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Synthesis of *Z*-(Pinacolato)allylboron and *Z*-(Pinacolato)alkenylboron Compounds through Stereoselective Catalytic Cross-Metathesis

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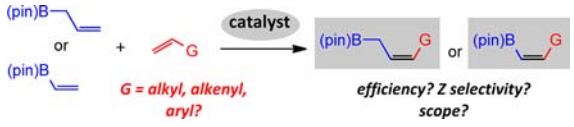
Supporting Information

ABSTRACT: The first examples of catalytic cross-metathesis (CM) reactions that furnish *Z*-(pinacolato)-allylboron and *Z*-(pinacolato)alkenylboron compounds are disclosed. Products are generated with high *Z* selectivity by the use of a W-based monoaryloxide pyrrolide (MAP) complex (up to 91% yield and >98:2 *Z*:*E*). The more sterically demanding *Z*-alkenylboron species are obtained in the presence of Mo-based MAP complexes in up to 93% yield and 97% *Z* selectivity. *Z*-selective CM with 1,3-dienes and aryl olefins are reported for the first time. The utility of the approach, in combination with catalytic cross coupling, is demonstrated by a concise and stereoselective synthesis of anticancer agent combretastatin A-4.

Organoboron compounds are vital to chemical synthesis, and among them, (pinacolato)allylboron [allyl-B(pin)] and (pinacolato)alkenylboron [alkenyl-B(pin)] reagents hold a prominent position.[1] The former set is used in countless stereoselective additions,[2] and the latter are partners in a myriad of catalytic cross couplings.[3] Since the stereochemical outcome of transformations with such entities is contingent on whether a *Z*- or an *E*-organoboron is employed,[4,5] of considerable value are methods for facile and efficient access to stereodefined acyclic allyl-B(pin) and alkenyl-B(pin) compounds. Contrary to the *E* isomers, however, protocols for selective synthesis of higher-energy *Z*-allyl- or *Z*-alkenylboron species are uncommon, and especially scarce are related processes that are catalytic. Ni-catalyzed hydroboration of dienes has been shown to afford *Z*-allyl-B(pin) products;[6] Ir-, Rh-[7] and, most recently, Ru-catalyzed[8] methods for trans-boron-hydride additions to terminal alkynes have been devised to furnish *Z*-alkenyl-B(pin) compounds. Such protocols were introduced as alternatives to noncatalytic procedures, which, while highly stereoselective, are multistep and require strong base (e.g., *n*-BuK[9a] or *n*-BuLi[9b]) or acid (e.g., glacial acetic acid).[10] Stereoselective cross-metathesis (CM)[11] of commercially available allyl- or alkenyl-B(pin) with terminal alkenes offers an attractive general strategy for synthesis of *Z*-allyl- or *Z*-alkenylboron entities (Scheme 1), one that is entirely distinct from catalytic alkyne hydroborations mentioned above; nonetheless, all existing CM protocols deliver the corresponding *E* isomers predominantly.[12] Herein, we demonstrate that catalytic CM can be used to access *Z*-allyl- or *Z*-alkenylboron compounds efficiently and with high stereoselectivity.[13] Transformations are promoted by W or Mo complexes, offering a generalizable, and at times unique, entry to stereoselective synthesis of a range of valuable organoboron reagents and intermediates.

Scheme 1



We began by examining reactions with allyl-B(pin) **4**. A challenge in promoting this class of transformations does not lie as much in attaining high efficiency but rather in whether erosion of kinetic stereoselectivity due to post-CM isomerization can be avoided as the reaction progresses toward high conversion.[13a] Thus, although we had determined earlier that *Z*-selective homocoupling of allyl-B(pin) can be promoted efficiently with W-based monoaryloxide pyrrolide (MAP) complexes,[14] access to the less hindered disubstituted alkenes would require identifying a catalyst that strikes the desired balance between reactivity and selectivity. As the screening data in entries 1−4 of Table 1 indicate, when Mo-based MAP complexes **1a**,**b** or **2a**,**b** are used, CM of allyl-B(pin) **4** and 1-decene proceeds readily to 50−75% conversion, but *Z* selectivity is moderate (69:31−87:13 *Z*:*E*). Control experiments indicate stereoselectivity is diminished as the reactions proceed further; this is especially true when the more reactive adamantylimido alkylidenes derived from **1a** are involved (63% conv and ∼1:1 *Z*:*E* after 24 h), although such complexes likely deliver high kinetic *Z* selectivity consistent with the previously suggested stereochemical model (large size difference between the adamantyl and aryloxy ligands).[13a,c] With the more hindered Mo arylimido systems, there is less post-CM isomerization (vs **1a**,**b**), but kinetic selectivity is probably also lower on the basis of the above rationale. In the presence of the less active but more stereodifferentiating W alkylidene **3** (increased size differential between imido and aryloxide groups),[13a,c] **6a** is isolated with 95:5 *Z*:*E* selectivity (entry 5, Table 1);[15] oxidative workup delivers *Z*-allylic alcohol **6a** in 65% overall yield. To the best of our knowledge, this is the first report of a W-catalyzed *Z*-selective CM. Reactions with commonly used and moderately *E*-selective Ru-based carbenes require 12 h at 40 °C (e.g., Grubbs second-generation: 18% yield of **6a**, 73% *E*, in

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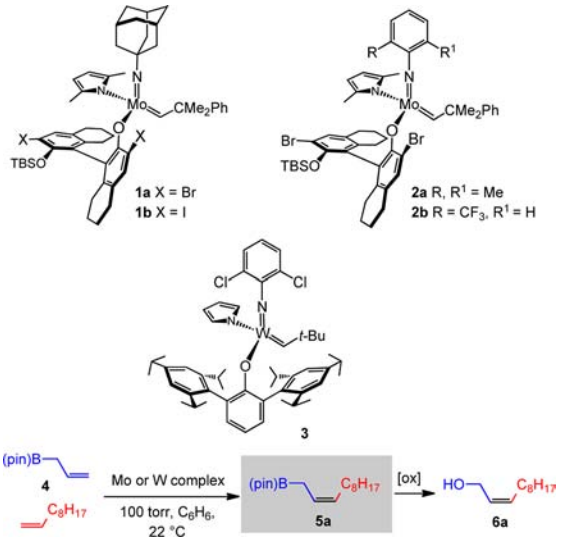
Table 1. *Z*-Selective CM with Allyl-B(pin) 4: Catalyst Screening[a]



entry	complex; mol %	time (h)	conv (%)[b]	yield of **6a** (%)[c]	*Z*:*E*[b]
1	**1a**; 3.0	4.0	50	nd	87:13
2	**1b**; 3.0	24	66	nd	81:19
3	**2a**; 5.0	5.0	75	nd	78:22
4	**2b**; 5.0	4.0	52	nd	69:31
5	**3**; 5.0	***2.0***	***78***	***65***	***95:5***

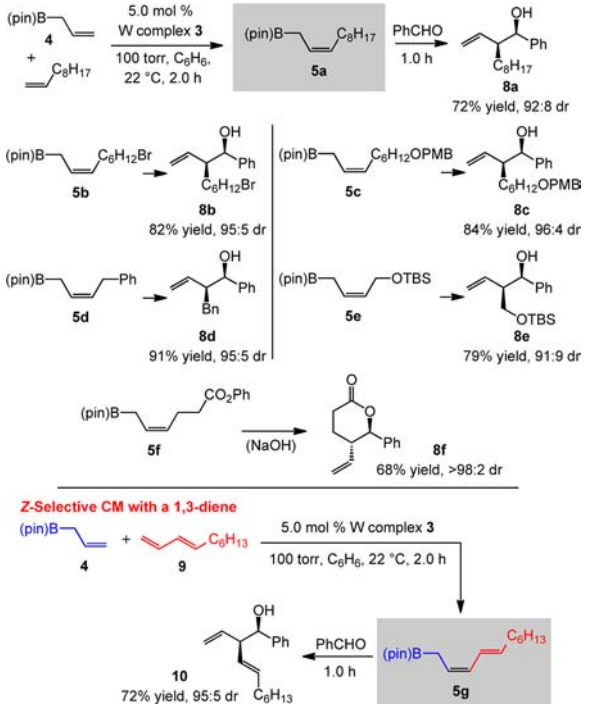
[a]Reactions performed in C_6H_6 under N_2 atm with 5.0 equiv of 1-decene. Oxidative workup: H_2O_2, NaOH, 22 °C, 2.0 h. [b]Determined by analysis of ^{1}H NMR spectra of unpurified mixtures (of **5a** for conv and of **6a** for *Z*:*E*) and refer to consumption of the limiting substrate (±2%). See the Supporting Information for details. [c]Yield of isolated and purified **6a** (isomeric mixture). nd = not determined.

2.0 h at 22 °C);[12a] when Mo(CHCMe$_2$Ph)(N(2,6-(*i*-Pr)$_2$C$_6$H$_3$)-(OCMe(CF$_3$)$_2$)$_2$ (**7**) is used, **6a** is obtained in 54% yield and with moderate *E* selectivity (76:24 *E*:*Z*).[16]

Various terminal alkenes undergo *Z*-selective CM with allyl-B(pin) **4** within two hours at ambient temperature (Scheme 2). The *Z*-disubstituted allyl-B(pin) compounds, sensitive to purification and isolation, were directly treated with benzaldehyde to afford the derived homoallylic alcohols; the diastereoselectivity levels with which **8a**–**8f** and **10** are obtained serve as an indicator of the isomeric purity of the corresponding allyl-B(pin) intermediate.[12] Disubstituted allylboron compounds are formed in 91:9 to >98:2 *Z*:*E* selectivity (based on dr), and the unsaturated alcohols are isolated in 68–91% yield. In one instance (**8e**), the use of Mo complex **2a** is required, since the sizable silyl ether likely causes the W alkylidenes derived from **3** to be less efficient (30% conv, 23% yield). Furthermore, the disubstituted alkene in **5e** is relatively hindered, and *Z*-to-*E* interconversion by post-CM isomerization with the more active Mo catalyst is less of a factor (vs a more accessible alkene such as **5a**). Another notable finding in Scheme 2 relates to the first instance of a *Z*-selective CM reaction with a 1,3-diene,[17] affording **10** in 72% yield and 95:5 dr; such products were not reported in connection to the Ni-catalyzed protocol.[6]

Next, we probed the possibility of *Z*-selective CM with vinyl-B(pin) **11**. This class of transformations, Mo- or W-catalyzed variants of which are unknown, poses several distinct challenges. In contrast to formerly reported processes[13a] as well as those mentioned above, the p orbital at the boron center of a B(pin)-substituted alkylidene can stabilize electron density at the

Scheme 2. *Z*-Selective Catalytic CM with Allyl-B(pin) 4[a]

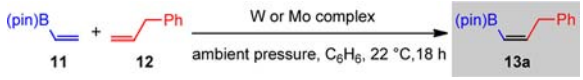


[a]Reactions were performed in C_6H_6 at 22 °C with 5.0 equiv of cross partner. All yields are overall for two steps. Synthesis of **8e** involved the use of Mo complex **2a** under otherwise identical conditions, and formation of **8f** involved treatment with NaOH. See the Supporting Information for details.

alkylidene carbon to diminish catalyst activity. Furthermore, vinylboron **11** is more sterically demanding than the cross partners examined thus far (including allyl-B(pin) **4**).[13a]

Catalyst screening was performed with **11** and *β*-branched terminal alkene **12** (Table 2); there is appreciable conversion to **13a** (50–98% conv) and ≥86:14 *Z*:*E* selectivity under conditions where, unlike reactions with **4**, vinyl-B(pin) **11** is present in excess. In additional contrast to syntheses of the more exposed alkenes of *Z*-allyl-B(pin)s **5a**–**g** (Scheme 2), it is Mo complexes **2a**,**b** that provide the highest efficiency and stereoselectivity: **13a** is obtained in ∼68% yield and 93:7 *Z* selectivity (entries 3 and 4, Table 2). CM is highly *Z*-selective with the less sterically demanding **1a**, but CM proceeds to only

Table 2. *Z*-Selective CM with Vinyl-B(pin) 11: Catalyst Screening[a]



entry	complex; mol %	conv (%)[b]	yield (%)[c]	*Z*:*E*[b]
1	**1a**; 3.0	56	nd	96:4
2	**1b**; 3.0	50	nd	93:7
3	**2a**; 5.0	***95***	***68***	***93:7***
4	**2b**; 5.0	***98***	***69***	***93:7***
5	**3**; 5.0	66	nd	86:14

[a]Performed under N_2 atm with 5.0 equiv of **11**. [b]Determined by analysis of ^{1}H NMR spectra of unpurified mixtures and refer to consumption of the limiting substrate (±2%). See the Supporting Information for details. [c]Yield of isolated and purified **13a** (isomeric mixture). nd = not determined.

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56% conversion (entry 1, Table 2); this is likely due to lower stability of the derived alkylidenes, including the methylidene generated from ethylene byproduct (ambient pressure used). Reaction with W-based **3** proceeds less readily than with most Mo variants, but surprisingly, and for reasons that are unclear, it is less stereoselective (entry 5; 86:14 *Z*:*E*). We elected to use complex **2a** for further studies (vs **2b**) for its relative ease of preparation.

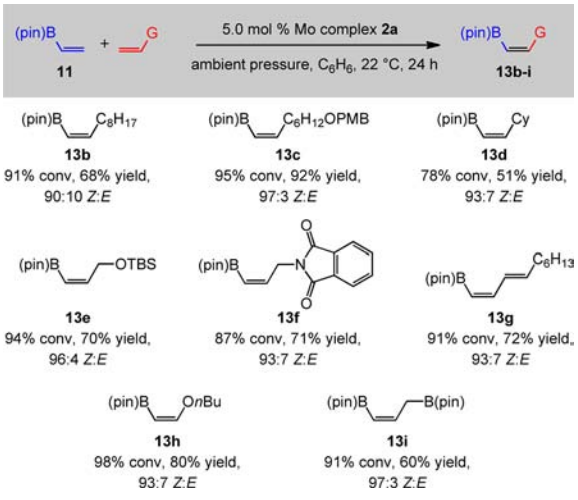
Two additional points regarding CM with **11** merit note: (1) Unlike reactions with excess amounts of unhindered terminal alkenes, including allyl-B(pin) **4**, stereoselectivities do not improve under a vacuum. This might arise from competitive formation of the relatively stable B(pin)-substituted alkylidene, preventing the availability of methylidene complexes, which are more reactive and thus capable of promoting isomerization.[18] Moreover, use of excess vinyl-B(pin) **11** reduces the concentration of alkyl-substituted alkylidenes, species that are better capable of causing loss of stereoselectivity (vs B(pin)-substituted alkylidenes).[19] (2) Reactions with 5.0 mol % second-generation Grubbs catalyst or the corresponding phosphine-free variant are efficient but afford **13a** in ∼90:10 *E*:*Z* selectivity (∼70% yield).[16] When Mo bis-alkoxide **7** is used, there is only 33% conversion of **12** after 10 min (no further conversion after 24 h), and **13a** is isolated in 15% yield and 68:32 *Z*:*E*.[16,20] The latter inefficiency might be attributed to the low stability of the highly Lewis acidic bis(hexafluoro)-alkoxide Mo alkylidene, rendered more electron-deficient by its B(pin) substituent. The significantly higher conversion values furnished by the more robust MAP complexes (Table 2) are therefore noteworthy.[21]

An assortment of *Z*-alkenyl-B(pin) compounds can be obtained in 51−92% yield after purification, in contrast to allylboron compounds, and 90:10−97:3 *Z*:*E* (Scheme 3). Reactions with a sizable cyclohexyl (**13d**) or silyl ether (**13e**) substituent or an electron-deficient allylic amide (**13f**) proceed to 78−94% conversion, affording the *Z*-alkenyl-B(pin) products in 51−71% yield and 93:7−96:4 *Z*:*E* ratio. Stereoselective synthesis of *Z*,*E*-diene **13g** (72% yield, 93% *Z*) provides another example of CM involving an acyclic 1,3-diene. Enol ether **13h** is formed in 93:7 *Z*:*E* selectivity and isolated as the pure *Z* isomer (>98%) in 80% yield. Allyl-B(pin) **13i**, obtained in 60% yield[22] and 97:3 *Z*:*E*, belongs to a class of reagents with demonstrated utility in stereoselective synthesis;[23] the CM strategy can allow access to related entities that bear differentiated boryl units. *Z*-Alkenyl-B(pin) entities represented by **13g−i** were not prepared by Ir-, Rh-, or Ru-catalyzed alkyne hydroborations.[7,8]

We then turned to reactions involving the most sterically demanding combination of substrates thus far, CM between vinyl-B(pin) and styrenes; in the context of *Z*-selective transformations, aryl olefins have only been used in ring-opening/CM processes.[13c] CM of **11** and styrene proceeds with maximum *Z* selectivity when the more stereodifferentiating adamantylimido Mo MAP complex **1a** is employed; **14a** is isolated in 66% yield and 95:5 *Z*:*E* ratio.[24] Reactions with electron-rich methoxy-substituted styrenes proceed with similarly high *Z* selectivity (**14b,c** in 69% yield and 93:7−95:5 *Z*:*E*). CM with *p*-(trifluoromethyl)styrene is highly efficient, proceeding to 97% conversion to afford **14d** in 93% yield and 95:5 *Z*:*E*. In general, higher efficiencies are observed with excess styrene (vs **11**); this might be attributed to the more reactive benzylidenes being better capable of undergoing CM with **11** vs an electronically stabilized B(pin)-substituted alkylidene (from initial reaction with **11**) reacting with an aryl olefin. Furthermore, electron-rich styrenes (cf. **14c** and **14e**) are less prone to homodimerization (reaction with another electron-rich olefin) than CM with electron deficient **11** and can therefore be employed in relatively slight excess (1.5 equiv). Finally, in contrast to transformations with alkyl olefins (Scheme 3), reduced pressure (100 Torr) leads to improved selectivity probably because the methylidene derived from adamantylimido **1a** is more reactive and readily subject to decomposition (e.g., **14a** formed in 60:40 *Z*:*E* at ambient pressure).[13a]

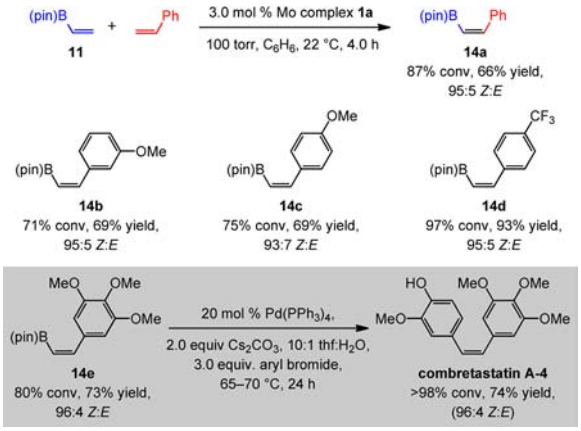
It is significant that the catalytic protocol is effective for synthesis of trimethoxyaryl-substituted vinyl-B(pin) **14e** (73% yield, 96:4 *Z*:*E*; Scheme 4); Pd-catalyzed cross coupling with the appropriate aryl bromide affords combretastatin A-4, a member of a class of antitumor agents. Stereoselective synthesis of the medicinal agent, 10 000 times more active than its *E* isomer,[25] demonstrates the power of combining catalytic CM and Suzuki−

Scheme 3. *Z*-Selective Catalytic CM with Vinyl-B(pin) 11: Generality[a]



[a]Reactions were performed in C_6H_6 at 22 °C with 5.0 equiv of **11**; yields are of *Z*/*E* mixtures, except for **13h** (>98% *Z*). See the Supporting Information for details.

Scheme 4. *Z*-Selective CM with Vinyl-B(pin) 11 and Styrenes[a]



[a]Reactions were performed in C_6H_6 at 22 °C with 5.0 equiv of styrene under N_2 atm, except for **14c** and **14e** where 1.5 equiv was used; yields are of *Z*/*E* mixtures. See the Supporting Information for details.

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Miyaura-type processes to obtain congested *Z*-alkenes by an approach that is more concise than those adopted formerly.[24,26]

The studies described above put forth several key additions to a limited repertoire of efficient *Z*-selective CM reactions.[13,27] A W- and two Mo-based alkylidenes have emerged as optimal catalysts, underscoring the importance of the structural and chemical diversity of high oxidation-state alkylidenes to the development of methods that bear substantial scope. Equally notable is the facility with which the reactions of sterically demanding substrates proceed; this is in contrast to the activity levels exhibited thus far by *Z*-selective Ru-based carbenes.[26]

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare the following competing financial interest(s): A.H.H. and R.R.S. are founders of a company that utilizes the reported approach.

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(18) Lower conversion is observed with excess alkene (vs **11**), likely because the alkyl-substituted alkylidene is shorter living than one with a B(pin) unit.

(19) Vinyl-B(pin) **11** undergoes relatively facile, and likely not readily reversible, homocoupling to generate ethylene, providing another rationale for the higher conversion observed when it is used in excess.

(20) The low *Z*:*E* ratio is congruent with the ability of this commonly used complex to afford moderate *Z* selectivity, which might be diminished through post-CM isomerization. Wang, C.; Yu, M.; Kyle, A. F.; Jakubec, P.; Dixon, D. J.; Schrock, R. R.; Hoveyda, A. H. *Chem.—Eur. J.* **2013**, *19*, 2726.

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