

Ru(II)-Catalyzed Chemo- and Regioselective Cyclotrimerization of Three Unsymmetrical Alkynes through Boron Temporary Tether. One-Pot Four-Component Coupling via Cyclotrimerization/Suzuki–Miyaura Coupling

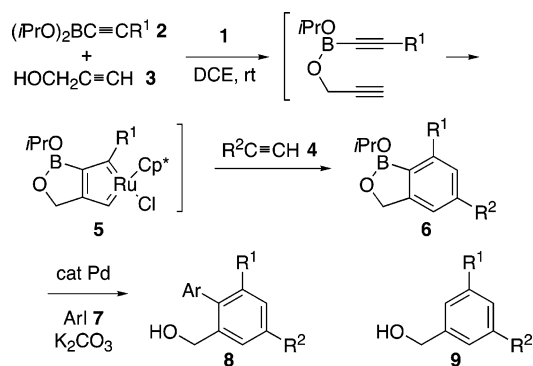
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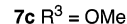
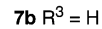
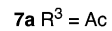
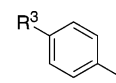
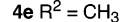
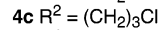
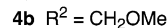
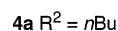
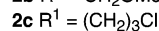
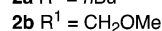
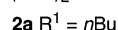
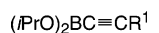
The transition-metal-catalyzed [2+2+2] alkyne cyclotrimerization is a straightforward approach to construct substituted benzenes from simple acyclic precursors.¹ One crucial disadvantage of this potentially useful methodology is the difficulty in controlling chemo- and regioselectivity. Although the selective cyclotrimerization of three different alkyne components was accomplished using stoichiometric transition-metal reagents,² the development of catalytic variants is highly important from the viewpoint of atom-economy.³ In this context, intramolecular approaches utilizing diynes or triynes have been explored as a promising tool to afford selectively polycyclic arenes.⁴ However, additional synthetic operations are required, if the resultant polycyclic framework is not desirable. An unnecessary ring moiety must be cleaved and transformed into required side chains. Moreover, the preparation of polyalkyne substrates equipped with a cleavable tether as well as substituents or functional groups at appropriate positions might be troublesome. One effective strategy to address this issue is the temporary connecting of monoalkynes with a displaceable tether group.⁵ In this Communication, we report the chemo- and regioselective catalytic cyclotrimerization of unsymmetrical three alkyne components by means of the temporary tethering approach with ruthenium catalysis (Scheme 1).

Scheme 1



We have previously reported that the cycloaddition of unsymmetrical 1,6-diynes with terminal monoalkynes proceeded at room temperature in the presence of a Ru(II) precatalyst, Cp*₂RuCl(cod) **1**, to afford bicyclic benzenes with excellent chemo- and regioselectivity.⁶ To realize Ru(II)-catalyzed cyclotrimerization of three different monoalkynes, we chose a temporary tether through a C–B–O linkage^{7–9} rather than widely prevalent C–Si–O or O–Si–O linkages,⁵ because relatively long Si–C and Si–O bonds might cause a deleterious effect on the formation of a key

ruthenacycle intermediate **5**.¹⁰ At the outset, 1.1 equiv of propargyl alcohol **3** was added dropwise over 15 min to a solution of 5 mol % **1**, 1-hexynylboronate **2a**, and 4 equiv of 1-hexyne **4a** in 1,2-dichloroethane (DCE) at room temperature, and the solution was stirred for 24 h. In the ¹H NMR spectrum of the crude product



7d



7e

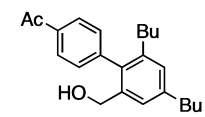
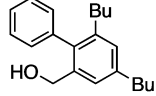
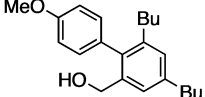
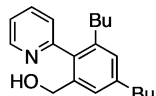
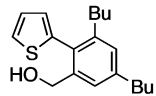
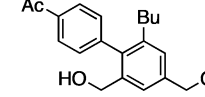
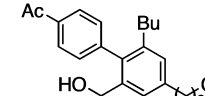
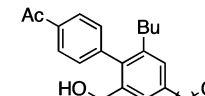
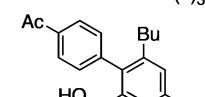
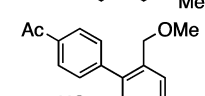
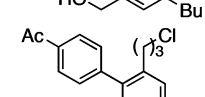
mixture, the absorptions of aromatic and benzylic methylene protons were observed together with those of two *n*-butyl chains, indicative of the cyclotrimerization of the three alkyne components taking place. Unfortunately, the expected arylboronate **6** could not be obtained in pure form, due to the facile exchange of the boronate ligands. Accordingly, we further attempted the Suzuki–Miyaura coupling¹¹ of crude **6**. Thus, **6** was treated with 5 mol % Pd(PPh₃)₄, 1.5 equiv of *p*-iodoacetophenone **7a**, and K₂CO₃ in refluxing THF/H₂O for 24 h to give rise to the desired **8aaa** in 32% yield together with a protodeboration product **9** in 22% yield. Significantly, both of these products were obtained as a single regioisomer.¹² To minimize the protodeboration, the cross-coupling was optimized, and we found that the reaction completed within 2 h in toluene/H₂O at 70 °C to afford **8aaa** exclusively in 71% yield. The couplings with less reactive iodobenzene **7b** and *p*-iodoanisole **7c** required prolonged reaction time of 20 h. In addition, the desired product **8aac** was accompanied by the phenyl-substituted product **8aab** as a result of the aryl-group interchange between the phosphorus-bound phenyl groups and the *p*-methoxyphenyl ligand.¹³ When the combination of tricyclohexylphosphine and Pd₂(dba)₃ was employed instead of Pd(PPh₃)₄, **8aac** was successfully obtained as a sole product in 70% yield.

Having optimized the coupling conditions, the generality of the one-pot four-component coupling was examined as summarized in Table 1. With a shorter reaction time of 5 h, the cyclotrimerization of **2a**, **3**, and **4a** proceeded satisfactorily, and the biphenyl derivative **8aaa** was obtained in 73% yield after the Suzuki–Miyaura coupling with **7a** (run 1). Similarly, **7b** and **7c** underwent cross-coupling with the same arylboronate intermediate to furnish **8aab** and **8aac** in comparable yields (runs 2 and 3). Although a longer reaction time was required to ensure the cross-coupling with 2-iodopyridine

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Table 1. One-Pot Four-Component Couplings

run	[2+2+2] ^a	S-M ^b	product (yield/%)
1	2a/4a, 5 h	7a, 3 h	 8aaa (73)
2	2a/4a, 5 h	7b, 6 h	 8aab (71)
3	2a/4a, 5 h	7c, 6 h	 8aac (70)
4	2a/4a, 5 h	7d, 24 h	 8aad (53)
5	2a/4a, 5 h	7e, 24 h	 8aae (69)
6	2a/4b, 5 h	7a, 4 h	 8aba (69)
7	2a/4c, 5 h	7a, 3 h	 8aca (76)
8	2a/4d, 5 h	7a, 4 h	 8ada (73)
9	2a/4e, 24 h	7a, 5 h	 8aea (70)
10	2b/4a, 24 h	7a, 4 h	 8baa (63)
11	2c/4a, 24 h	7a, 4 h	 8caa (66)

^a In DCE (4 mL), **2**, **3** (1.1 equiv), and **4** (4 equiv) were reacted in the presence of 5 mol % **1** under Ar at room temperature. ^b A crude arylboronate was reacted with **7** (1.5 equiv) in toluene/H₂O in the presence of 2.5 mol % Pd₂(dba)₃ and 11 mol % PCy₃.

7d and 2-iodothiophene **7e**, the desired hetero-biaryls **8aad** and **8aae** were obtained in 53% and 69% yields, respectively (runs 4 and 5).

With respect to alkyne components, terminal alkynes bearing chloro, ester, or ether functionalities **4b–d** can be employed to obtain the corresponding biaryls in 69–76% yields (runs 6–8). Interestingly, methyl propargyl ether **4b** caused no deleterious effect. This implies that the boron-tethered diyne intermediate was selectively formed with the alcohol **3** rather than with the ether **4b**. Gaseous propyne **4e** (1 atm) was also selectively incorporated into the final biaryl product **8aea** in good yield (run 9).

Two more alkynylboronates bearing an ether or a chloroalkyl substituent **2b** and **2c** were subjected to the one-pot four-component

coupling (runs 10 and 11). Although the cyclotrimerization of these boronates with **3** and **4a** requires longer reaction time as compared to that with **2a**, the Suzuki–Miyaura coupling of the resultant arylboronates with **7a** successfully gave rise to biaryl products **8baa** and **8caa** in 63% and 66% yields, respectively.

In conclusion, the catalytic intermolecular cyclotrimerization of three different unsymmetrical alkynes was accomplished by means of the ruthenium catalysis and the temporary tethering approach with the C–B–O linkage. The crude arylboronates were further applied to the Suzuki–Miyaura coupling with various aryl iodides using Pd₂(dba)₃/PCy₃ as a catalyst precursor in aqueous toluene to afford biaryls. As a result, the novel four-component coupling approach to highly substituted biaryls was successfully established by combining these two operations into a sequential one-pot process.

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Supporting Information Available: Experimental procedure and analytical data for biaryls **8** and **9** (PDF and CIF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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