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One-pot sequential four-component coupling via Cp*RuCl-catalyzed cyclotrimerization and Suzuki–Miyaura coupling

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Abstract—The catalytic intermolecular cyclotrimerization of alkynylboronates, propargyl alcohols, and terminal alkynes was accomplished by means of the ruthenium catalysis and the temporary tethering approach with the C–B–O linkage to give rise to highly substituted arylboronates with excellent selectivity. The resultant arylboronates were further converted to highly substituted biaryls via the Suzuki–Miyaura coupling with various aryl iodides using $Pd_2(dba)_3/PCy_3$ as a catalyst precursor in aqueous toluene. As a consequence, the four-component coupling approach to highly substituted biaryls was successfully established by combining these two operations into a sequential one-pot process.

1. Introduction

Transition-metal-catalyzed multi-component coupling cyclizations are powerful methods for assembling complex cyclic frameworks from inexpensive acyclic starting materials.[1] In particular, a sequential catalytic process that effects multiple reactions in a single-pot is highly desirable, because it would reduce wastes produced from the separation of intermediates.[2] Toward this end, each catalytic reaction should be refined as to be mutually compatible, and thus, a judicious choice of the catalyst combination as well as a substrate design play critical roles in the one-pot sequential catalytic process. In this context, we recently reported the one-pot sequential [2+2+2] cyclotrimerization/Suzuki–Miyaura coupling process, in which the catalytic cyclotrimerization of three different unsymmetrical alkynes was achieved regioselectively by means of a boron temporary tether, and the subsequent Suzuki–Miyaura coupling of the resultant cyclic arylboronates with aryl iodides successfully gave rise to the desired biaryls in reasonable yields.[3] Herein, we report the full detail of the study on the one-pot sequential four-component coupling synthesis of biaryls.

2. Results and discussion

2.1. Exploratory study on the Cp*RuCl-catalyzed cyclotrimerization of three unsymmetrical alkynes by means of boron temporary tether

The transition-metal-catalyzed [2+2+2] alkyne cyclotrimerization has received continuous attention as a straightforward route to substituted benzenes.[4] Because of its atom-economical[5] and convergent nature, the cyclotrimerization approach to substituted benzene rings is considerably advantageous over conventional strategies requiring the sequential substitutions of a benzene ring by way of electrophilic aromatic substitutions or orthometalation techniques.[6] Although the selective cyclotrimerization of three different alkynes was accomplished using stoichiometric transition metal reagents,[7–9] the development of a catalytic protocol is highly desirable in terms of the atom-economy. In this context, intramolecular approach utilizing diynes or triynes have been explored as a promising tool to afford polycyclic arenes selectively.[10] However, additional synthetic operations are required, if the resultant polycyclic framework is not desirable. An unnecessary ring moiety needs to 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 can be troublesome.

One effective strategy to address these issues is the

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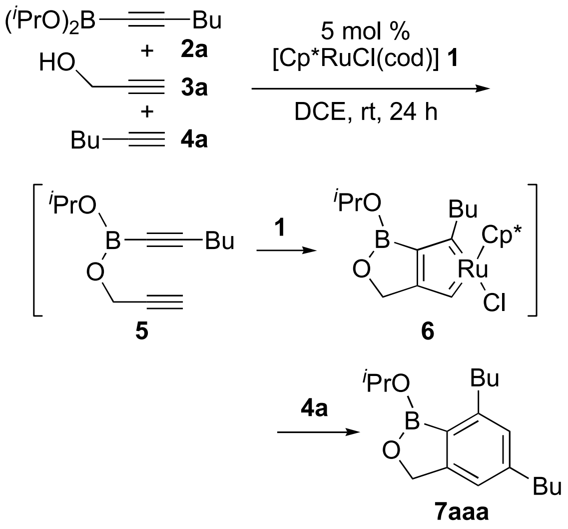
temporary connecting of monoalkynes with a disposable tether group.[11] To realize the selective cyclotrimerization of three different alkynes through a temporary tether, Cp*RuCl(cod) **1** (Cp* = η^5-C_5Me_5, cod = 1,5-cyclooctadiene) is the desired catalyst precursor, because the previous density functional calculations revealed that the oxidative cyclization on the Cp*RuCl fragment yielding a key ruthenacycle intermediate is the rate-determining step, and, therefore, the ruthenium catalysis favors 1,6-diynes rather than monoalkynes.[12] In addition, the cycloaddition of unsymmetrical diyne with terminal monoalkynes proceeds with excellent regioselectivity at room temperature under the ruthenium catalysis.[12a] As a temporary tether, a C–B–O linkage is the better choice rather than widely prevalent C–Si–O or O–Si–O linkages,[13] because relatively long Si–C and Si–O bonds might cause deleterious effect on the formation of the ruthenacycle intermediate. Surprisingly, such boron tethers have remained less explored in transition-metal catalysis, while the boron temporary tethers were successfully applied to Diels–Alder reactions.[14] Various unsaturated organoboranes have been employed for transition-metal-catalyzed reactions,[15] but, to the best of our knowledge, the temporary boron tether approach has been confined to the ruthenium-catalyzed enyne metathesis using alkynyl- or allylboronates reported by Schreiber and Micalizio.[16]

With these in mind, we carried out the exploratory study on the cyclotrimerization of 1-hexynylboronate **2a**, propargyl alcohol **3a**, and 1-hexyne **4a** (Scheme 1). Propargyl alcohol **3a** (1.1 equiv) was added dropwise over 15 min to a solution of 5 mol% **1**, 1-hexynylboronate **2a**, and 1-hexyne **4a** (4 equiv) in 1,2-dichloroethane (DCE) at room temperature, and the solution was stirred for 24 h. In the ^{1}H NMR spectrum of the crude product 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 via the expected diyne and ruthenacycle intermediates **5** and **6**. Unfortunately, the resultant arylboronate **7aaa** could not be purified at this stage, due to the facile exchange of the boronate ligands. Accordingly, we further attempted the Suzuki–Miyaura coupling[17] of the crude **7aaa** without purification.



Scheme 1.

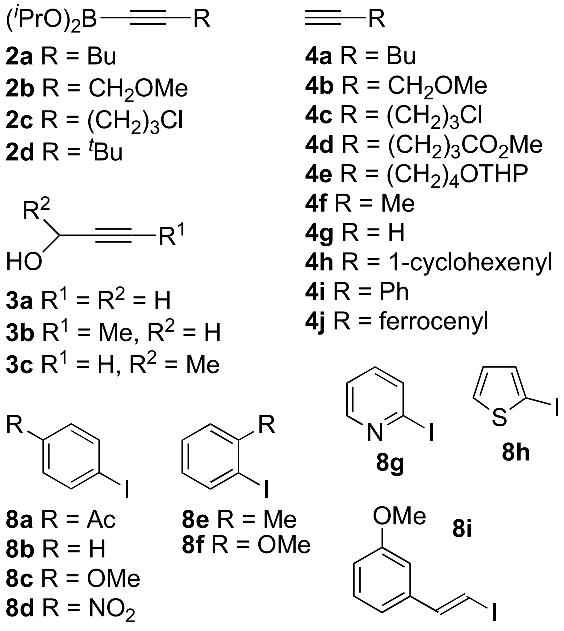
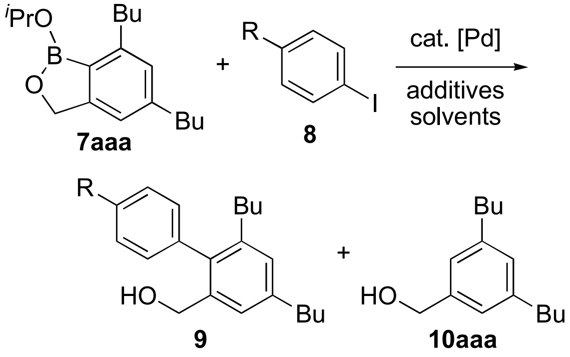


Figure 1. Starting materials used in this study.

2.2. Suzuki–Miyaura coupling of cyclotrimerization product

The newly prepared **7aaa** was subjected to the Suzuki–Miyaura coupling with aryl iodides as shown in Scheme 2 and Table 1. Upon treatment with 5 mol% $Pd(PPh_3)_4$, *p*-iodoacetophenone **8a** (1.5 equiv), and K_2CO_3 in refluxing THF/H_2O for 24 h, the desired **9aaaa** was obtained in 32% yield together with a protodeboration product **10aaa** in 22% yield (entry 1). Significantly, both of these products were obtained as a single regioisomer. To minimize the unwanted protodeboration, the cross coupling conditions were optimized. In the absence of water, protodeboration was effectively suppressed and **9aaaa** was obtained exclusively in 68% yield (entry 2). Furthermore, we found that the reaction reached to completion within 2 h in heterogeneous solvent system toluene/H_2O at 70 °C to afford **9aaaa** in 71% yield (entry 3). The couplings with less reactive iodobenzene **8b** and *p*-iodoanisole **8c** required prolonged reaction time of 20 h otherwise under the same reaction conditions (entries 4 and 5). In addition, the desired product **9aaac** was



Scheme 2.