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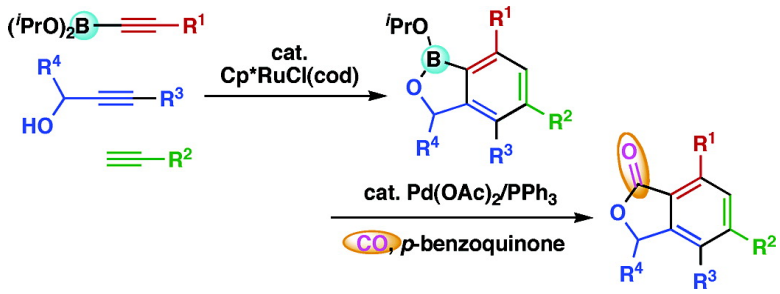

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Cp*RuCl-Catalyzed Formal Intermolecular Cyclotrimerization of Three Unsymmetrical Alkynes through a Boron Temporary Tether: Regioselective Four-Component Coupling Synthesis of Phthalides

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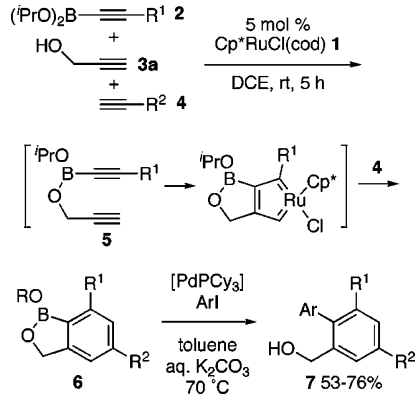
Abstract: Highly substituted phthalides were efficiently synthesized by sequential Cp*RuCl-catalyzed cyclotrimerization of alkynylboronates, propargyl alcohols, and terminal alkynes and palladium(II)-catalyzed carbonylation of the resultant arylboronates. The intermediate arylboronate was isolated and unambiguously characterized by X-ray crystallography. The perfect regioselectivity of the ruthenium-catalyzed formal intermolecular cyclotrimerization was discussed on the basis of the density functional calculations of a boraruthenacycle intermediate

Introduction

The transition-metal-catalyzed [2 + 2 + 2] alkyne cyclotrimerization has received continuous attention as a straightforward route to substituted benzenes.[1] The selective cyclotrimerizations of three different alkynes have been accomplished using stoichiometric transition-metal reagents.[2−4] Although the development of a catalytic protocol is highly desirable in terms of the atom economy,[5] the catalytic cyclotrimerization of three different alkynes has not been realized to date, except for the palladium-catalyzed formal cyclotrimerization of electron-deficient alkynes, 1,3-diynes, and terminal alkynes via 1,3-enyne intermediates.[6] In this context, intramolecular approaches utilizing diynes or triynes have been explored as promising tools to afford polycyclic arenes selectively.[7] If the resultant polycyclic framework is not desirable, an unnecessary ring moiety can be cleaved and transformed into suitable side chains. However, tedious ring-cleaving procedures and/or the preparation of polyalkyne substrates with a cleavable tether and functionalized substituents at appropriate positions can be troublesome. To address these issues, we recently reported the Cp*RuCl-catalyzed regioselective [2 + 2 + 2] cyclotrimerization of alkynylboronates, propargyl alcohol, and terminal alkynes, which proceeds through unsymmetrical diynes with a temporal C−B−O linkage (Scheme 1).[8]

Scheme 1



In this novel temporary connecting approach,[9−11] we successfully carried out the subsequent Suzuki−Miyaura coupling[12] of the resultant arylboronates with aryl iodides to obtain variously substituted biaryls as single regioisomers in reasonable yields. In this paper, we report the full details of our studies on the Cp*RuCl-catalyzed formal intermolecular cyclotrimerization through a boron temporary tether, featuring (1) the mechanistic analysis on the basis of the density functional calculations of a model boraruthenacycle intermediate, (2) the isolation and characterization of a partially hydrolyzed arylboronate product,

(1) (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.
(2) (a) Wakatsuki, Y.; Kuramitsu, T.; Yamazaki, H. *Tetrahedron Lett.* **1974**, 4549−4552. (b) Yamazaki, H.; Wakatsuki, Y. *J. Organomet. Chem.* **1977**, *139*, 157−167.
(3) (a) Takahashi, T.; Kotora, M.; Xi, Z. *J. Chem. Soc., Chem. Commun.* **1995**, 361−362. (b) Takahashi, T.; Xi, Z.; Yamazaki, A.; Liu, Y.; Nakajima, K.; Kotora, M. *J. Am. Chem. Soc.* **1998**, *120*, 1672−1680. (c) Takahashi, T.; Tsai, F.-Y.; Li, Y.; Nakajima, K.; Kotora, M. *J. Am. Chem. Soc.* **1999**, *121*, 11093−11100.
(4) (a) Suzuki, D.; Urabe, H.; Sato, F. *J. Am. Chem. Soc.* **2001**, *123*, 7925−7926. (b) Tanaka, R.; Nakano, Y.; Suzuki, D.; Urabe, H. Sato, F. *J. Am. Chem. Soc.* **2002**, *124*, 9682−9683.
(5) (a) Trost, B. M. *Science* **1991**, *254*, 1471−1476. (b) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 259−281.
(6) Gevorgyan, V.; Radhakrishnan, U.; Takeda, A.; Rubina, M.; Rubin, M.; Yamamoto, Y. *J. Org. Chem.* **2001**, *66*, 2835−2841.
(7) (a) Saito, S.; Yamamoto, Y. *Chem. Rev.* **2000**, *100*, 2901−2915. (b) Yamamoto, Y. *Curr. Org. Chem.* **2005**, *9*, 503−519.
(8) Yamamoto, Y.; Ishii, J.; Nishiyama, H.; Itoh, K. *J. Am. Chem. Soc.* **2004**, *126*, 3712−3713.

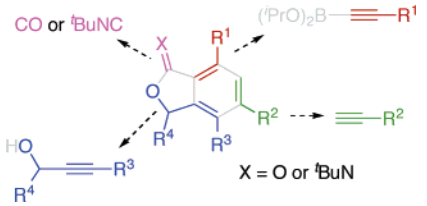


Figure 1. Novel four-component coupling approach to substituted phthalides and the imidate analogue.

and (3) the development of the novel four-component coupling strategy to synthesize multiply substituted 1(3*H*)-isobenzofuranones (phthalides) by combining the Cp*RuCl-catalyzed formal intermolecular cyclotrimerization and the palladium(II)-catalyzed carbonylation (Figure 1).

Results and Discussion

Regioselective Formation of Cyclic Arylboronates via Cp*RuCl-Catalyzed Cyclotrimerization of Three Unsymmetrical Alkynes through a Boron Temporary Tether. To realize the Ru(II)-catalyzed cyclotrimerization of three different monoalkynes, we chose a temporary tether through a C−B−O linkage[8,10] rather than widely prevalent C−Si−O or O−Si−O linkages,[9,11] because relatively long Si−C and Si−O bonds might cause a deleterious effect on the formation of a key ruthenacycle intermediate. The oxidative cyclization of two alkyne molecules on the ruthenium center was proposed as the rate-determining step on the basis of the previous theoretical study,[13b] and therefore, a diyne intermediate formed from an alkynylboronate and propargyl alcohol by ester exchange must selectively undergo the ruthenacycle formation. Indeed, 1.1 equiv of propargyl alcohol (**3a**) was added dropwise over 15 min to a solution of 5 mol % Cp*RuCl(cod) (**1**) (Cp* = η^5-C_5Me_5, cod = 1,5-cyclooctadiene), alkynylboronates **2**, and 4 equiv of terminal alkynes **4** in 1,2-dichloroethane (DCE) at room temperature, and the solution was stirred at ambient temperature for 5−24 h to give rise to cyclic arylboronates **6** (R = ^{i}Pr), which were further converted to substituted biaryls **7** via Suzuki−Miyaura coupling with aryl iodides (Scheme 1).[8] It is noteworthy that the biaryls were obtained as single regioisomers, indicative of the cycloaddition of the boron-tethered diynes **5** with terminal alkynes **4** being completely regioselective. In our previous studies, it was found that similar unsymmetrical diynes bearing a substituent on one alkyne terminal reacted with monoalkynes to afford meta isomers with excellent regioselectivity as high as meta:ortho = 95:5.[13] We also found that diynes bearing an internal conjugated carbonyl group exhibit moderate regioselectivity favoring the insertion of monoalkynes into Ru−C bonds anti to the carbonyl group.[14] To shed light on the origin of the perfect regioselectivity observed for the present formal intermolecular cyclotrimerization, we carried out density functional theory (DFT) calculations of model boraruthenacycle intermediate **I** (for details of the computation methods, see the Supporting Information). Previous DFT calculations revealed that lactone-fused ruthenacycle **II** is unsymmetrical in terms of the natural charges, and the alkyne insertion was considered to take place at the more negatively charged α carbon anti to the carbonyl group (see Supporting Information Figure S2).[14] A similar trend was also found for the boraruthenacycle **I** (Figure 2). In this particular case, the decrease of the natural charge on the C4 carbon is more pronounced than that in **II** as a result of the strong electron-withdrawing effect of the boronate moiety. Therefore, it is concluded that the electronic directing effect allows the monoalkyne to react at the more electronegative C1 carbon anti to the boronate moiety.

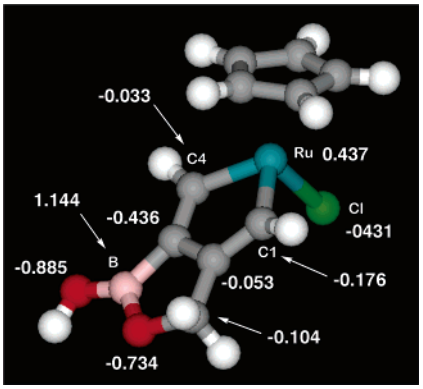


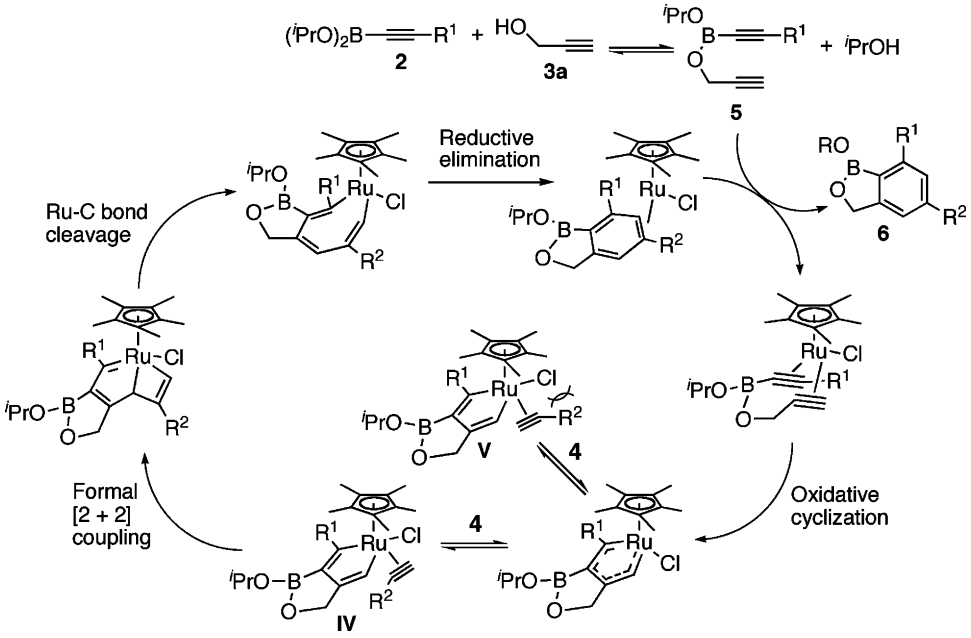
Figure 2. DFT-optimized structure of ruthenacycle intermediate model **I** with natural charges.

The proposed mechanism is outlined in Scheme 2. The ^{1}H NMR measurement of a solution of alkynylboronate **2a** and propargyl alcohol **3a** in $CDCl_3$ revealed that they were in equilibrium with diyne **5** (R^1 = ^{n}Bu) at ambient temperature. When diyne substrate **5** is consumed by the oxidative cyclization on the Cp*RuCl fragment, this equilibrium shifts to supply **5** with the catalytic cycle. The coordination of monoalkyne **4** to the boraruthenacycle intermediate reversibly gives rise to alkyne complexes. The coordinated alkyne is considered to be inserted exclusively into the Ru−C bond anti to the boronate moiety as a consequence of the synergistic effect of both the steric influence of the substituent R^1 and electronic directing effect of the electron-deficient boron center. In addition, the steric repulsion between the chloro ligand and the substituent on the coordinated monoalkyne might destabilize an alkyne complex, **V**. Therefore, the preferential pathway via alternative alkyne complex **IV** leads to the exclusive formation of the observed arylboronate regioisomer **6**.

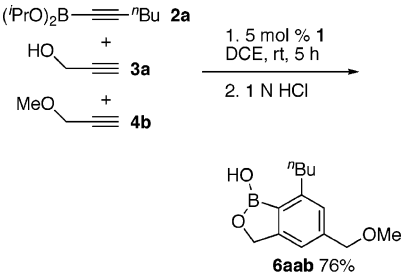
Isoration, Cheracterization, and Reactivity of Boraphthalide. The subsequent one-pot Suzuki−Miyaura coupling of cyclotrimerization products **6** gave rise to variously substituted biaryls **7** (Scheme 1). Although arylboronates **6** (R = ^{i}Pr) could

(9) The cyclotrimerization utilizing the silicon temporary tether was communicated; see: Chouraqui, G.; Petit, M.; Aubert, C.; Malacria, M. *Org. Lett.* **2004**, *6*, 1519−1521.
(10) For examples of boron temporary tethers, see: (a) Narasaka, K.; Shimada, S.; Osoda, K.; Iwasawa, N. *Synthesis* **1991**, 1171−1172, (b) Shimada, S.; Osoda, K.; Narasaka, K. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 1254−1257. (c) Nicolaou, K. C.; Liu, J.-J.; Yang, Z.; Ueno, H.; Sorenssen, E. J.; Claiborne, C. F.; Guy, R. K.; Hwang, C.-K.; Nakada, M.; Nantermet, P. G. *J. Am. Chem. Soc.* **1995**, *117*, 634−644. (d) Batey, R. A.; Thadani, A. N.; Lough, A. J. *J. Am. Chem. Soc.* **1999**, *121*, 450−451. (e) Batey, R. A.; Thadani, A. N.; Lough, A. J. *Chem. Commun.* **1999**, 475−476. (f) Micalizio, G. C.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2002**, *41*, 152−154. (g) Micalizio, G. C.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2002**, *41*, 3272−3276.
(11) For reviews of the temporary connecting approach, see: (a) Bols, M.; Skrydstrup, T. *Chem. Rev.* **1995**, *95*, 1253−1277. (b) Fensterbank, L.; Malacria, M.; Sieburth, S. M. *Synthesis* **1997**, 813−854. (c) Gauthier, D. R., Jr.; Zandi, K. S.; Shea, K. J. *Tetrahedron* **1998**, *54*, 2289−2338.
(12) (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483. (b) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147−168. (c) Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron* **2002**, *58*, 9633−9695. (d) Bellina, F.; Carpita, A.; Rossi, R. *Synthesis* **2004**, 2419−2440.
(13) (a) Yamamoto, Y.; Ogawa, R.; Itoh, K. *Chem. Commun.* **2000**, 549−550. (b) Yamamoto, Y.; Arakawa, T.; Ogawa, R.; Itoh, K. *J. Am. Chem. Soc.* **2003**, *125*, 12143−12160.
(14) Yamamoto, Y.; Kinpara, K.; Saigoku, T.; Nishiyama, H.; Itoh, K. *Org. Biomol. Chem.* **2004**, *2*, 1287−1294.

Scheme 2



Scheme 3



not be isolated in pure form because of their facile hydrolysis, the corresponding half-esters (R = H, so-called boraphthalide) are likely the intermediates for Suzuki−Miyaura coupling under the present aqueous conditions. The parent nonsubstituted boraphthalide was first reported in 1957,[15] and since then, boraphthalides have been employed as Suzuki−Miyaura coupling partners in organic synthesis for some time.[16] In particular, dimethoxyboraphthalide prepared by means of the direct ortho-metalation of 2,5-dimethoxybenzyl alcohol was elegantly applied to the construction of the biaryl moiety of vancomycin by Nicolaou and co-workers.[16b−f] Whereas boraphthalides are such valuable aromatic building blocks, no general synthetic route to the disubstituted derivatives was found in the literature.[17] To elucidate the intermediacy of the arylboronates **6**, we attempted to obtain partially hydrolyzed boraphthalide **6aab** (Scheme 3). The reaction of alkynylboronate **2a**, propargyl alcohol (**3a**) (1.1 equiv), and methyl propargyl ether (**4b**) (4 equiv) was conducted in the presence of 5 mol % **1** in DCE at room temperature for 5 h. Subsequent acidic hydrolysis of the resultant arylboronate afforded desired **6aab** in 76% yield. Its structure was unambiguously established by X-ray crystallography. As shown in Figure 3, **6aab** is a substituted boraphthalide, comprising a cyclic ester of *o*-hydroxymethylphenylboronic acid. The B1−C2 distance

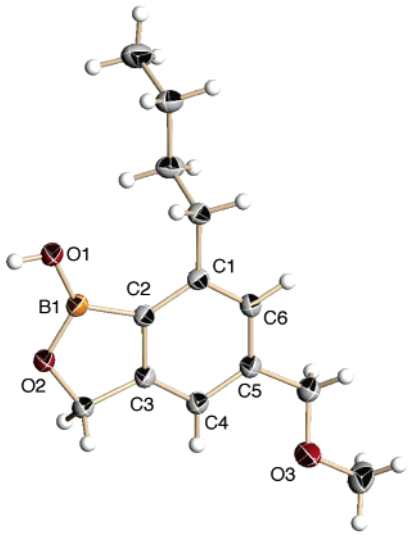


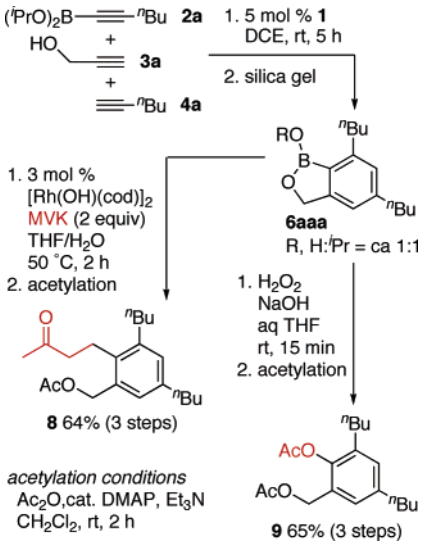
Figure 3. ORTEP diagram of **6aab** (50% ellipsoids). Selected bond lengths (Å) and angles (deg): B1−O1 = 1.3447(14), B1−O2 = 1.3896(15), B1−C2 = 1.5557(15), C1−C2 = 1.4019(14), C2−C3 = 1.3961(14), C3−C4 = 1.3907(14), C4−C5 = 1.3917(15), C5−C6 = 1.4016(15), C6−C1 = 1.3882(14), O1−B1−O2 = 122.56(10), O1−B1−C2 = 129.41(10), C2−B1−O2 = 108.03(9).

(15) (a) Torssell, K. *Ark. Kemi* **1957**, *10*, 507−511. (b) Snyder, H. R.; Reedy, A. J.; Lennarz, W. J. *J. Am. Chem. Soc.* **1958**, *80*, 835−838. (c) Haynes, R. R.; Snyder, H. R. *J. Org. Chem.* **1964**, *29*, 3229−3233.

(16) (a) Brown, A. G.; Crimmin, M. J.; Edwards, P. D. *J. Chem. Soc., Perkin Trans. 1* **1992**, 123−130. (b) Nicolaou, K. C.; Ramanjulu, J. M.; Natarajan, S.; Bräse, S.; Li, H.; Boddy, C. N. C.; Rübsam, F. *Chem. Commun.* **1997**, 1899−1900. (c) Nicolaou, K. C.; Natarajan, S.; Li, H.; Jain, N. F.; Hughes, R.; Solomon, M. E.; Ramanjulu, J. M.; Boddy, C. N. C.; Takayanagi, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 2708−2714. (d) Nicolaou, K. C.; Li, H.; Boddy, C. N. C.; Ramanjulu, J. M.; Yue, T.-Y.; Natarajan, S.; Chu, X.-J.; Bräse, S.; Rübsam, F. *Chem.*—Eur. *J.* **1999**, *5*, 2584−2601. (e) Nicolaou, K. C.; Boddy, C. N. C.; Li, H.; Koumbis, A. E.; Hughes, R.; Natarajan, S.; Jain, N. F.; Ramanjulu, J. M.; Bräse, S.; Solomon, M. E. *Chem.*—Eur. *J.* **1999**, *5*, 2602−2621. (f) Nicolaou, K. C.; Koumbis, A. E.; Takayanagi, M.; Natarajan, S.; Jain, N. F.; Bando, T.; Li, H.; Hughes, R. *Chem.*—Eur. *J.* **1999**, *5*, 2622−2636. (g) Gallant, M.; Belley, M.; Carrière, M.-C.; Chateauneuf, A.; Denis, D.; Lachance, N.; Lamontagne, S.; Metters, K. M.; Sawyer, N.; Slipetz, D.; Truchon, J. F.; Labelle, M. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3813−3816. (h) Link, J. T.; Sorensen, B. K.; Patel, J.; Emery, M.; Grynfarb, M.; Goos-Nilsson, A. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2209−2212.

(17) (a) Lennarz, W. J.; Snyder, H. R. *J. Am. Chem. Soc.* **1960**, *82*, 2172−2175. (b) Hawwkins, R. T.; Lennarz, W. J.; Snyder, H. R. *J. Am. Chem. Soc.* **1960**, *82*, 3053−3059. (c) Grassberger, M. A. *Liebigs Ann. Chem.* **1985**, 683−688.

Scheme 4

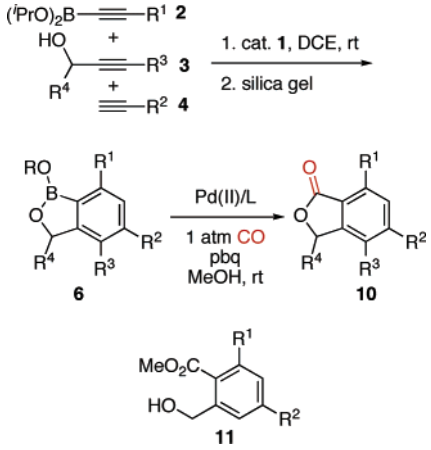


of 1.5557(15) Å is similar to B−C bond lengths in typical three-coordinate boron compounds.[18] The exocyclic B1−O1 bond length is shorter than that of the endocyclic B1−O2 bond (1.3447(14) Å vs 1.3896(15) Å). The sum of the valence angles around the B1 center of 360° shows the typical sp^2 hybridization.

Whereas the boraphthalides are potentially versatile intermediates in organic synthesis, their use has been confined to Suzuki−Miyaura coupling.[8,16] Thus, we next explored the reactivity of the boraphthalides (Scheme 4). The standard cyclotrimerization procedure and purification by silica gel short column chromatography afforded **6aaa** as a mixture of the borapthalide and its isopropyl ester. In the presence of 3 mol % $[Rh(OH)(cod)]_2$, Hayashi−Miyaura-type catalytic Michael reaction[19] of **6aaa** with methyl vinyl ketone (MVK) efficiently proceeded in aqueous THF at 50 °C to afford **8** in 64% yield after acetylation. Without purification of **6aaa**, the yield of **8** was reduced and a protiodeboration side product was observed. The oxidation of **6aaa** at room temperature followed by exhaustive acetylation gave phenol acetate **9** in 65% yield. In contrast, **6aaa** failed to undergo previously reported catalytic reactions such as the Cu(II)-catalyzed amination[20] and the Pd(II)-catalyzed Sonogashira-type alkynylation.[21]

Development of Palladium-Catalyzed Carbonylation of Boraphthalide. In our sequential coupling processes, the in situ formation of the boron-tethered diynes from the alkynylboronates and propargyl alcohol plays a pivotal role in the first cyclotrimerization stage, and the boronate terminal can be utilized for the C−C or C−O bond formations in the second step. On the contrary, the hydroxy terminal of propargyl alcohol simply remains intact after the overall sequential process. Thus, to fully utilize both the boronate and the hydroxy termini, we further envisaged that the catalytic carbonylation of the aryl-

Scheme 5



boronate intermediates **6** would afford substituted phthalides as a consequence of the simultaneous formations of C−C and C−O bonds (Scheme 5). The catalytic alkoxycarbonylation of arylboronates, however, has remained almost unexplored,[22] and to the best of our knowledge, only one example of the synthesis of lactones from cyclic arylboronates was briefly examined in a recent technical note.[23] This is in striking contrast to the palladium-catalyzed carbonylation of *o*-halobenzyl alcohols being well established.[24]

To realize the sequential four-component coupling synthesis of phthalides, we first explored the carbonylation of **6aaa** ($R^1 = R^2 = {}^n$Bu) as summarized in Table 1. The freshly prepared **6aaa** from **2a**, **3a**, and **4a** was filtered through a silica gel short column and treated with 1 equiv of $Pd(OAc)_2$ in MeOH at room temperature for 1 h under a CO atmosphere. Purification by silica gel column chromatography afforded the desired phthalide **10aaa** in 73% yield in two steps (run 1). In contrast, a catalytic reaction never proceeded in the absence of a phosphine ligand,

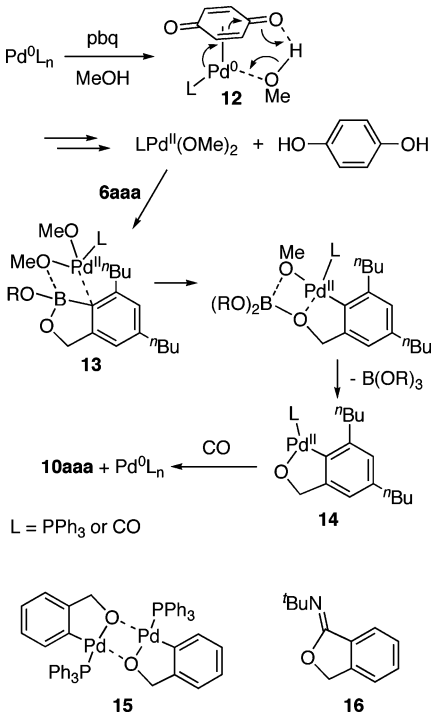
Table 1. Optimization of Carbonylation of **6aaa** Leading to **10aaa**[a]

run	[Pd]/mol %	L, [L]/mol %	pbq amt/equiv	time/h	yield[b]/%
1	100	none	0	1	73
2	5	PPh_3, 6	2	3	64[c]
3[d]	5	PPh_3, 6	2	2	73
4[d]	5	PPh_3, 12	2	1	71
5[d]	5	PPh_3, 12	1	1	73
6[d]	1	PPh_3, 2.4	1	24	44
7[d]	5	dppf, 6	1	24	41
8[d]	5	PCy_3, 12	1	3	58

[a] In the presence of $Pd(OAc)_2$, freshly prepared **6aaa** was treated with 1 atm of CO in MeOH at room temperature. [b] Isolated yields based on alkynylboronate **2a** in two steps. [c] **11aaa** was also obtained in 10% yield. [d] With acidic workup.

(18) Odom, D. In *Comprehensive Organometallic Chemistry*; Wilkinson, G., Stone, F. G. A., Abel, E. W., Eds.; Pergamon: Oxford, 1982; Vol. 1, pp 253−310.
(19) (a) Sakai, M.; Hayashi, H.; Miyaura, N. *Organometallics* **1997**, *16*, 4229−4231. (b) Takaya, Y.; Ogasawara, M.; Hayashi, T.; Sakai, M.; Miyaura, N. *J. Am. Chem. Soc.* **1998**, *120*, 5579−5580. (c) Sakuma, S.; Itooka, R.; Miyaura, N. *J. Org. Chem.* **2000**, *65*, 5951−5955. (d) Hayashi, T.; Takahashi, M.; Takaya, Y.; Ogasawara, M. *J. Am. Chem. Soc.* **2002**, *124*, 5052−5058. (e) Itooka, R.; Iguchi, Y.; Miyaura, N. *J. Org. Chem.* **2003**, *68*, 6000−6004.
(20) Quach, T. D.; Batey, R. A. *Org. Lett.* **2003**, *5*, 4397−4400.
(21) Zou, G.; Zhu, J.; Tang, J. *Tetrahedron Lett.* **2003**, *44*, 8709−8711.
(22) (a) Miyaura, N.; Suzuki, A. *Chem. Lett.* **1981**, 879−882. (b) Ohe, T.; Ohe, K.; Uemura, S.; Sugita, N. *J. Organomet. Chem.* **1988**, *344*, C5−C7. (c) Cho, C. S.; Ohe, T.; Uemura, S. *J. Organomet. Chem.* **1995**, *496*, 221−226.
(23) Zhou, Q, J.; Worm, K.; Dolle, R. E. *J. Org. Chem.* **2004**, *69*, 5147−5149.
(24) For examples of palladium-catalyzed carbonylation of *o*-halobenzyl alcohols leading to phthalides, see: (a) Mori, M.; Chiba, K.; Inotsume, N.; Ban, Y. *Heterocycles* **1979**, *12*, 921−924. (b) Cowell, A.; Stille, J. K. *J. Am. Chem. Soc.* **1980**, *102*, 4193−4198. (c) Orito, K.; Miyazawa, M.; Kanbayashi, R.; Tokuda, M.; Suginome, H. *J. Org. Chem.* **1999**, *64*, 6583−6596. (d) Kayaki, Y.; Noguchi, Y.; Iwasa, S.; Ikariya, T.; Noyori, R. *Chem. Commun.* **1999**, 1235−1236. (e) Lee, Y.; Fujiwara, Y.; Ujita, K.; Nagamoto, M.; Ohta, H.; Shimizu, I. *Bull. Chem. Soc. Jpn.* **2001**, *74*, 1437−1443. (f) Wu, X.; Mahalingam, A. K.; Wan, Y.; Alterman, M. *Tetrahedron Lett.* **2004**, *45*, 4635−4638.

Scheme 6



L. The catalytic reaction was carried out with 5 mol % $Pd(OAc)_2$, 6 mol % PPh_3, and 2 equiv of *p*-benzoquinone (pbq) for 3 h under otherwise the same conditions to give **10aaa** and methoxycarbonylation product **11aaa** in 64% and 10% yields, respectively (run 2). To convert **11aaa** to **10aaa**, the crude reaction mixture was treated with a catalytic amount of aqueous HCl before chromatographic purification. As a result, **10aaa** was obtained as a sole product in 73% yield (run 3). The reaction never took place in THF, indicative of a protic solvent being essential. No carbonylation product was observed, when $PdCl_2(PhCN)_2$ was employed instead of $Pd(OAc)_2$. The increased amount of PPh_3 (12 mol %) accelerated the reaction rate (run 5), and the reduced amount of pbq (1 equiv) gave no deteriorative effect (run 6). On the other hand, the reduced catalyst loading of 1 mol % resulted in low conversion (run 6). Neither bidentate 1,1′-bis(diphenylphosphino)ferrocene (dppf), which was used in the previous example,[23] nor bulky electron-rich tricyclohexylphosphine (PCy_3), which is the optimal ligand for the synthesis of biaryls,[8] improved the yield of **10aaa** (runs 7 and 8).

The possible mechanism of the present catalytic carbonylation was outlined in Scheme 6. The catalytic cycle probably starts from the transmetalation between the arylboronate and a palladium(II) species, and the resultant arylpalladium intermediate **14** undergoes subsequent carbonyl insertion and the reductive elimination of phthalide **10aaa** to give rise to a palladium(0) species. Thus, the catalytic cycle requires the oxidation step to regenerate a catalytically active palladium(II) species. To this end, we used *p*-benzoquinone as a stoichiometric oxidant because air oxidation conditions might be accompanied by the formation of phenols from arylboronates. More importantly, the use of MeOH as a solvent plays a significant role. The reoxidation step probably proceeds via a Pd(0)−quinone complex as previously suggested by Bäckvall and co-workers.[25] MeOH acts as a proton donor to palladium-coordinated quinone **12**. As a consequence, a methoxypalladium(II) species, [LPd-$(OMe)_2$], might be formed with the concomitant extrusion of hydroquinone. Previous studies revealed that transition-metal hydroxides or alkoxides facilitate the transmetalation with organoboron compounds by donating their hydroxy or alkoxy ligand to the highly oxophilic boron center.[19d,26] The methoxypalladium(II) complex is also considered to undergo transmetalation efficiently even at ambient temperature via cyclic transition state **13** to finally afford the oxapalladacycle intermediate **14**. Recently, Echavarren and co-workers synthesized closely related dimeric oxapalladacycle phosphine complex **15** starting from *o*-iodobenzyl alcohol, and its structure was clearly established by X-ray crystallography.[27] Moreover, **15** proved to react with ^{t}BuNC at 23 °C to give rise to imidate **16** in 54% yield (vide infra).

Scope and Limitations of Four-Component Coupling Synthesis of Substituted Phthalides. Phthalides are fascinating oxygen heterocycles which are found in various natural products and possess a wide range of pharmacological properties.[28] Whereas such valuable substituted phthalides have been conventionally synthesized from appropriately substituted benzene precursors,[24,29] the direct catalytic assembly of the isobenzofuranone framework from several acyclic precursors is highly attractive in terms of the atom economy.[5] Along this line, the transition-metal-catalyzed intramolecular cycloadditions of enynes or diynes have been developed.[14,30] These examples, however, often require tedious and/or less atom economical synthetic operations for the preparation of ester-tethered substrates. Poor regioselectivity is also a crucial disadvantage for the cycloaddition of unsymmetrical diynes and monoynes.[14,30] Besides, complexity-generating multicomponent coupling reactions become increasingly important in terms of the diversity-oriented synthesis toward the rapid construction of small molecular libraries.[31] With these issues in mind, we investigated the scope and limitations of our novel four-component coupling strategy (Figure 1).

Under optimal reaction conditions, substituted phthalides were synthesized from various alkyne precursors listed in Figure 4, and the results were summarized in Table 2. The present four-component coupling tolerated functional groups such as an ether, a chloride, or an ester (runs 2−4). The corresponding phthalides **10aab**−**10aad** were obtained in 67−72% yields. Although prolonged reaction times were required for the cyclotrimerization of aromatic monoalkynes such as ethynylbenzene (**4e**) and

(25) Grennberg, H.; Gogoll, A.; Bäckvall, J.-E. *Organometallics* **1993**, *12*, 1790−1793.
(26) Nishikawa, T.; Yamamoto, Y.; Miyaura, N. *Organometallics* **2004**, *23*, 4317−4324.
(27) Fernández-Rivas, C.; Cárdenas, D. J.; Martín-Matute, B.; Monge, Á; Gutiérrez-Puebla, E.; Echavarren, A. M. *Organometaalics* **2001**, *20*, 2998−3006.
(28) (a) Ramachandran, P. V.; Chen, G.-M.; Brown, H. C. *Tetrahedron Lett.* **1996**, *37*, 2205−2208. (b) Kitayama, T. *Tetrahedron: Asymmetry* **1997**, *8*, 3765−3774. (c) Knepper, K.; Ziegert, R. E.; Bräse, S. *Tetrahedron* **2004**, *60*, 8591−8603 and references therein.
(29) Selected examples: (a) Beak, P.; Snieckus, V. *Acc. Chem. Res.* **1982**, *15*, 306−322. (b) Ishii, Y.; Ikariya, T.; Saburi, M.; Yoshikawa, S. *Tetrahedron Lett.* **1986**, *27*, 365−368. (c) Kondo, T.; Kodai, K.; Mitsudo, T.; Watanabe, Y. *J. Chem. Soc., Chem. Commun.* **1994**, 755−756. (d) Hosoya, T.; Kuriyama, Y.; Suzuki, K. *Synlett* **1995**, 635−638. (e) Hayat, S.; Atta-ur-Rahman, Choudhary, M. I.; Khan, K. M.; Bayer, E. *Tetrahedron Lett.* **2001**, *42*, 1647−1649.
(30) For selected examples, see: (a) Kawasaki, T.; Saito, S.; Yamamoto, Y. *J. Org. Chem.* **2002**, *67*, 2653−2658. (b) Bhatarah, P.; Smith, E. H. *J. Chem. Soc., Parkin Trans. 1* **1992**, 2163-2168. (c) Witulski, B.; Zimmermann, A. *Synlett* **2002**, 1855−1859. (d) Sato, Y.; Tamura, T.; Mori, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2436−2440. (e) Tanaka, K.; Nishida, G.; Wada, A.; Noguchi, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 6510−6512.
(31) (a) Schreiber, S. L. *Science* **2000**, *287*, 1964−1969. (b) Burke, M. D.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 46−58.

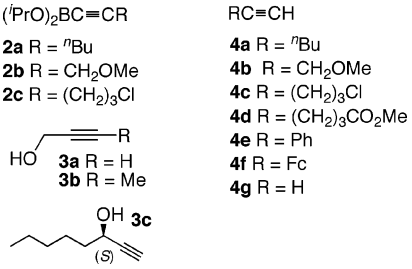
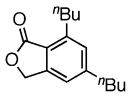
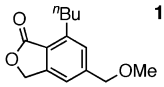
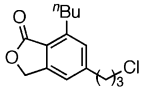
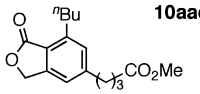
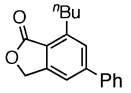
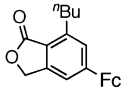
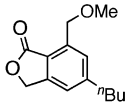
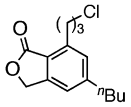
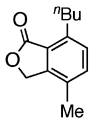
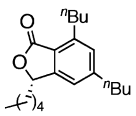


Figure 4. Starting alkynes used in this study.

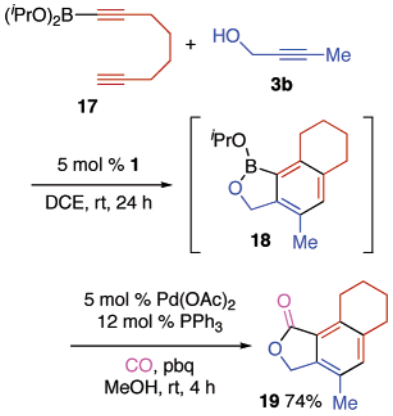
ethynylferrocene (**4f**), the corresponding biaryl phthalides **10aae** and **10aaf** were isolated in 56% and 57% yields, respectively (runs 5 and 6). Gaseous acetylene **4g** (1 atm) was also used as the third alkyne component, leading to the selective formation of phthalide **10aag** in 61% yield (run 7). The use of alkynylboronates **2b** and **2c** selectively afforded **10baa** and **10caa** in 72% and 73% respective yields, which are the regioisomers of **10aab** and **10aac**, respectively (runs 8 and 9). In addition to **3a**, 2-butyn-1-ol (**3b**) was employed as an internal propargyl alcohol component albeit with a longer reaction time of 72 h. The regioselective cyclotrimerization of 1-hexynylboronate **2a**, **3b**, and acetylene (**4g**) was followed by the palladium-catalyzed carbonylation to afford 1,2,3,4-substituted benzene **10abg** in 47% yield (run 10). As demonstrated by these results, multiply substituted phthalide regioisomers can be synthesized with a defined substitution pattern by means of the present sequential catalytic process.

Table 2. Synthesis of Phthalides via Sequential Four-Component Coupling[a]

run	alkynes time[b] / h	product (yield[c] / %)
1	**2a** / **3a** / **4a** 5 / 1	 **10aaa** (73)
2	**2a** / **3a** / **4b** 5 / 1	 **10aab** (69)
3	**2a** / **3a** / **4c** 5 / 2	 **10aac** (72)
4	**2a** / **3a** / **4d** 5 / 2	 **10aad** (67)
5	**2a** / **3a** / **4e** 24 / 3	 **10aae** (56)
6	**2a** / **3a** / **4f** 24 / 2	 **10aaf** (57)
7	**2a** / **3a** / **4g** 24 / 2	 **10aag** (61)
8	**2b** / **3a** / **4a** 24 / 2	 **10baa** (72)
9	**2c** / **3a** / **4a** 24 / 2	 **10caa** (73)
10	**2a** / **3b** / **4g** 72 / 2	 **10abg** (47)
11	**2a** / **3c** / **4a** 24 / 2	 **10aca** (58)

[a] The cyclotrimerization of **2**, **3** (1.1 equiv), and **4** (4 equiv) was carried out in the presence of 5 mol % (10 mol % for run 10) **1** in DCE under Ar at room temperature. The carbonylation was carried out with 5 mol % $Pd(OAc)_2$ and 12 mol % PPh_3, pbq (1 equiv) in MeOH at room temperature under CO. [b] Cyclotrimerization/carbonylation. [c] Yield in two steps.

Scheme 7



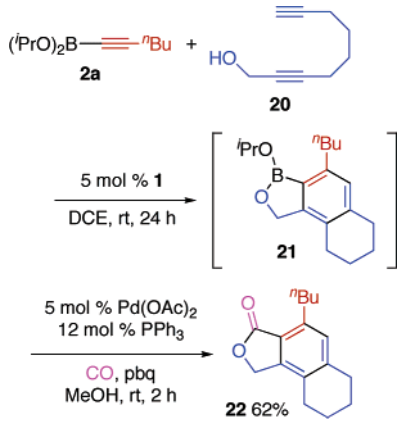
Scheme 7

The asymmetric synthesis of 3-alkylphthalides has been an intriguing subject, because they exhibit interesting biological activities.[28,30c] In our hand, optically active 3-alkylphthalides can be synthesized starting from readily available chiral propargyl alcohols. Indeed, the ruthenium-catalyzed cyclotrimerization of **2a**, commercial (*S*)-1-octyn-3-ol (**3c**), and **4a** was followed by the palladium-catalyzed carbonylation to afford optically pure 3-pentylphthalide **10aca** in 58% yield in two steps (Table 2, run 11).

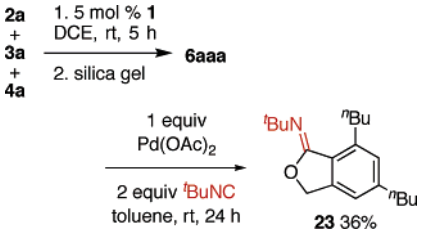
A fused tricyclic phthalide recently isolated from a soft coral, alcyopterosin E, exhibits mild cytotoxicity toward the Hep-2 (human larynx carcinoma) cell line.[32a] Such a tricyclic benzene skeleton can be constructed using completely intramolecular cyclotrimerization of triynes, and in fact, the first total synthesis of alcyopterosin E was recently accomplished along this line.[32b] In our hand, similar tricyclic phthalide frameworks were efficiently assembled by expanding the present protocol to the partially intramolecular versions of diynylboronate **17** or diynol **20**, which are expected to proceed regioselectively through temporary connected triyne intermediates. The 1,6-octadiynylboronate **17** and 2-butyn-1-ol (**3b**) (2 equiv) were treated with 5 mol % **1** in DCE at room temperature for 24 h. The resultant tricyclic boronate **18** was then subjected to the palladium-catalyzed carbonylation under the optimal conditions. Although the prolonged time of 4 h was required for the carbonylation, the desired tricyclic phthalide **19** was obtained in 74% yield with complete regioselectivity (Scheme 7). In a similar way, the combination of 1-hexynylboronate **2a** and 2,8-heptadiyne-

(32) (a) Palermo, J. A.; Brasco, M. F. R.; Spagnuolo, C.; Seldes, A. M. *J. Org. Chem.* **2000**, *65*, 4482. For the first total synthesis, see: (b) Witulski, B.; Zimmermann, A.; Gowans, N. D. *Chem. Commun.* **2002**, 2984−2985.

Scheme 8



Scheme 9



1-ol (**20**) (1.1 equiv) led to the selective formation of **22** in 62% yield via the corresponding tricyclic boronate intermediate **21** (Scheme 8).

Finally, we briefly examined the four-component coupling including an isocyanide in place of CO (Scheme 9). Recently, the reactions of aza- or oxapalladacycles with isocyanides were independently investigated by Vicente and Echavarren,[27,33] and the palladium-catalyzed syntheses of amidines and imidates from aryl halides were developed by Whitby and co-workers.[34] The ruthenium-catalyzed cyclotrimerization of **2a**, **3a**, and **4a** and the palladium-mediated reaction of the resultant cyclic arylboronate **6aaa** with ^{t}BuNC at room temperature for 24 h gave cyclic imidate **23** in 36% yield after purification with alumina column chromatography.

(33) Vicente, J.; Saura-Llamas, I.; Grünwald, C.; Alcaraz, C.; Jones, P. G.; Bautista, D. *Organometallics* **2002**, *21*, 3587−3595.

Conclusion

In conclusion, the ruthenium-catalyzed formal intermolecular cyclotrimerization of alkynylboronates, propargyl alcohols, and terminal alkynes by means of the boron temporary tether afforded cyclic arylboronates as single regioisomers. On the basis of the DFT calculations, the perfect regioselectivity was attributed to the steric and electronic directing effect of the unsymmetrical boraruthenacycle intermediate, which allows terminal alkynes to react at the less substituted and more electronegative α carbon.

The intermediacy of the cyclic arylboronates in our four-component coupling process was elucidated by the isolation and X-ray crystallographic analysis of their partial hydrolysis product boraphthalide. The boraphthalide-type intermediate also proved to undergo rhodium-catalyzed Michael addition or oxidation, leading to a phenol derivative. Moreover, we developed the palladium(II)-catalyzed carbonylation of the boraphthalides to establish the novel four-component coupling synthesis of substituted phthalides.

Acknowledgment. We gratefully acknowledge financial support from the Tokuyama Science Foundation and Japan Combinatorial Chemistry Focus Group Award in Synthetic Organic Chemistry, Japan.

Supporting Information Available: Experimental procedure, analytical data for the products, and CIF file. This material is available free of charge via the Internet at http://pubs.acs.org.

JA051377D

(34) (a) Saluste, C. G.; Whitby, R. J.; Furber, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 4156−4158. (b) Saluste, C. G.; Crumpler, S.; Furber, M.; Whitby, R. J. *Tetrahedron Lett.* **2004**, *45*, 6995−6996.