

Synthesis of bi- and tricyclic arylboronates *via* Cp*RuCl-catalyzed cycloaddition of α,ω -diynes with ethynylboronate†

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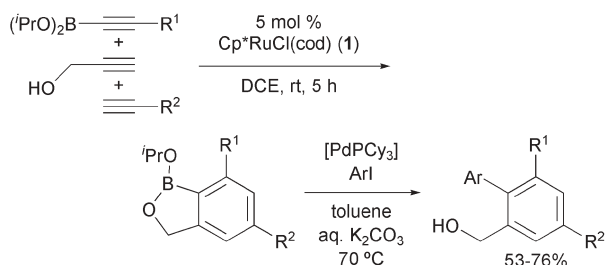
In the presence of 5–10 mol% Cp*RuCl(cod), 1,6- and 1,7-diynes were allowed to react with an ethynylboronate at ambient temperature to give rise to bi- and tricyclic arylboronates in 64–93% isolated yields.

Arylboronic acids and esters have been extremely versatile reagents in organic transformations such as Suzuki–Miyaura coupling,¹ rhodium-catalyzed asymmetric 1,4-additions to activated olefins,² or Petasis–Mannich condensation.³ Arylboronic acid derivatives have been conventionally prepared by the reactions of arylmagnesium or -lithium reagents with trialkyl borates, although polar unsaturated functional groups such as an ester or a ketone are incompatible to this method.⁴ To address this issue, transition-metal-catalyzed couplings of arylhalides, -triflates, or -diazoniums with tetraalkoxydiboranes or dialkoxyboranes have been developed by several research groups.⁵ More significantly, the transition-metal-catalyzed direct borylation of aromatic C–H bonds has emerged as an environmentally benign process.⁶ In addition, the progress of benzannulation or cycloaddition techniques realized the synthesis of highly substituted arylboronic acid derivatives, which are otherwise difficult to prepare.^{7,8} In this context, we recently developed the ruthenium-catalyzed cyclotrimerization of alkynylboronates, propargyl alcohol, and a terminal alkynes giving rise to arylboronates, which were subjected to one-pot Suzuki–Miyaura coupling to afford highly substituted biaryls as single regioisomers (Scheme 1).⁹ Independently, Aubert and co-workers accomplished the cycloaddition of the Co₂(CO)₈-complexed alkynylboronates with α,ω -diynes bearing various tether lengths, and as a result, bicyclic arylboronates were obtained in

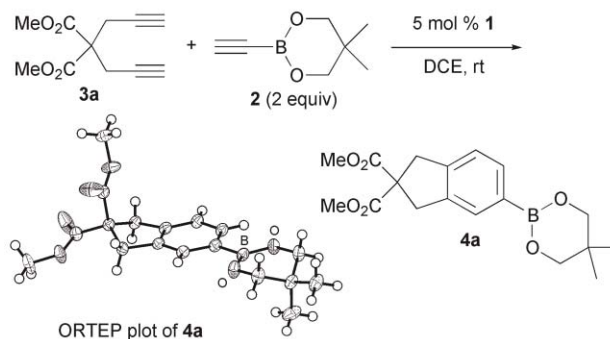
45–61% yields.¹⁰ The same authors also attempted the cobalt-catalyzed cycloaddition of alkynylboronates and α,ω -diynes, but failed to obtain the bicyclic arylboronates. Herein we wish to report the *direct* cycloaddition of an ethynylboronate with 1,6- and 1,7-diynes by means of the ruthenium catalysis, leading to the formation of bicyclic arylboronates in good yields under mild reaction conditions.

To realize an efficient catalytic protocol, we required an ethynylboronate because internal alkynes proved to be inefficient monoalkyne substrates for the ruthenium-catalyzed cycloaddition.¹¹ Thus, we used 2-ethynyl-5,5-dimethyl-1,3,2-dioxaborinane **2** reported by Vaultier and co-workers.¹² As shown in Scheme 2, ethynylboronate **2** was allowed to react with dimethyl dipropargylmalonate **3a** in the presence of precatalyst Cp*RuCl(cod) **1** (Cp* = η^5 -C₅Me₅, cod = 1,5-cyclooctadiene) at ambient temperature. To suppress diyne dimerization, a solution of **3a** in 1,2-dichloroethane (DCE) was added at room temperature *via* syringe pump over 1 h to a DCE solution of 5 mol% **1** and 2 equiv of **2**. As a result, the desired cycloadduct **4a** was isolated in 77% yield after purification with silica gel column chromatography. A similar yield was obtained with increased amounts of **2** (4 equiv). On the other hand, the yield was improved up to 86%, when the reaction mixture was stirred for 1 h after the syringe-pump addition of **3a**. The obtained product was characterized as bicyclic arylboronate **4a** by ¹H and ¹³C NMR, IR, mass, and elemental analyses. The structural assignment was also confirmed by X-ray crystallography (Scheme 2).‡

The generality of this protocol was demonstrated by the reactions of various diyne substrates **3a–h** with **2** (Table 1). The present method well tolerated reactive functional groups including an ester, a ketone, and a nitrile. As a consequence, arylboronates **4a–c** were obtained in 80–86% yields (runs 1–3). The quaternary



Scheme 1



Scheme 2

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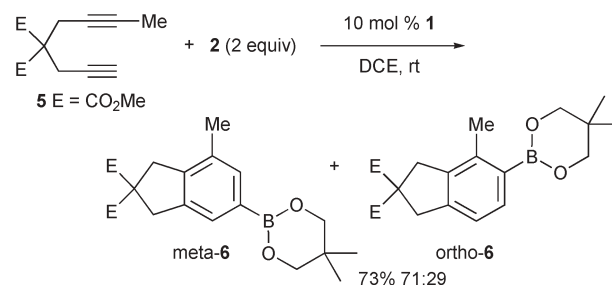
Table 1 Synthesis arylboronates **4** from various diynes **3a–3h** with **2**^a

Run	Diyne	Product, yield (%)
1		 4a 86
2		 4b 81
3		 4c 80
4		 4d 64
5		 4e 93
6		 4f 70
7		 4g 77
8		 4h 87

^a A solution of **3** in DCE was added to a DCE solution of 5 mol% (10 mol% for runs 4, 6, and 7) Cp*RuCl(cod) **1** and 2 equiv of ethynylboronate **2** by syringe pump over 1 h, and the solution was stirred for 1 h at room temperature.

center of the diyne tether is not essential for the cycloaddition. Although increased catalyst loading (10 mol%) was required, the parent 1,6-heptadiyne **3d** underwent cycloaddition with **2** to furnish the corresponding product **4d** in 64% yield (run 4). Similarly, *N,N*-dipropargyltosylamide **3e** and propargyl ether **3f** gave borylated heterocycles **4e** and **4f** in 93% and 70% yields, respectively (runs 5 and 6). In addition to these 1,6-diynes, 1,7-diynes **3g** and **3h** were able to react with **2** to give the corresponding cycloadducts **4g** and **4h** in 77% and 87% yields, respectively. In particular, **4h** is a versatile building block for the synthesis of functionalized anthraquinone derivatives (*vide infra*).

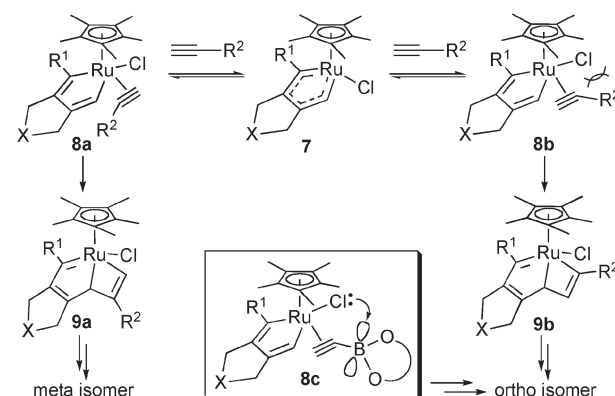
We next examined the regioselectivity of the reaction with unsymmetrical diyne **5** possessing a terminal methyl group on one of the two alkyne moieties (Scheme 3). In our previous study, it was found that similar unsymmetrical diynes reacted with monoalkynes to afford *meta* isomers with excellent regioselectivity as high as *meta* : *ortho* = 95 : 5.¹¹ On the other hand, the reaction of **5** with **2** was carried out in the presence of 10 mol% **1** at room

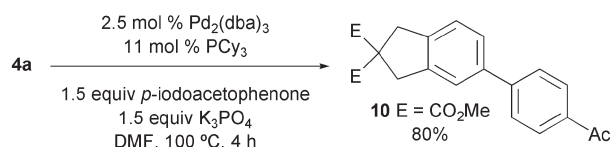
**Scheme 3**

temperature to afford a regioisomer mixture of cycloadduct **6** in 73% combined yield with a moderate selectivity of *meta* : *ortho* = 71 : 29.

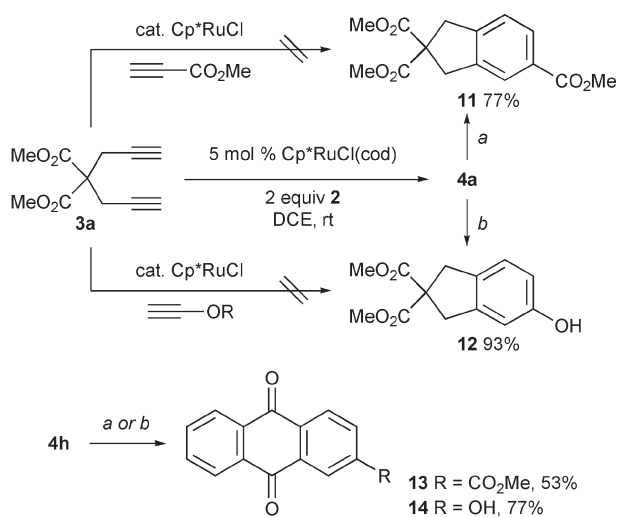
The plausible regioselection mechanism is outlined in Fig. 1. The catalytic reaction starts with the oxidative cyclization of a diyne on the Cp*RuCl fragment, leading to ruthenabicyclic intermediate **7**. On the basis of density functional theory calculations, we and others have independently proposed the novel alkyne cyclotrimerization mechanism, in which the intermediacy of unprecedented ruthenatricyclic complex **9** was proposed for the conversion of ruthenabicyclic–alkyne complex **8** to the final product.^{11,13} The coordinated alkyne is considered to react predominantly at the less substituted Ru–C bond as a consequence of the steric influence of the substituent R¹. In addition, the steric repulsion between the chloro ligand and the substituent R² on the coordinated monoalkyne might destabilize ruthenabicyclic–alkyne complex **8b**.¹¹ Therefore, the preferential pathway *via* alternative complex **8a** leads to the predominant formation of a *meta*-substituted product. In the case for ethynylboronate **2**, however, the attractive interaction between the non-bonding electron pair on the chlorine ligand and the vacant orbital on the boron center might render intermediate **8c** leading to the *ortho* product somewhat favorable, resulting in the diminished regioselectivity.

To demonstrate the synthetic utility of the present method, we also examined some transformations of the obtained arylboronates. The Suzuki–Miyaura coupling of **4a** and *p*-iodoacetophenone (1.5 equiv) was carried out in the presence of 2.5 mol% Pd₂(dba)₃ (dba = dibenzylideneacetone), 11 mol% PCy₃, and 1.5 equiv of K₃PO₄ in DMF at 100 °C to give biaryl **10** in 80% yield (Scheme 4). Electron-deficient monoalkynes such as acetylenedicarboxylates or propiolates are very reactive substrates for

**Fig. 1** Proposed regioselection mechanism.



Scheme 4



conditions: a: 5 mol % Pd(OAc)₂, 11 mol % PPh₃, BQ (1 equiv), 1 atm CO, MeOH, rt, 1.5 h. b: H₂O₂, aq. NaOH, THF, rt, 15 min.

Scheme 5

the Cp*RuCl-catalyzed cyclotrimerization.¹¹ Consequently, the cycloaddition of α,ω -diynes with those alkynes has never been accomplished under ruthenium-catalyzed conditions. On the other hand, the cycloadduct of **3a** and methyl propiolate was indirectly obtained *via* the cycloaddition of **3a** and **2** followed by the catalytic methoxycarbonylation of resultant **4a** (Scheme 5). Although the catalytic alkoxycarbonylation of arylboronates has remained almost unexplored,¹⁴ we recently devised the new protocol to synthesize phthalides by the catalytic carbonylation of boraphthalides.¹⁵ Gratifyingly, our protocol proved to be effective for **4a**. The treatment of **4a** with 5 mol% Pd(OAc)₂, 11 mol% PPh₃, and 1 equiv of *p*-benzoquinone (BQ) in dry MeOH under CO atmosphere at room temperature. The starting material was completely consumed within 1.5 h to afford the desired benzoate **11** in 77% yield. Electron-rich alkoxyacetylenes are also incompatible substrates for our ruthenium catalysis, although their cycloadducts are valuable phenol derivatives. In contrast, the oxidation of **4a** with H₂O₂ under basic conditions gave bicyclic phenol **12** in 93% yield. These methods were further applied to anthraquinone boronate **4h** to deliver naturally occurring anthraquinone derivatives **13** and **14**.^{16,17}

In conclusion, we realized for the first time the catalytic [2 + 2] cycloaddition of α,ω -diynes with an alkynylboronate by means of the ruthenium catalysis. Consequently, the novel protocol allowed us to prepare functionalized bi- or tricyclic arylboronates *via* Cp*RuCl-catalyzed reaction of 2-ethynyl-5,5-dimethyl-1,3,2-dioxaborinane with various 1,6- and 1,7-diynes. The present protocol tolerates reactive functional groups including an ester, a ketone, a nitrile, and a sulfonamide. The obtained arylboronate

products were further transformed into valuable benzoate and phenol derivatives *via* palladium-catalyzed methoxycarbonylation or oxidation with H₂O₂.

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Notes and references

† Crystallographic data: Intensity data were collected at 173 K on a Bruker SMART APEX diffractometer with Mo K α radiation (0.71073 Å) and graphite monochromator. The structure was solved by direct methods and refined by the full-matrix least-squares on *F*² (SHELXTL). **4a** [C₁₈H₂₃BO₆, *M*_w = 346.17]; space group *P* $\bar{1}$, triclinic; unit-cell dimensions *a* = 6.0252(4) Å, *b* = 12.4955(9) Å, *c* = 13.2849(9) Å, α = 62.7990(10)°, β = 84.221(2)°, γ = 84.2950(10)°, *V* = 883.45(11) Å³; *Z* = 2, *D*_{calc} = 1.301 g cm⁻³; Total 6887 reflections were measured and 4645 were independent [*R*(int) = 0.0307]. Final *R*₁ = 0.0726, *wR*₂ = 0.2234 [*I* > 2 σ (*I*)], and GOF = 0.991 (for all data, *R*₁ = 0.0790, *wR*₂ = 0.2337). CCDC 271948. See <http://dx.doi.org/10.1039/b506977g> for crystallographic data in CIF or other electronic format.

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