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Stereo- and Regioselective Formation of Silyl-Dienyl Boronates

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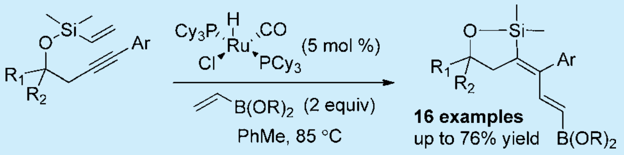
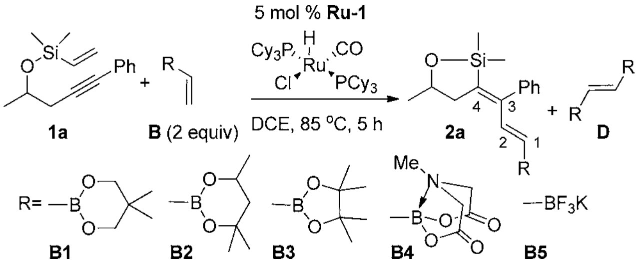
Ⓢ *Supporting Information*

ABSTRACT: The intramolecular *trans*-silylruthenation of internal alkynes and subsequent insertion of vinyl boronates is described. This approach provides complete regiocontrol through a stereoselective *trans-5-exo-dig* cyclization which affords a tetrasubstituted olefin as a vinylsilane and a highly functionalized *Z,E* diene motif.



Vinyl boronates[1−3] and vinyl silanes[4] are valuable reagents and are often utilized as intermediates in synthetic transformations.[5,6] The Suzuki−Miyaura cross-coupling with organoboranes is arguably the most utilized transition metal catalyzed C−C bond forming reaction.[7] This protocol established boronic acids and the corresponding esters as fundamental components in modern organic synthesis.[8] Given the versatility of these vinylmetalloid compounds, a great deal of effort has been applied to incorporate these moieties into complex molecules. Several methods used to prepare vinyl silanes and vinyl boronic esters include hydroboration of alkynes, metal catalyzed addition of diboron reagents,[9,10] olefin metathesis with vinyl boronates,[11−13] and silaboration chemistry.[14−17] In addition to these processes we sought to apply our recently developed ruthenium hydride methodology[18] toward the coupling of unsymmetrical internal alkynes and vinyl boronates. This concept would deliver regio- and stereodefined silyl-dienylboronates with diverse functional handles at the 1 and 4 positions of a diene scaffold (Scheme 1, **2a**). Previously, Marciniec prepared bifunctional dienes from silyl-acetylenes and vinyl boronates; however, a mixture of stereoisomers and alkyne dimerization was observed.[6] Our approach produces a tetrasubstituted *Z,E* diene motif which is a considerable challenge to obtain despite the diene subunit's prevalence in nature.[19−21]

Scheme 1. Vinyl Boronate Coupling



Our study began by examining substrate **1a** and vinyl boronate **B1** using the standard conditions from our acrylate coupling methodology.[18] The reaction worked well in 1,2-dichloroethane (DCE) and toluene at 85 °C. The vinyl boronate to alkyne ratio played a crucial role in the reaction. With 1.2, 1.5, and 2.0 equiv of vinyl boronate, the crude yields of **2a** by ^{1}H NMR were 62%, 65%, and 90%, respectively. This effect is presumably due to competitive formation of boronate dimer (**D**) which consumes vinyl boronate (**B**) prior to coupling.[22] We also noted that product isolation was difficult most likely due to boronate hydrolysis upon exposure to silica gel. Measures were taken to deactivate the silica gel with triethylamine, trimethylchlorosilane, or boric acid[23] with no improvement in isolated yield. Using neutral alumina provided similar results to silica gel. We explored several vinyl boronates to potentially improve the isolation of **2a**. Careful examination of the literature revealed several candidates that were commercially available or readily prepared (Scheme 1). Pinacol boronate **B3** is easily prepared but highly volatile with a known proclivity to polymerize.[24] Examination revealed that the highest crude yield of **2a** by ^{1}H NMR with **B3** was 70%. Burke and co-workers introduced MIDA compound **B4**,[25] while Molander and co-workers produced compound **B5**.[26] These are both air stable solids that have repeatedly demonstrated their usefulness in cross-coupling chemistry;[26] however, these two reagents did not participate in our chemistry due to their attenuated electronics. It was observed that the most successful boronate was **B2**. Compound **B2** was easily prepared from readily available materials in multigram quantities following the procedure of Whiting.[24]

To further optimize this reaction, attempts to minimize the formation of boronate dimer (**D**) were undertaken. A solvent and temperature screen revealed that toluene, DCE, and 1,4-dioxane all performed well at 85 °C (Table 1, entries 1−3). Refluxing THF (entry 4) gave no dimer but required a longer reaction time with reduced (58%) product yield. No reactivity was observed in refluxing acetonitrile (entry 5) presumably due to solvent coordination to ruthenium. Lowering the temperature in toluene led to longer reaction times and decreased the amounts of both dimer **D** and diene **2a** being formed (entry 6).

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Table 1. Solvent Screen

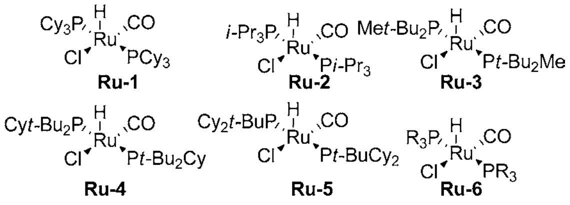
entry	solvent	temp (°C)	time (h)	yield **2a** (**D**)[a]
1	DCE	85	5	75 (5)
2	toluene	85	3.5	75 (3)
3	1,4-dioxane	85	4	67 (3)
4	THF	70	7	58 (0)
5	MeCN	70	7	N/R
6	toluene	70	7	63 (1)
7	toluene	100	3	78 (5)

[a] Yield determined by ^{1}H NMR vs mesitylene internal standard.

Increasing the temperature to 100 °C gave a 78% yield of **2a** but also increased the amount of dimer **D** (entry 7). Toluene at 85 °C proved optimal for the reaction (entry 2) with regard to reaction time and amount of dimer formation. Dimer **D** was independently synthesized using these optimized reaction conditions to verify its formation.[27]

In an effort to increase the amount of **2a** and sequester the formation of **D**, other catalysts were examined. Ruthenium-phosphine complexes with various steric and electronic properties were prepared and tested (Table 2). Ruthenium hydride complex **Ru-1** was shown to be superior to analogous hydride catalysts (entry 1). Complex **Ru-2** demonstrated a good yield of product (72%) but required longer reaction times. Complexes **Ru-3**, **Ru-4**, and **Ru-5** bearing electron-rich phosphine ligands also catalyzed the reaction; however, increasing the steric bulk around ruthenium led to a decreased yield of **2a**. In line with this observation, complex **Ru-6**, bearing bulky electron-deficient phosphine ligands, exhibited poor catalytic activity in the coupling. After significant development, 5 mol % **Ru-1** with 2 equiv of **B2** in toluene (0.5 M in alkyne) at 85 °C was implemented as the standard conditions for this reaction.

Table 2. Catalyst Screen



PR_3 = (3,5-bis(trifluoromethyl)phenyl)diisopropylphosphine

entry	catalyst	time (h)	yield **2a** (%)[a]	dimer (**D**)[a]
1	**Ru-1**	3.5	75	3
2	**Ru-2**	8	72	4
3	**Ru-3**	5	67	10
4	**Ru-4**	2	61	11
5	**Ru-5**	8	60	6
6	**Ru-6**	8	15	0

[a] Yield determined by ^{1}H NMR vs mesitylene internal standard.

Our mechanistic hypothesis, as illustrated in Figure 1, begins with dissociation of one phosphine ligand from **Ru-1**, which reveals a 14-electron ruthenium species (**I**). Subsequent substrate coordination, hydroruthenation of the vinyl silane (**II**), and *β*-silyl transfer deliver the silyl ruthenium intermediate (**III**). With two vinyl metalloid species present in the reaction mixture, it is presumed that the vinyl silicon out-competes the vinyl boronate for hydroruthenation. Intramolecular silyl-ruthenation of the alkyne provides vinyl ruthenium (**IV**). Considering the stereochemical outcome of the products this intermediate can arise from a direct *trans*-addition[28,29] or *cis*-addition followed by isomerization.[18] Intermolecular insertion of the vinyl boronate (**V**) and *β*-hydride elimination liberate the product and regenerate the active hydride catalyst **I**.

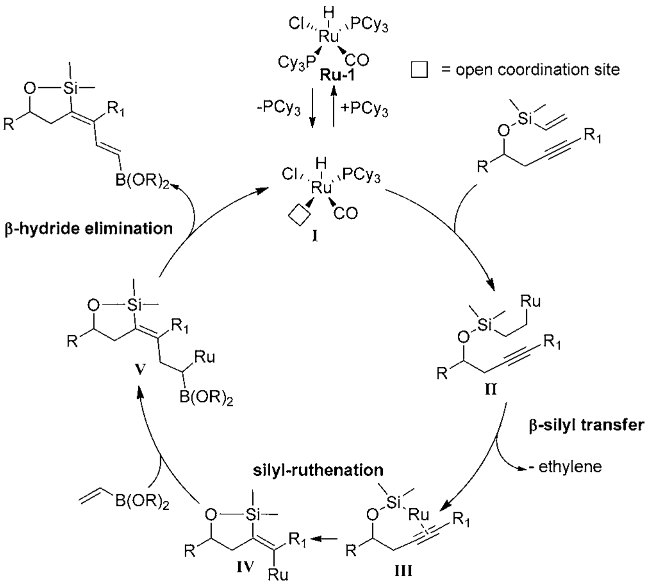
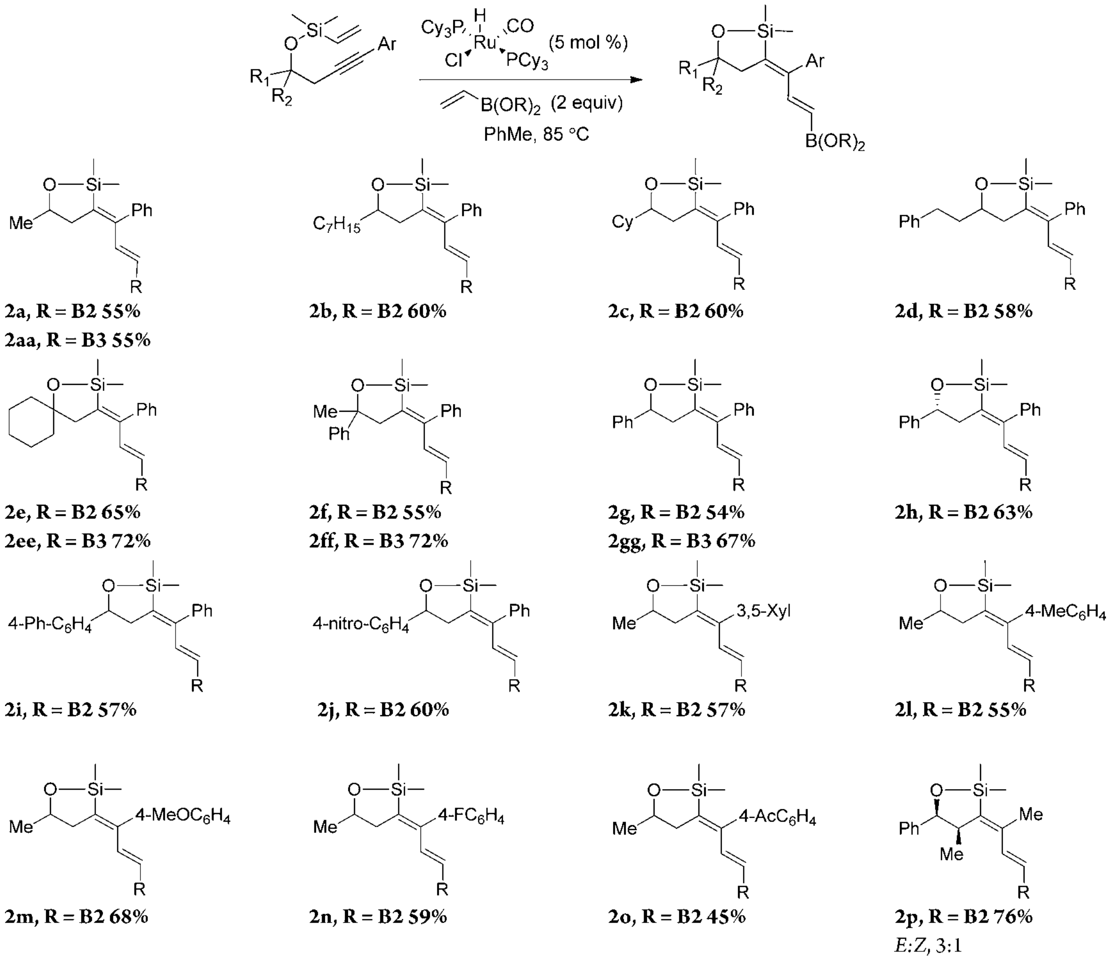


Figure 1. Mechanistic hypothesis.

Using the optimized conditions, a study of substrate scope was conducted, and the conditions were found to be amenable to various alkyne substrates (Table 3). Maintaining a phenyl ring at the alkyne terminus, alkyl functionality at R_1 was well tolerated with methyl (**2a**, 55%), *n*-heptyl (**2b**, 60%), cyclohexyl (**2c**, 60%), and dihydrocinnamyl (**2d**, 58%) providing dienes **2a**–**2d** in good yields. Tertiary homopropargylic tethered alcohols also performed well generating dienes **2e** (65%) and **2f** (55%) efficiently. Aryl substituents at the homopropargyl position, phenyl (**2g**, 54% and **2h**, 63%), biphenyl (**2i**, 57%), and *para*-nitro (**2j**, 60%), were well tolerated. Next, we examined aryl substitutions at the pendant alkyne. *Ortho* substitution (i.e., 2-chlorophenyl-) was incompatible, presumably due to sterics. Fortunately, *meta* substitution worked well giving 3,5-xylyl compound **2k** in 57% yield. Examining electronic differences at the *para* position, we observed that 4-methyl (**2l**, 55%), 4-fluoro (**2n** 59%), and electron donating 4-methoxy (**2m**, 68%) provided higher yields than electron-withdrawing 4-acetyl (**2o**, 45%).

With the isolated yields of dienes **2a**–**2o** under 70% we chose to inspect a few substrates with the pinacol boronate **B3**. These substrates produced a lower crude yield, but the dienes proved more stable to isolation with minimal product loss. In the case of Table 3, the isolated yield of **2aa** was consistent with **2a**; however, **2ee**, **2ff**, and **2gg** displayed increased yields of 7–18% when compared to **2e**, **2f**, and **2g**, respectively. Dienes **2g** and **2i** were synthesized on a 2 mmol scale, and the isolated yields obtained were within experimental error (±3%) of those conducted at 0.3 mmol. In addition, methyl substituted alkyne **1p** was synthesized and subjected to the protocol. The reaction generated diene **2p** in 76% yield (Table 3, entry 16); however, **2p** was obtained as an inseparable mixture of double bond isomers. Similar mixtures were observed in our previous investigation with acrylates.[18] Diene **2p** was subjected to iododeboration in order to verify the isomeric ratio.[27]

Table 3. Dienylsilylboronate Substrates

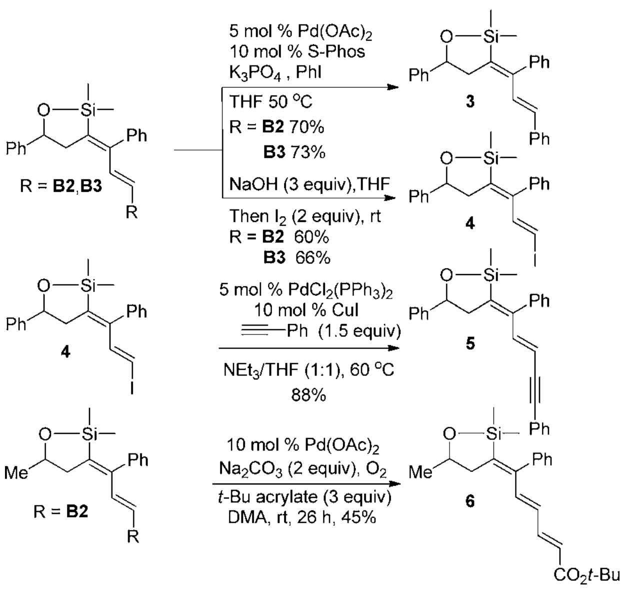


2a, R = B2 55%
2aa, R = B3 55%
2b, R = B2 60%
2c, R = B2 60%
2d, R = B2 58%
2e, R = B2 65%
2ee, R = B3 72%
2f, R = B2 55%
2ff, R = B3 72%
2g, R = B2 54%
2gg, R = B3 67%
2h, R = B2 63%
2i, R = B2 57%
2j, R = B2 60%
2k, R = B2 57%
2l, R = B2 55%
2m, R = B2 68%
2n, R = B2 59%
2o, R = B2 45%
2p, R = B2 76%
E:*Z*, 3:1

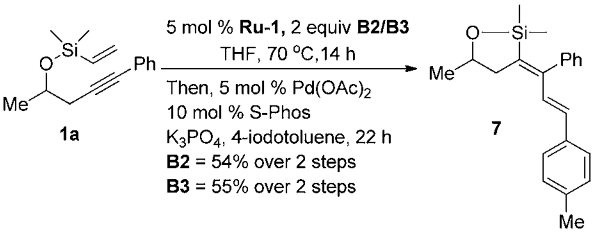
Synthetically, the silyl-dienyl boronates could be further manipulated into more diverse molecules by using metal-catalyzed coupling methods (Scheme 2).[30,31] Suzuki coupling[32] with diene **2e** containing **B2** or **B3** and iodobenzene produced **3** in comparable yields with retention of configuration. Iododeboration[13] provided silyl-dienyl iodide **4** in 60% and 66% isolated yields, respectively. Attempts to form the *Z,Z* dienyl bromide[13] from diene **2e** was not successful and gave a complex mixture. Iodide **4** was subsequently used as a coupling partner with Sonogashira[33] conditions to afford dienyne **5** in 88% yield. An oxidative Heck[34] reaction with **2a** and *tert*-butyl acrylate gave triene **6** in 45% yield. These elaborations provide access to useful building blocks that may be manipulated further to provide various complex structural motifs.

After significant examination, suitable conditions[35] were established for the tandem silyl-boration of alkyne **1a** and *in situ* Suzuki coupling of diene **2a** with 4-iodotoluene (Scheme 3). This protocol provided diene **7** in 54% isolated yield over two steps. With identical conditions and diene **2aa**, we obtained compound **7** in a 55% isolated yield over two steps.

Scheme 2. Derivatization



Scheme 3. Tandem Hydride Coupling–Suzuki Coupling



In conclusion, vinylsilanes were shown to be more reactive than vinyl boronates to hydroruthenation. We have demonstrated the formation of silyl-dienyl boronates by a *trans*-silylation protocol with internal alkynes and vinyl boronates. The highly substituted dienes were formed in a single step and can be transformed into more complex diene products by iododeboration and metal-catalyzed coupling methods. In addition, a valuable tandem ruthenium hydride coupling/Suzuki coupling reaction was established.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and spectral data. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01434.

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Notes

The authors declare no competing financial interest.

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