Alkyne Cross-Coupling

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Stereocontrolled Synthesis of Vinyl Boronates and Vinyl Silanes via Atom-Economical Ruthenium-Catalyzed Alkene–Alkyne Coupling

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Abstract: *The synthesis of vinyl boronates and vinyl silanes was achieved by employing a Ru-catalyzed alkene–alkyne coupling reaction of allyl boronates or allyl silanes with various alkynes. The double bond geometry in the generated vinyl boronates can be remotely controlled by the juxtaposing boron- and silicon groups on the alkyne substrate. The synthetic utility of the coupling products has been demonstrated in a variety of synthetic transformations, including iterative cross-coupling reactions, and a Chan-Lam-type allyloxylation followed by a Claisen rearrangement. A sequential one-pot alkene-alkyne-coupling/allylation-sequence with an aldehyde to deliver a highly complex α-silyl-β-hydroxy olefin with a handle for further functionalization was also realized.*

The ene reaction was first reported by Alder in 1943 and represents a prime example of an atom-economic reaction.[1] Our research program directed towards the atom-economic generation of valuable building blocks for organic synthesis led us to investigate the formation of vinyl boronates via Ru-catalyzed alkene-alkyne coupling.[2,3] The importance of organoboron compounds in organic synthesis raises the significant question of their compatibility with different catalytic systems. The widespread interest in organoboron compounds further propelled our studies in designing a highly regio- and stereoselective strategy to gain access to substituted vinylboron building blocks.[4–7] In many transformations, including the Suzuki–Miyaura coupling, organoboron compounds are utilized to transfer the C-group rather than the B-group.[8,9] In particular, allyl boronates are well documented to undergo addition reactions into carbonyl compounds and activated olefins.[10] In the context of our Ru-catalyzed alkene–alkyne coupling, a similar reactivity might involve a boron transfer. That raised the question of whether a process involving a C−H activation rather than a C−B activation was feasible. The powerful Ru-catalyzed alkene–alkyne coupling furnishes two stereodefined olefins in a single transformation without the need for prefunctionalization. An efficient and controllable approach to substituted vinylboranes with predictable regio- and stereoselectivity is in high demand within the synthetic community and remains a considerable challenge.

Hilt and co-workers observed a Co-catalyzed Alder ene process involving H-migration rather than B-migration, wherein (*Z*)-olefins are generated.[11] Three examples were described, requiring 3.0 eq of alkyne added slowly over a period of 7 h. For product purification, a bulb-to-bulb distillation was employed. We therefore undertook an examination of the Ru-catalyzed alkene–alkyne coupling of allyl boronates with various alkynes, which we report herein. This strategy allows us to access bifunctional 1,4-dienes in a selective manner. Subsequent sequential cross-coupling sets the stage for the integration of the 1,4-diene motif into a variety of molecular scaffolds. The initial experiments were performed with dec-1-yn-1-yltrimethylsilane (**1a**) and allyl pinacolato borane (**2**) in the presence of 10 mol% [CpRu(MeCN)$_3$]PF$_6$ as the catalytic system at 23°C in acetone (Table 1). This set of conditions afforded the desired product **3a** in 62% yield after 3 h in high (*E*)-selectivity (Table 1, entry 1). Coordinating solvents, such as DMF, led to mixtures of isomers, even when employed in a solvent mixture. Freshly distilled cyclopentanone as the solvent led to a 75% yield at 23°C, and it was noted that the reaction proceeded to completion after 3 h at 50°C to give a 90% yield of the desired product (Table 1, entry 5). The addition of external

Table 1: Reaction development: Ru-catalyzed formation of vinyl boronates.

1a **2** **3a**

Entry	Catalyst System (mol%)	Solvent	T [°C]	Yield [%][a]
1	[CpRu(MeCN)$_3$]PF$_6$ (10 mol%)	Ac	23	62
2	[CpRu(MeCN)$_3$]PF$_6$ (10 mol%)	CyP	23	75
3	[CpRu(MeCN)$_3$]PF$_6$ (10 mol%)	DMF	23	29[b]
4	[CpRu(MeCN)$_3$]PF$_6$ (10 mol%)	Ac	50	85
5	[CpRu(MeCN)$_3$]PF$_6$ (10 mol%)	CyP	50	90
6	[CpRu(MeCN)$_3$]PF$_6$ (10 mol%)	CyP	60	84
7	[CpRu(MeCN)$_3$]PF$_6$ (5 mol%)	CyP	50	78[c]
8	[CpRu(MeCN)$_3$]PF$_6$ (2 mol%)	CyP	50	43[c]
9	[CpRu(MeCN)$_3$]PF$_6$ (1 mol%)	CyP	50	26[c]
10	[CpRu(MeCN)$_3$]PF$_6$ + PPh$_3$ (10 mol%)	CyP	50	41
11	[CpRu(MeCN)$_3$]PF$_6$ + TPFPP (10 mol%)	CyP	50	76
12	[CpRu(MeCN)$_3$]PF$_6$ + P(OCH$_2$CF$_3$)$_3$ (10 mol%)	CyP	50	29

Conditions: **1** (0.100 mmol), **2** (0.150 mmol), concentration: 0.50 M, reaction time: 3 h. [a] Isolated yield, [b] NMR-yield (mesitylene was used as the standard), [c] Concentration: 1.0 M Ac = acetone; CyP = cyclopentanone; DMF = *N*,*N*-dimethylformamide, TPFPP = tris(perfluorophenyl)phosphine.

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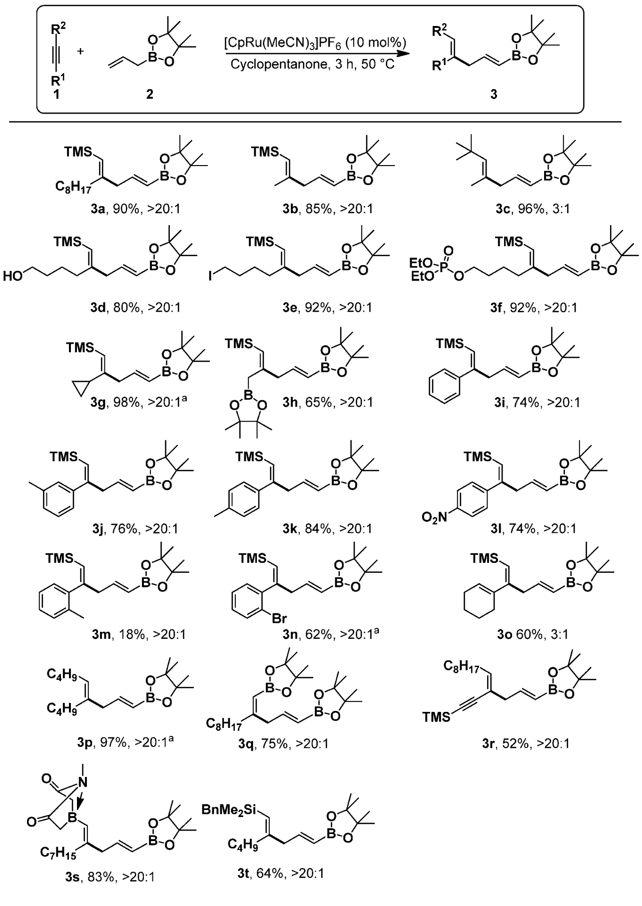
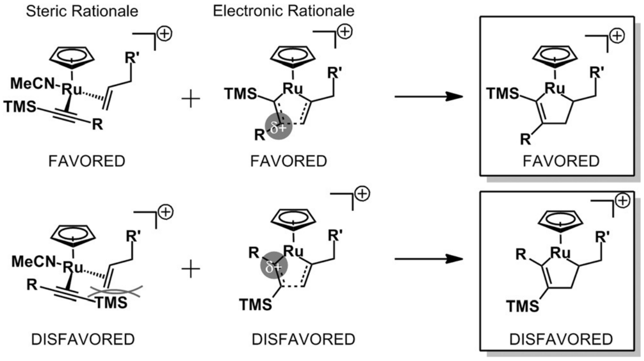
phosphine ligands hampered the progress of the reaction. A control experiment confirmed that the transformation does not occur in the absence of any catalyst. The purification was performed on boric-acid-treated silica gel.[12] This method leads to significantly higher isolated yields, especially on small scales. Furthermore, the reaction becomes more operationally practical, and the scope can be significantly broadened to non-distillable, high molecular-weight vinyl boronates.

With the optimized conditions in hand, we examined the scope of this alkene–alkyne coupling (Scheme 1).[13] The application of TMS-substituted alkynes led to product formation in high regioselectivity. In all of the examined cases, the (*E*)-vinyl borane was formed exclusively. The >20:1 ratio refers to the branched to linear ratio. To determine the nature of the regioselectivity, we investigated the effect of the silicon by comparing 4,4-dimethyl-2-pentyne to 1-(trimethylsilyl)-1-propyne. A branched to linear selectivity of 3:1 was observed in the non-silicon case, whereas the silylated alkyne afforded a single product. This suggests that the silicon exhibits a stereoelectronic effect. The phenomenon is explained in Scheme 2. The stability of the positive charge in β-position is rationalized by the β-silicon effect; therefore the formation of the branched product is electronically favored. This regioselectivity is further amplified by a steric effect. The bulky TMS group clashes with the olefin in the disfavored transition-state, whereas this clash does not occur in the transition state for the branched product. Both linear and branched aliphatic substituents were tolerated in the reaction. Hydroxy-, iodo-, and phosphate-substituted alkynes also performed well under the optimized reaction conditions (**3d–3f**). Notably, propargyl boronate **1h** was also tolerated to give **3h**, setting the stage for further functionalization such as an allylation reaction (see below).



Scheme 1. Alkyne scope of the Ru-catalyzed synthesis of vinyl boronates. Conditions: **1** (0.250 mmol), **2** (0.375 mmol), 10 mol% [CpRu(MeCN)$_3$]PF$_6$, in cyclopentanone (0.5 mL) at 50 °C, 3 h. Isolated yield is reported as a percentage; >20:1 refers to the branched/linear ratio. [a] Acetone 70 °C, sealed tube 12 h.

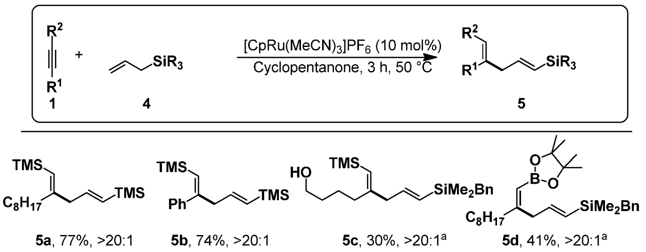


Scheme 2. Rationale for the regioselectivity of the reaction.

Aromatic alkynes, which are known to be troublesome in some Ru-catalyzed reactions, were well tolerated. Aromatics with *meta*- and *para*-substituents with electron-donating groups (EDG) and electron-withdrawing groups (EWG) worked equally well. *ortho*-Substituted aromatics led to poor conversions, presumably owing to steric hindrance. However, this problem could be overcome by running the reaction at 70 °C for 12 h, leading to yields of 62% for an *ortho*-bromo substitutent while retaining full selectivity. However, an enyne led to a mixture of regioisomers in a 3:1 ratio in synthetically useful yields of 60%.

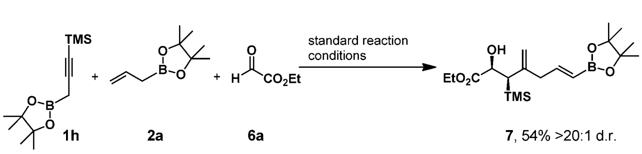
The application of symmetrical alkynes led to the desired product in high *E*-selectivity when aliphatic substituents were applied (**3p**). Yamamoto and Lee first explored the use of alkynyl boronates in the alkene–alkyne coupling.[14,15] Lee noted a strong directing effect of the pinacolato-boronate leading to unprecedented (*Z*)-selectivity in the formation of the internal olefin.[15] In our hands, alkynyl boronates as substrates generally led to (*Z*)-configured trisubstituted olefins and an (*E*)-configured 1,2-disubstituted unit. The olefin geometry in divinylborane **3q** was unequivocally determined by 1D-NOE analysis (for details see the Supporting Information). To the best of our knowledge, we herein describe the first application of an alkynyl MIDA-boronate in an alkene–alkyne coupling. Surprisingly, the exclusive formation of the (*E*)-isomer **3s** was observed, as confirmed by 1D-NOE analysis (Supporting Information). The steric bulk of the B(MIDA)-substituent most likely accounts for the observed selectivity. This discovery sets the stage for the application of iterative cross-coupling, as described by Burke.[16] The high predictability of the olefin geometry enables the synthesis of valuable 1,4-diene building blocks. Such scaffolds are difficult to integrate into complex molecular environments by other means. We also investigated the application of diynes to achieve selectivity for one alkyne unit. In concordance with the results of Lee, it was found that the selectivity of the reaction could be directed to the sterically less demanding alkyne in a highly selective fashion (**3r**).[17] Not only was a high chemoselectivity observed, but full control of regio- and stereochemistry was also achieved. **3s** represents a valuable building block to integrate highly decorated 1,4-dienes into complex molecular scaffolds in a highly selective fashion. Alkynyl benzyldimethyl silanes were also utilized as substrates in this transformation, giving rise to bifunctional 1,4-dienes. The valuable coupling product **3t** could be obtained in 64% yield. The geometry of the newly formed double bonds was found to be (*E*), as determined by 1D-NOE analysis (Supporting Information). The complementarity of **3q** and **3t** is notable especially in terms of their use in cross-coupling.

In comparison to allyl boronates, we also investigated the application of allyl silanes in this transformation (Scheme 3). Allyl trimethyl silanes performed equally well with both aliphatic and aromatic alkynes to furnish divinyl silanes **5a** and **5b**. The application of sterically-encumbered allyl benzyldimethylsilanes could be achieved under slightly modified reaction conditions. Elevated reaction temperatures and increased reaction times were the key to success. By juxtaposing the boron- and silicon-groups in the starting materials, full inversion of the olefin geometry can be observed at the trisubstituted olefin. 1,4-Diene linchpin **5d** is an attractive building block that can be utilized in iterative cross-coupling.



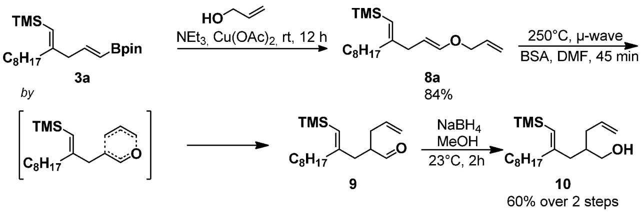
Scheme 3. Alkyne scope of the Ru-catalyzed synthesis of vinyl silanes. Conditions: **1** (0.250 mmol), **4** (0.375 mmol), 10 mol% [CpRu-$(MeCN)_3]PF_6$, in cyclopentanone (0.5 mL) at 50 °C, 3 h. Isolated yield (%). [a] Acetone, sealed tube, 70 °C, 12 h.

Valuable α-silyl-β-hydroxy olefins **7** were formed by a sequence of the alkene–alkyne-coupling and allylation in a one-pot fashion (Scheme 4). Propargyl boronate **1h** was smoothly coupled with allyl boronate **2a** delivering **3h**. The addition of an aldehyde to the reaction resulted in a highly diastereoselective allylation in one-pot to furnish compound **7**.



Scheme 4. One-pot protocol to deliver α-silyl-β-hydroxy olefin **7** from propargyl boronate **1h**.

A recent discovery by Merlic allows access to allyl ethers from vinyl boronates through a copper-promoted Chan-Lam-type allyloxylation reaction with allyl alcohol.[18] This protocol was successfully applied to synthesize vinyl allyl ether **8a** from **3a** in excellent yields of 84% (Scheme 5). A subsequent Claisen rearrangement with BSA (*N*,*O*-bistrimethylsilylacetamide) as an acid scavenger under microwave irradiation at 250 °C for 45 min led to the formation of aldehyde **9**. A one-pot reduction using $NaBH_4$ furnished γ-hydroxy olefin **10** in 60% yield over two steps. These compounds are known to undergo carboetherification reactions and are valuable building blocks in organic synthesis.[19]



Scheme 5. Chan-Lam-Type allyloxylation and subsequent Claisen rearrangement to access γ-hydroxy olefin **8**.

With our newly developed strategy, the core of pharmaceutically-active natural products such as untenospongin B,[20] litseaverticillol D[21] and E[22] could be accessed rapidly through iterative cross-coupling (Figure 1).

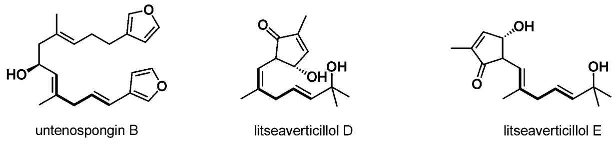
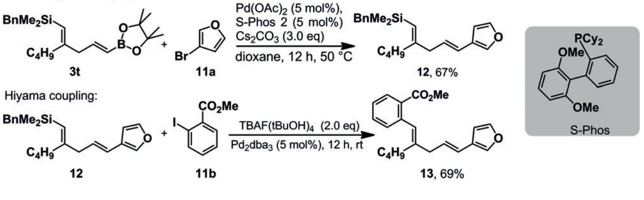


Figure 1. Potentially accessible pharmaceutically active natural products.

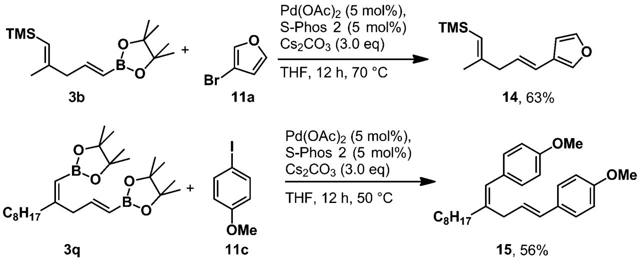
We therefore set out to investigate the applicability of a Suzuki–Miyaura reaction in the presence of a benzyldimethylsilyl group. Linchpin 1,4-diene **3t** smoothly reacts with 3-bromofuran **11a** under Buchwald conditions to access the vinyl silane **12** in 67% yield (Scheme 6).[23] The vinyl benzyldimethylsilyl functionality is well tolerated under the reaction conditions and can be activated with fluoride in an iterative Hiyama cross-coupling employing ligand-less conditions developed in our group.[24] We found TBAF(*t*BuOH)$_4$ to be the fluoride source of choice in the Hiyama reaction of



Scheme 6. Funtionalization through iterative cross-coupling.

12 with methyl iodobenzoate **11b** furnishing the desired product **13**.[25] This practical and bench-stable fluoride source is very convenient to use. To the best of our knowledge, this displays its first application in a Hiyama cross-coupling reaction.

The core structure of utenospongin B (Figure 1) could also be generated through a Suzuki–Miyaura reaction of **3b** with 3-bromofuran **11a** to deliver **14** in 63 % yield (Scheme 7).



Scheme 7. Suzuki–Miyaura cross-coupling to access the core of utenospongin B.

Vinyl silane addition into an aldehyde can lead to valuable derivatives of this pharmaceutically active natural product. Evans and Mikami have described asymmetric methods for these addition reactions.[26,27] A double Suzuki–Miyaura coupling of divinyl boronate **3q** with iodo anisole **11c** led to the desired distyrene derivative **15** in synthetically useful yields under Buchwald conditions.

In summary, we have developed a highly chemo-, regio-, and stereoselective Ru-catalyzed alkene–alkyne coupling of allyl boronates and allyl silanes with various alkynes to yield synthetically valuable vinyl boronates. A rare C–H activation, rather than C–B activation, complements the work by Hilt, but provides the opposite olefin geometry of the vinyl boronate. The conditions for the alkene–alkyne coupling of allyl boranes were significantly simplified. Neither slow addition nor excess alkyne was required for a successful reaction. The purification of the vinyl boronates was also considerably improved. The scope comprises both aliphatic and aromatic alkynes, and gives access to linchpin substrates that can be further manipulated through iterative cross-coupling reactions for the installation of functional groups at will. The geometry of the newly generated trisubstituted olefin can be controlled by juxtaposing the boron and silicon groups in the substrate. Further derivatization can be performed through Chan-Lam-type allyloxylation to yield vinyl allyl ethers. These building blocks can be engaged in Claisen rearrangement and subsequent one-pot reduction to furnish γ-hydroxyolefins. A one-pot alkene–alkyne coupling/allylation sequence yielding a highly functionalized α-silyl-β-hydroxy olefin was also realized.

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