-diiodobenzenes were recently utilized as monomers for functional polymers.[4] Although chloro- and bromobenzenes have been conventionally prepared by means of electrophilic aromatic halogenation,[5] the direct iodination of aromatic precursors is problematic due to the low electrophilicity of molecular iodine. Thus, aromatic iodination requires a Lewis acid activator or oxidative and/or acidic reaction conditions, which hamper the synthesis of iodobenzenes bearing labile functionalities.[5,6] In addition, when a substituted benzene is subjected to electrophilic halogenation, the newly introduced halogen atom (X) is directed to the ortho, para, or meta positions, depending on the nature of the substituent (R) of the precursor (Figure 1A). Accordingly, this substrate-directed regioselectivity makes the synthesis of unsymmetrical halobenzenes difficult, often leading to a mixture of some regioisomeric products.

To address these issues, we developed a novel, two-step strategy to assemble *p*-diiodobenzenes as outlined in Figure 1B.

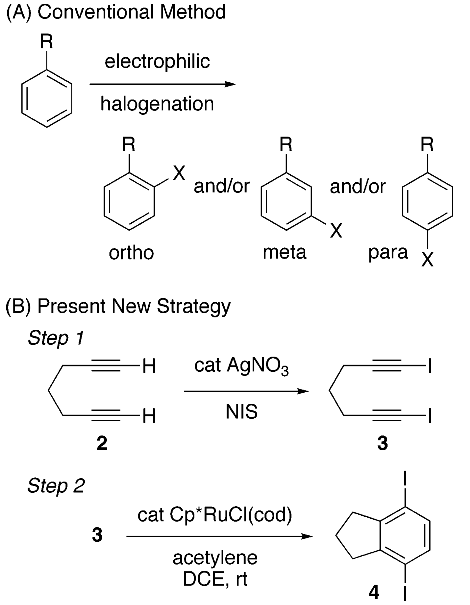


Figure 1. (A) Conventional electrophilic aromatic halogenation (X = halogen atom) and (B) novel two-step access to fused iodobenzenes **4** from 1,6-diynes **2**, involving (step 1) silver-catalyzed iodination of **2** leading to iododiynes **3**, and (step 2) ruthenium-catalyzed cycloaddition of **3** with acetylene, resulting in the formation of iodobenzenes **4**.

First, 1,6-diynes **2** are converted to diiododiynes **3** via the silver-catalyzed C*sp*-H halogenation.[7] Second, the cycloaddition of **3** with acetylene can be carried out in 1,2-dichloroethane (DCE) at room temperature with our own protocol using a organoruthenium catalyst, Cp*RuCl(cod) (**1**: Cp* = η^5-pentamethylcyclopentadienyl, cod = 1,5-cyclooctadiene). The ruthenium-catalyzed partially intramolecular alkyne cyclotrimerization has proved to be highly selective and tolerant to a broad range of functional groups.[8] Overall, this two-step procedure allows us to achieve catalytic assembly of bicyclic *p*-diiodobenzenes **4** with the exact control of the substitution pattern. Thus,

---

† Current address: Department of Applied Chemistry, Graduate School of Science and Engineering, Tokyo Institute of Technology, O-okayama, Meguro-ku, Tokyo 152-8552, Japan.

(1) Merkushev, E. B. *Synthesis* **1988**, 923−937.

(2) *Metal-catalyzed Cross-coupling Reactions*; Diederich, F.; Stang, P. J., Eds.; Wiley: Weinheim, 1998.

(3) Nagasaki, T.; Sakai, K.; Segawa, M.; Katsuyama, Y.; Haga, N.; Koike, M.; Kawada, K.; Takechi, S. *J. Labeled Cpd. Radiopharm.* **2001**, *44*, 993−1004.

(4) (a) Bao, Z.; Chen, Y.; Cai, R.; Yu, L. *Macromolecules* **1993**, *26*, 5281−5286. (b) Bao, Z.; Chan, W. K.; Yu, L. *J. Am. Chem. Soc.* **1995**, *117*, 12426−12435. (c) Schlüter, S.; Frahn, J.; Karakaya, B.; Schlüter, A. D. *Macromol. Chem. Phys.* **2000**, *201*, 139−142.

(5) Smith, M. B.; March, J. *March's Advanced Organic Chemistry*, 5th ed.; Wiley: New York, 2001, Chapter 11, p 704, and references sited therein.

(6) Recently, mild and efficient aromatic iodination was reported, see: Johnsson, R.; Meijer, A.; Ellervik, U. *Tetrahedron* **2005**, *61*, 11657−11663. Also see iodonium-triggered cyclization leading to iodoarenes: (a) Goldfinger, M. B.; Crawford, K. B.; Swager, T. M. *J. Am. Chem. Soc.* **1997**, *119*, 4578−4593. (b) Yao, T.; Campo, M. A.; Larock, R. C. *J. Org. Chem.* **2005**, *70*, 3511−3517. (c) Zhang, X.; Sarkar, S.; Larrock, R. C. *J. Org. Chem.* **2006**, *71*, 236−243.

(7) Hofmeister, H.; Annen, K.; Laurent, H.; Wiechert, R. *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 727−729.

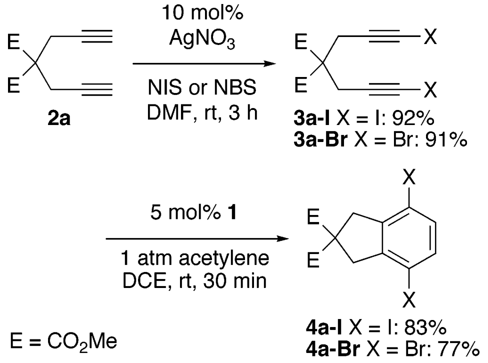
10.1021/ja061619p CCC: $33.50 © 2006 American Chemical Society

environmentally benign process with high atom- and step-economy is realized as a result of the dramatic reduce of chemical wastes such as stoichiometric amounts of an activator for molecular iodine and undesired regioisomeric side products.[9] To the best of our knowledge, transition-metal-catalyzed [2 + 2 + 2] cyclocotrimerization of iodoalkynes has not been explored,[10,11] whereas thermal and stoichiometric-metal-mediated cyclotrimerization of chloroalkynes were reported previously.[12,13d] This is partly because low-valent transition metals are capable of undergoing oxidative addition toward the C*sp*-I bond in iodoalkynes, resulting in the formation of a transition metal acetylide,[13] which might be an intermediate for recently reported catalytic homo-coupling of iodoalkynes.[14] Although the mild and regioselective methods to synthesize iodoarenes have recently been reported,[6,11d,f−g] the C*sp*-H iodination/cyclotrimerization strategy would provide a powerful route to the bicyclic *p*-diiodobenzene framework, which is otherwise difficult to be accessed.

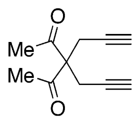
Results and Discussion

Scope and Limitations of Sequential Ag-Catalyzed C*sp*-H Iodination/Ru-Catalyzed Cycloaddition. Upon treatment with *N*-iodosuccinimide (NIS) in the presence of 10 mol % $AgNO_3$ in *N*,*N*-dimethylformamide (DMF) at room temperature, dipropargylmalonate **2a** was converted to diiododiyne **3a−I** in 92% yield (Scheme 1).[15] Subsequently, **3a−I** was treated with the ruthenium catalyst under acetylene atmosphere at room temperature for 30 min to give diiodobenzene **4a−I** in 83% yield. In a similar manner, the corresponding bromide **3a-Br**, which was obtained from **2a** and *N*-bromosuccinimide (NBS) in high yield, underwent the ruthenium-catalyzed cycloaddition with acetylene to afford *p*-dibromobenzene **4a-Br** in 77% yield.

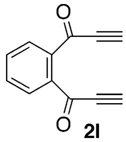
Scheme 1



Having confirmed the feasibility of our two-step protocol, its generality was then explored as summarized in Table 1. Our method well tolerated malononitrile, an ether or a sulfonamide tether in diynes **2b−d**, resulting in the formation of diiodides **4b−d** over 60% overall yields (entries 1−3). It is noteworthy that even simpler phthalan derivative **4c** was unknown compound, probably because conventional electrophilic aromatic iodination conditions is incompatible to the acid-labile isobenzofuran structure. Protecting groups such as an acid labile ketal in **2e** and a benzyl ether in **2f** were also compatible to the present method (entries 4 and 5). When multiple benzene rings are present in a single molecule, electrophilic iodination would result in a mixture of several products. In our hand, spirocyclic compound **4g** bearing a fluorene moiety was successfully obtained from diyne **2g** in ca. 70% overall yield (entry 6). In a similar manner, diynes **2h−j** bearing a single terminal alkyne moiety were transformed into unsymmetrical iodobenzenes **4h−j** (entries 7−9). The most impressive is the synthesis of *p*-iodobenzoate derivative **4j**, because a *meta*-halogenated product is expected for electrophilic halogenation of a benzene derivative possessing an electron-withdrawing group such as an ester. In striking contrast to these diynes, acetylacetone derivative **2k** and electron-deficient diyne **2l** failed to undergo Ag-catalyzed C*sp*-H iodination, resulting in the formation of intractable materials.



2k



2l

The present protocol can be carried out with an increased scale (Table 1, entry 2). Actually, Ag-catalyzed iodination of 5 mmol of **2c** gave 4 mmol of **3c**, which was then treated with 5 mol % **1** under acetylene atmosphere for 30 min to deliver 1.4 g of **4c** (76% overall yield). The second cycloaddition step can also be conducted with a higher concentration, reducing an amount of solvent waste. Upon treatment of 4 mmol of **3c** with **1** and acetylene in 10 mL of DCE (0.4 M), 1.3 g of **4c** was obtained (87%), although the completion of the reaction requires 1 h.

---

(8) (a) Yamamoto, Y.; Arakawa, T.; Ogawa, R.; Itoh, K. *J. Am. Chem. Soc.* **2003**, *125*, 12143−12160. (b) Yamamoto, Y.; Kinpara, K.; Saigoku, T.; Nishiyama, H.; Itoh, K. *Org. Biomol. Chem.* **2004**, *2*, 1287−1294. (c) Yamamoto, Y.; Saigoku, T.; Nishiyama, H.; Itoh, K. *Org. Biomol. Chem.* **2005**, *3*, 1768−1775. (d) Yamamoto, Y.; Ishii, J.; Nishiyama, H.; Itoh, K. *J. Am. Chem. Soc.* **2005**, *127*, 9625−9631. (e) Yamamoto, Y.; Ishii, J.; Nishiyama, H.; Itoh, K. *Tetrahedron* **2005**, *61*, 11501−11510.

(9) For atom-economy: (a) Trost, B. M. *Science* **1991**, *254*, 1471−1476. (b) Trost, B. M. *Angew. Chem. Int. Ed.* **1995**, *34*, 259−281. For step-economy: (c) Wender, P. A.; Miller, B. L. In *Organic Synthesis: Theory and Applications*; Hudlicky, T., Ed.; JAI: Greemwich, 1993; Vol. 2, p 27−66. (d) Wender, P. A.; Handy, S.; Wright, D. L. *Chem. Ind. (London)* **1997**, 765−769.

(10) (a) Shore, N. E.; In *Comprehensive Organic Synthesis*, Trost, B. M.; Fleming, I.; Paquette, L. A., Eds.; Pergamon: Oxford, 1991; Vol. 5, pp 1129−1162. (b) Grotjahn, D. B. In *Comprehensive Organometallic Chemistry II*; Hegedus, L. S., Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon: Oxford, 1995; Vol. 12, pp 741−770. (c) Saito, S.; Yamamoto, Y. *Chem. Rev.* **2000**, *100*, 2901−2915. (d) Yamamoto, Y. *Curr. Org. Chem.* **2005**, *9*, 503−519. (e) Kotha, S.; Brahmachary, E.; Lahiri, K. *Eur. J. Org. Chem.* **2005**, 4741−4767.

(11) Several examples of transition-metal-catalyzed or -mediated Pauson-Khand reaction, [2 + 2] and [4 + 2] cycloadditions, and cycloisomerizations of haloalkynes have recently been reported, see: (a) Balsells, J.; Moyano, A.; Riera, A.; Pericàs, M. A. *Org. Lett.* **1999**, *1*, 1981−1984. (b) Villeneuve, K.; Riddell, N.; Jordan, R. W.; Tsui, G. C.; Tam, W. *Org. Lett.* **2004**, *6*, 4543−4546. (c) Yoo, W.-J.; Allen, A.; Villeneuve, K.; Tam, W. *Org. Lett.* **2005**, *7*, 5853−5856. (d) Miura, T.; Iwasawa, N. *J. Am. Chem. Soc.* **2002**, *124*, 518−519. (e) Fürstner, A.; Mamane, V. *Chem. Commun.* **2003**, 2112−2113. (f) Odedra, A.; Wu, C.-J.; Pratap, T. B.; Huang, C.-W.; Ran, Y.-F.; Liu, R.-S. *J. Am. Chem. Soc.* **2005**, *127*, 3406−3412. (g) Lin, M.-Y.; Maddirala, S. J.; Liu, R.-S. *Org. Lett.* **2005**, *7*, 1745−1748. (h) Lo, C.-Y.; Kumar, M. P.; Chang, H.-K.; Lush, S.-F.; Liu, R.-S. *J. Org. Chem.* **2005**, *70*, 10482−10487.

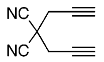
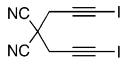
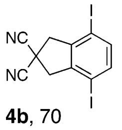
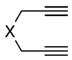
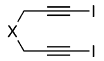
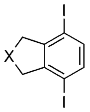
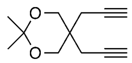
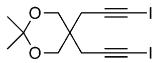
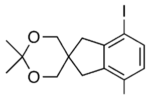
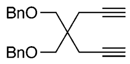
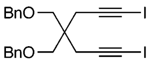
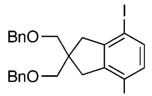
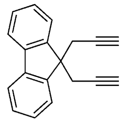
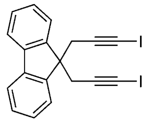
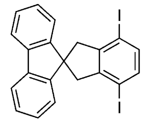
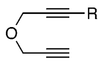
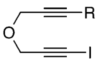
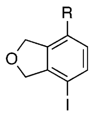
(12) (a) Tanaka, R.; Zheng, S.-Q.; Kawaguchi, K.; Tanaka, T. *J. Chem. Soc, Perkin Trans.* **1980**, *2*, 1714−1720. (b) Ballester, M.; Castañer, J.; Riera, J.; Tabernero, I. *J. Org. Chem.* **1986**, *51*, 1413−1419.

(13) (a) Sünkel, K. *J. Organomet. Chem.* **1988**, *348*, C12−C14. (b) Klein, H.-F.: Beck-Hemetsberger, H.; Reitzel, L.; Rodenhäuser, B.; Cordier, G. *Chem. Ber.* **1989**, *122*, 43−51. (c) Sünkel, K.; Birk, U.; Robl, C. *Organometallics* **1994**, *13*, 1679−1687. (d) Sünkel, K.; Birk, U. *Polyhedron* **1999**, *18*, 3187−3197.

(14) Damle, S. V.; Seomoon, D.; Lee, P. H. *J. Org. Chem.* **2003**, *68*, 7085−7087.

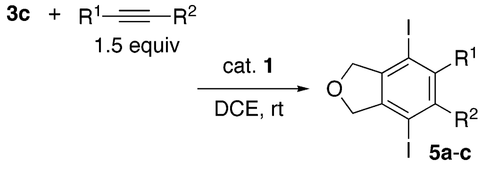
(15) The iododiynes obtained in this study can be handled safely at ambient temperature under air, although iodo-1,3-butadiyne was reported to be explosive (see: Schlubach, H. H.; Franzen, V. *Liebigs Ann.* **1951**, *573*, 115−120.).

Table 1. Synthesis of Halodiynes **3** and Halobenzenes **4** from Diynes **2**[a]

Entry	Diynes	Iododiynes, Yield/%	Iodobenzenes, Yield/%
1	 **2b**	 **3b**, 95	 **4b**, 70
2	 **2c** X = O	 **3c** X = O, 85 (80)[b]	 **4c** X = O, 83 (95)[c]
3	**2d** X = NTs	**3d** X = NTs, 90	**4d** X = NTs, 80
4	 **2e**	 **3e**, 95	 **4e**, 87
5	 **2f**	 **3f**, 80	 **4f**, 80
6	 **2g**	 **3g**, 75	 **4g**, 93
7	 **2h** R = Me	 **3h**, 75	 **4h**, 77
8	**2i** R = Ph	**3i**, 87	**4i**, 63
9	**2j** R = CO_2Me	**3j**, 44[d]	**4j**, 87

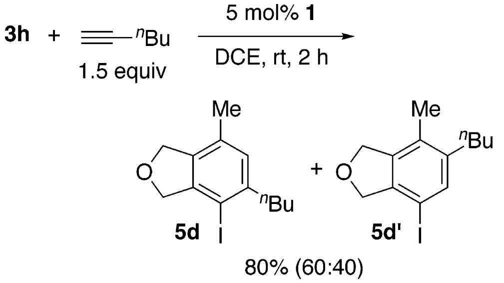
[a] Diynes **2** (2 mmol) were treated with 10 mol % $AgNO_3$ and NIS (3 equiv) in DMF (12 mL) at room temperature for 3 h. Iododiynes **3** (0.3 mmol) were treated with 5 mol % (15 mol % for entry 8) **1** in DCE (3.5 mL) under acetylene atmosphere at room temperature for 30 min (1 h for entry 8). [b] Yields from 5 mmol of diynes **2c**. [c] Yield from 4 mmol of **3c**. [d] A small amount of **2j** was remained intact.

Scheme 2

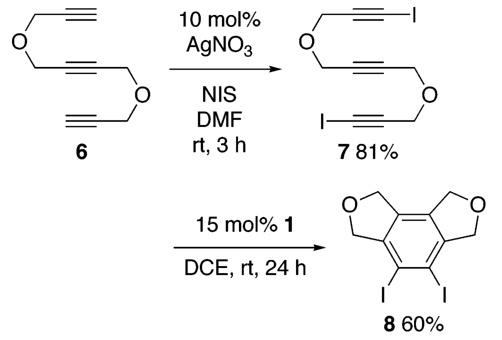


5a R^1 = H, R^2 = ^{n}Bu: cat. 5 mol%, 4 h, 83%
5b R^1 = H, R^2 = Ph: cat. 5 mol%, 5 h, 80%
5c R^1 = R^2 = Ph: cat. 15 mol%, 5 h, 70%

Scheme 3



Scheme 4



The monoalkyne component is not limited to acetylene. Diiododiyne **3c** was allowed to react with 1-hexyne or phenylacetylene (1.5 equiv) in the presence of 5 mol % **1** at ambient temperature for 4−5 h to afford pentasubstituted benzenes **5a** and **5b** in 83% and 80% yields, respectively (Scheme 2). Fully substituted diiodide **5c** was also obtained in 70% yield from **3c** and diphenylacetylene albeit with an increased catalyst loading of 15 mol %. To examine the regioselectivity of the cycloaddition step, unsymmetrical iododiyne **3h** was allowed to react with 1-hexyne to give rise to an inseparable mixture of regioisomers **5d** and **5d′** in 80% combined yield with the 60:40 ratio (Scheme 3).

We next turned our attention to completely intramolecular cyclotrimerization of a triyne. Applying the silver-catalyzed C*sp*-H iodination to symmetrical triyne **6** gave **7** in 81% yield, which was then treated with 15 mol % **1** in DCE at room temperature for 24 h to afford desired tricyclic *o*-diiodobenzene **8** in 60% yield (Scheme 4).

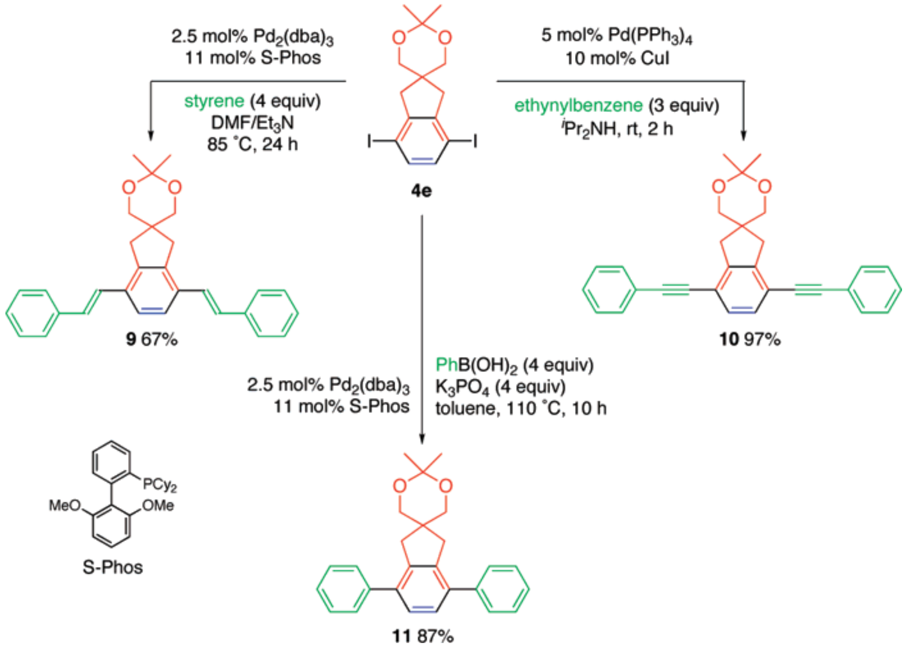
Application of *p*-Diiodobenzene to Dual Cross-Coupling Reactions. To demonstrate the utility of *p*-diiodobenzene products obtained from this study, we further carried out some cross-coupling reactions of representative product **4e** as summarized in Scheme 5. Diiodobenzene **4e** was subjected to Mizoroki−Heck reaction with styrene using the $Pd_2(dba)_3$/S-Phos (S-Phos: 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl)[16] catalyst system in DMF/Et_3N at 85 °C for 24 h to afford **9** in 67% yield. Sonogashira reaction of **4e** with ethynylbenzene was conducted under standard conditions to obtain **10** in excellent yield. Moreover, **4e** also underwent Suzuki−Miyaura coupling with phenylboronic acid under unhydrous conditions with the $Pd_2(dba)_3$/S-Phos catalyst system, resulting in the high yield formation of **11**.

As above, Ag-catalyzed C*sp*-H iodination/Ru-catalyzed cycloaddition/Pd-catalyzed cross-coupling sequences effectively assembled conjugated molecules from readily available starting materials. In particular, the combination with Suzuki-Miyaura coupling provides a powerful access to functionalized oligo-*p*-phenylenes, which would find wide applications to molecular

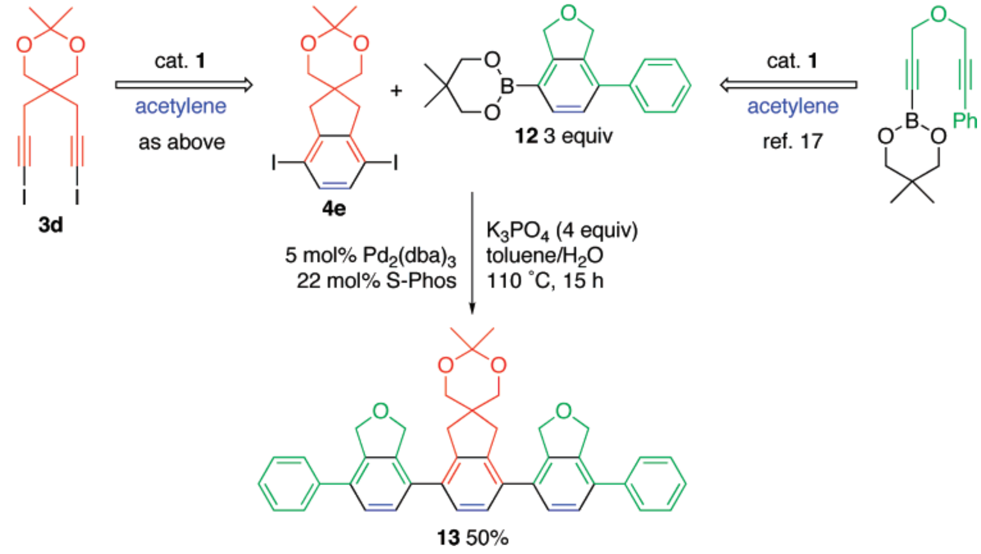
---

(16) Walker, S. D.; Barder, T. E.; Martinelli, J. R.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2004**, *43*, 1871−1876.

Scheme 5



Scheme 6



electronics.[17] In this context, we finally attempted the modular synthesis of penta- and hexa-*p*-phenylenes from diiodobenzenes and biarylboronic acid ester **12**,[18] all of which were prepared by using the Cp*RuCl-catalyzed cycloaddition technology.[19] At the outset, diiodobenzene **4e** was subjected to the coupling with boronate **12** under the above anhydrous conditions (2.5 mol % $Pd_2(dba)_3$, 11 mol % S-Phos, 4 equiv K_3PO_4, toluene, 110 °C, 24 h). The desired pentaphenylene was, however, obtained only in a trace amount, and 40% of **4e** was recovered intact. This was probably because cyclic esters of arylboronic acids are less reactive than the parent acids. Thus, **4e** was allowed to react with **12** in toluene/H_2O under otherwise identical conditions (Scheme 6). As a result, **4e** was completely consumed for 15 h and penta-*p*-phenylene **13** was obtained in 50% isolated yield.

Toward the synthesis of the hexa-*p*-phenylene, we next designed diiodobiaryl **16** as a diiodide module (Scheme 7). The Ag-catalyzed C*sp*-H iodination of malonate-derived tetrayne **14** delivered cycloaddition precursor **15** in high yield, which was subsequently treated with 15 mol % **1** under acetylene atmosphere at room temperature to give desired **16** in 87% yield. Thus, prepared **16** was finally allowed to react with boronate module **12** under the optimized conditions to afford hexa-*p*-phenylene albeit in a moderate yield (36%) along with recovered **16** (13%).

Summary

In conclusion, we successfully developed a novel regio-defined route to bicyclic iodobenzenes from readily available

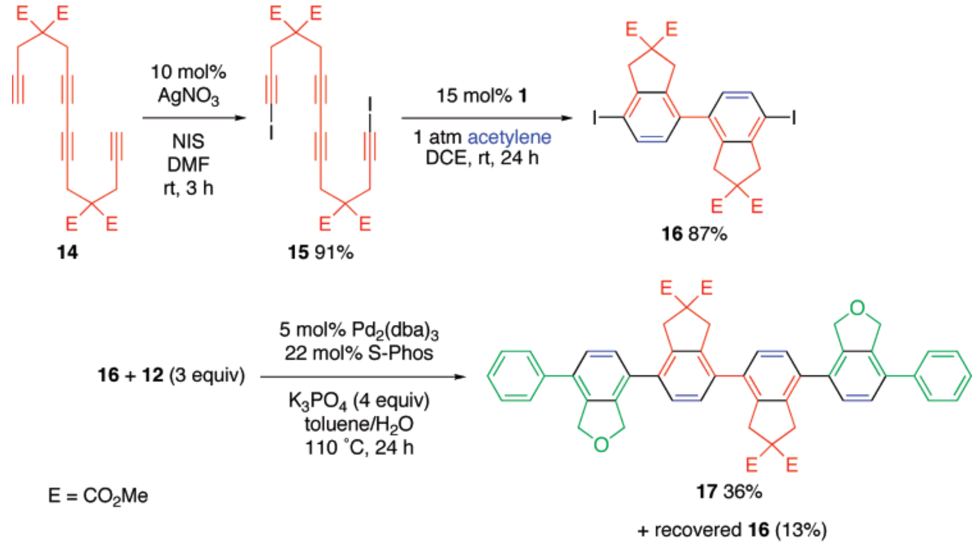
---

[17] (a) Martin, R. E.; Diedrich, F. *Angew. Chem. Int. Ed.* **1999**, *38*, 1350−1377. (b) Segura, J. L.; Martín, N. *J. Mater. Chem.* **2000**, *10*, 2403−2435.

[18] Yamamoto, Y.; Hattori, K.; Ishii, J.; Nishiyama, H. *Tetrahedron* **2006**, *62*, 4294−4305.

[19] For examples of cyclotrimerization of polyynes, leading to oligo-*p*-phenylenes, see: McDonald, F. E.; Smolentsev, V. *Org. Lett.* **2002**, *4*, 745−748.

Scheme 7



diynes via the Ag-catalyzed C*sp*-H iodination/Cp*RuCl-catalyzed cycloaddition sequence. One of the obtained *p*-diiodobenzenes was utilized as a halide component for cross-coupling reactions such as Mizoroki−Heck reaction, Sonogashira reaction, and Suzuki−Miyaura coupling. Moreover, we achieved the modular synthesis of penta- and hexa-*p*-phenylenes by Suzuki−Miyaura coupling of a diiodobenzene or diiodobiaryl with a biarylboronic acid ester.

Acknowledgment. This research was partially supported by the Ministry of Education, Science, Sports and Culture, Japan, Grant-in-Aid for Young Scientists (A), 17685008.

Supporting Information Available: Experimental procedures and analytical data for products. These materials are available free of charge via Internet at http://pubs.acs.org.

JA061619P