A Journal of the Gesellschaft Deutscher Chemiker

Angewandte International Edition GDCh Chemie

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Accepted Article

Title: Catalytic Enantioselective Synthesis of 1,4-Keto-Alkenylboronate Esters and 1,4-Dicarbonyls

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To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.201907757
Angew. Chem. 10.1002/ange.201907757

Link to VoR: http://dx.doi.org/10.1002/anie.201907757
http://dx.doi.org/10.1002/ange.201907757

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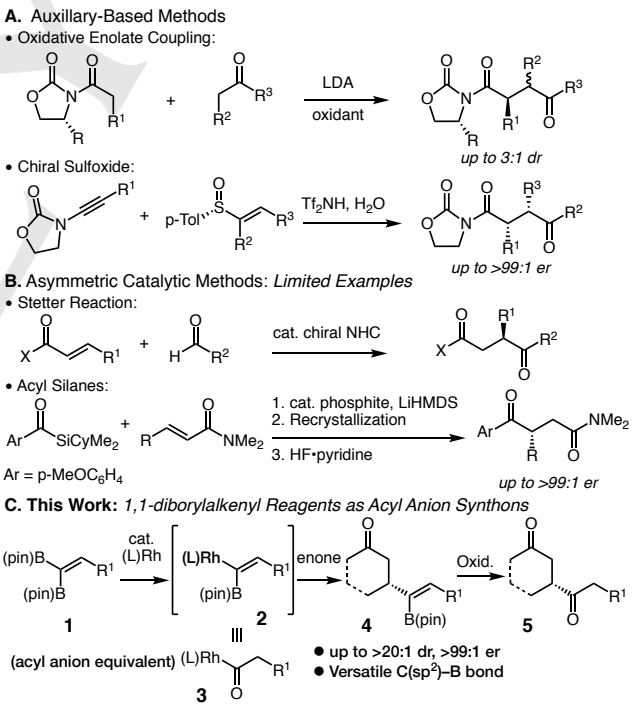
Catalytic Enantioselective Synthesis of 1,4-Keto-Alkenylboronate Esters and 1,4-Dicarbonyls.

Michael Z. Liang and Simon J. Meek*[a]

Abstract: A catalytic enantioselective method for the synthesis of 1,4-ketoalkenylboronate esters via a rhodium-catalyzed conjugate addition pathway is disclosed. A variety of novel, bench-stable alkenyl gem-diboronate esters are synthesized. These easily accessible reagents react smoothly with a collection of cyclic α,β-unsaturated ketones, generate a new C–C bond and stereocenter. Products are isolated in up to 99% yield, >20:1 *E*/*Z*, and >99:1 er. Mechanistic studies show the site-selectivity of transmetalation and reactivity is ligand dependent. The utility of the approach is highlighted by gram-scale synthesis of enantioenriched cyclic 1,4-diketones, and stereoselective transformations entailing hydrogenation, allylation, and isomerization.

1,4-Dicarbonyl compounds are common motifs in natural products and serve as versatile intermediates to the synthesis of pharmaceutical scaffolds.[1] These compounds are difficult to access as constructing their 1,4-relationship usually requires polarity inversion methods[2] or oxidative coupling processes and chiral, pre-functionalized starting materials. The stereoselective synthesis of 1,4-dicarbonyls is highly sought after and even though recent advances have been reported, notable deficiencies still remain in this area. Most current methods for enantioselective synthesis of 1,4-dicarbonyl moieties rely on the use of stoichiometric chiral auxiliaries as demonstrated by the pioneering work of Baran,[3] Thomson,[4] and Maulide[5] (Scheme 1 A). These methods employ pre-functionalized starting materials and are applicable only to generating acyclic 1,4-dicarbonyl motifs. Catalytic enantioselective methods for the synthesis of 1,4-carbonyls have largely centered around the enantioselective Stetter reaction,[6] and the acyl anion reactivity enabled by chiral NHCs.[7] In addition, related catalytic enantioselective umpolung reactions have been developed that employ acyl silanes,[8] acyl radicals,[9] and enamine radical cations,[10] which afford good enantioselectivities, however, reactions are limited to acyclic substrates, excluding access to cyclic scaffolds.

Previously, our group and others have developed catalytic enantioselective C–C bond forming methods that employ alkyl gem-diborons; for example, additions to carbonyls,[11] imines,[12] and allyl[13] electrophiles, and cross coupling.[14] In wherein the alkyl boron products serve as versatile groups for accessing a wide array of chemical functionality, including boron oxidation transformations that overall correspond to net umpolung reactivity. To address some of the deficiencies in the stereoselective preparation of cyclic 1,4-dicarbonyls, and other cyclic 1,4-functionality, we set out to examine the application of α-boryl–C(sp^2)–metal nucleophiles (e.g., **2**) in enantioselective conjugate addition;[15],[16] such a process concurrently generates a C–C bond and installs an alkenyl C(sp^2)-boronate ester as masked acyl synthon (**3**),[17] or a functional handle for other downstream transformations (Scheme 1C). To access the requisite α-boryl–C(sp^2) nucleophiles (e.g., **2**) we planned to take advantage of the reactivity of 1,1-diborylalkenyl reagents (**1**),[18] which have recently generated great interest in the synthetic community;[19] however, to-date their applications have been limited to non-enantioselective bond formations such as cross coupling.[20] Furthermore, 1,1-diborylalkenes are readily accessible bench stable reagents. Potential challenges that arise in the reaction of **1** are (i) site-specific transmetalation, (ii) the control of alkenyl boron geometry, and (iii) avoiding proto-deboration of starting material **1** or product **4**. Herein, we report on the first general method for the catalytic enantioselective synthesis of cyclic 1,4-keto-alkenylboronate esters with facile access to the corresponding 1,4-diketones.



Scheme 1. Enantioselective Synthesis of 1,4-Dicarbonyl Compounds.

We initiated our studies with the reaction of cyclohexenone **6** with 1,1-diborylalkenylhexene **7a** (Table 1). A key objective of the optimization centered on the ability to efficiently and selectively form the desired C–C bond in high enantioselectivity, and *E*/*Z* ratio while maintaining mild conditions to avoid protodeborative side reactions. When cyclohexenone **6** (1.0 equiv) and 1,1-diborylalkene **7a** (1.05 equiv) are subjected to aqueous basic

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10.1002/anie.201907757
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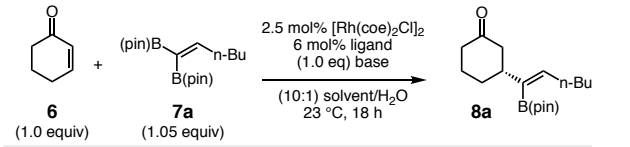
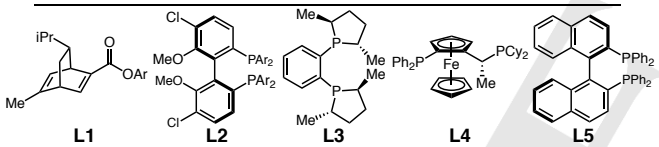
conditions in the presence of 2.5 mol % $[Rh(coe)_2Cl]_2$ and **L1** at 22 °C in dioxane/H_2O for 18 h, 57% conversion to 1,4-ketoalkenylboronate ester **8** is observed as a 1:2 mixture of E/Z isomers, in >99:1 er (*E*) and 50:50 er (*Z*), respectively). Of particular note, is disparity in er corresponding to each alkene isomer, while the *E*-isomer is formed in high er, the Z-isomer is formed as the racemate. Phosphine ligands **L2** and **L3** failed to significantly improve conversion and E/Z selectivity, and Josiphos ligand **L4** proved ineffective resulting in <2% conversion to **8**. With phosphine ligand **L5**, we found that **8** was generated in 17% as a single E-olefin isomer and in 99:1 er. Improved conversion was obtained with MTBE as solvent (entry 7), and through further optimization it was found that K_2CO_3 furnished **8** in the greatest efficiency (83% conv) (entry 9). These optimal conditions met our dual requirements for high selectivity and mild reaction conditions.

Table 1. Optimization of Rh(I)–Catalyzed α-Borylalkenyl 1,4-Addition[a]



6 (1.0 equiv) **7a** (1.05 equiv) **8a**

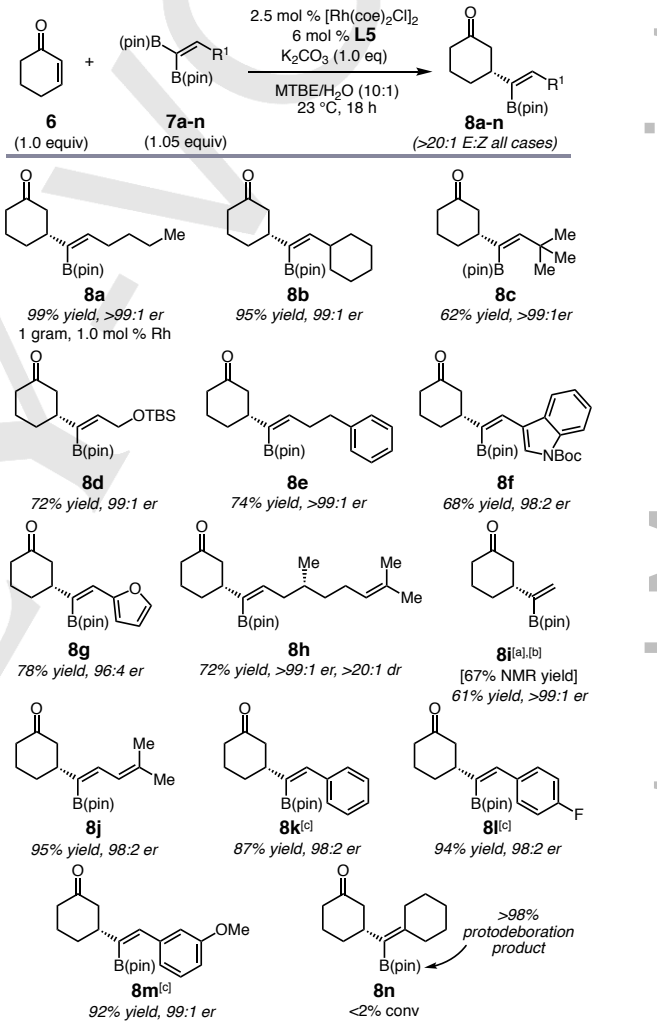
Entry	Ligand	Base	Solvent	Conv (%)[b]	E:Z ratio[b]	er[c]
1[d]	-	-	dioxane	100	1:3	-
2	**L1**	KOH	dioxane	57	1:2	>99:1(E);50:50(Z)
3	**L2**	KOH	dioxane	8	1:2	>99:1(E);50:50(Z)
4	**L3**	KOH	dioxane	20	1:3	>99:1(E);50:50(Z)
5	**L4**	KOH	dioxane	<2	–	–
6	**L5**	KOH	dioxane	17	>20:1	>99:1
7	**L5**	KOH	MTBE	64	>20:1	>99:1
8	**L5**	Na_2CO_3	MTBE	67	>20:1	>99:1
9	**L5**	K_2CO_3	MTBE	83	>20:1	>99:1



L1 Ar = 2-naphthyl **L2** Ar = 2-furyl **L3** **L4** **L5**

[a] Reactions performed under N_2 atmosphere. [b] Yields and E:Z ratios determined by analysis of 400, 500, or 600 MHz ^{1}H NMR spectra of crude reactions with DMF as internal standard. [c] Enantiomeric ratios (er) determined by HPLC analysis; see the SI for details. [d] With $[Rh(cod)OMe]_2$.

With the optimized conditions in hand, we set out to investigate the scope of the 1,1-diborylalkene component in 1,4-addition (Scheme 2). We found that a wide variety of functionality was tolerated and afforded products in excellent yields and enantiomeric ratios. Furthermore, all products were furnished as single *E* alkene isomers where applicable. An array of trisubstituted 1,1-diborylalkenes participate in the reaction including alkyl groups **8a–c** of varying steric bulk. In addition, the reaction is amenable to scalability as exemplified by the 1 gram synthesis of **8a** with 1.0 mol % Rh catalyst loading. Reactions with 1,1-diborylalkenes bearing TBS ether **8d** and 3-propylphenyl **8e** moieties proceeded efficiently as well. Heterocycles such as indole and furan **8f** and **8g** participated as does **8h**, derived from (R)-(+)-citronellal, offering opportunities to introduce complexity from chiral pool molecules. Unsubstituted parent ethylene 1,1-diboron was also found to be well tolerated, and upon oxidation **8i** furnishes a formal acetyl conjugate addition product. Unsaturated diene products are also accessible through this method; **8j** is formed in 95% yield and 98:2 er. Notable exceptions to the optimal reaction conditions are styrenyl and tetrasubstituted 1,1-diboron reagents. Such reagents undergo rapid metal-catalyzed protodeboration to the corresponding alkenyl-monoboron, which then undergo rapid alkenyl conjugate addition. To overcome this limitation and supress protodeboration a KIE effect was employed. By using D_2O in place of H_2O, reactivity could be restored albeit at the cost of incorporating a deuterium atom α to the carbonyl. Nonetheless, through the modified protocol products **8k–m** could be accessed in high yield and er. Tetrasubstituted 1,1-diboron **7n** proved resilient to the modified conditions (>98% protodeboration); considering the complete loss in er for Z-isomer products (Table 1, entries 2–4) it is unclear if **8n** could be formed enantioselectively.



Scheme 2. Alkenyl 1,1-Diboron Scope. Reactions performed under N_2 atm on 0.05 mmol scale with 1.0 equiv of **6**, 1.05 equiv. of **7a-n**, in 0.165 ml of MTBE/H_2O (10:1). Yields and enantiomeric ratios of the isolated products **8a–n** are indicated below each entry (average of two runs per substrate). [a] Conversion to **8i**; value determined by analysis of 600 MHz ^{1}H NMR spectra of crude mixtures with DMF as internal standard. [b] Product isolated and characterized as the 1,4-diketone upon oxidation. [c] Reaction with D_2O instead of H_2O.

A broad range of cyclic enones participate in the reaction with high efficiency (Scheme 3). Varying the enone ring size (5→8) **11–13**, and gem-dimethyl substitution on the ring **14** were allowed.

10.1002/anie.201907757

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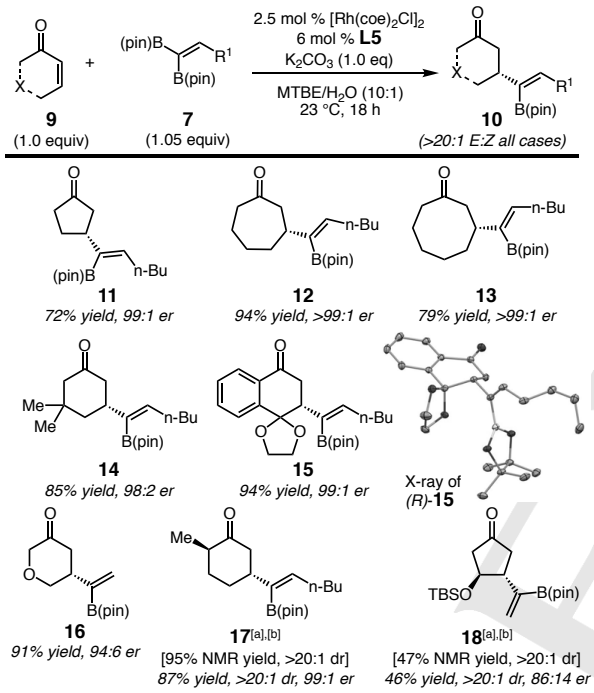
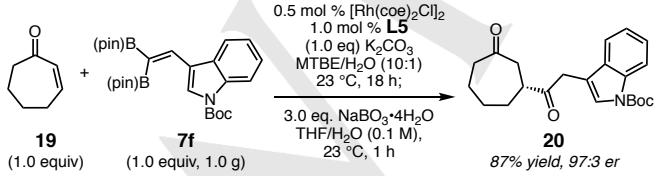
Spirocyclic enone **15**, formed in 94% yield and 99:1 er, is a solid and permitted an X-ray structure to be obtained and the absolute stereochemistry to be determined as *R*.[21] Cyclic enones containing an oxygen atom at the 4-position are also effective substrates, as demonstrated by the formation of **16** in 91% yield and in 94:6 er. Remarkably, 6-Me substituted enone **17**, formed from racemic starting material, participates in a dynamic kinetic resolution to provide product in 95% yield, >20:1 dr, and 99:1 er. Racemic prostaglandin related 3-TBSO-cyclopentenone can also participate in the reaction through a kinetic resolution to provide **18** in 47% NMR yield, >20:1 dr, and 86:14 er. At present, unfortunately, this current method does not appear to be compatible with acyclic enones, which do not participate in C–C bond formation.[22]

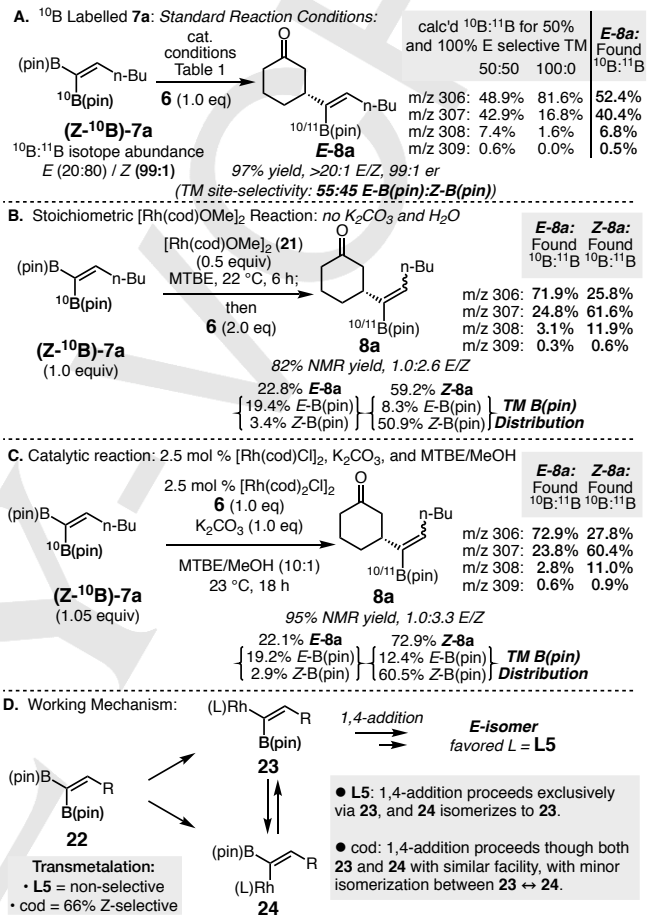


Scheme 3. Enone Scope. Reactions performed under N_2 atm on 0.05 mmol scale with 1.0 equiv of **9**, 1.05 equiv. of **7**, in 0.165 ml of MTBE/H_2O (10:1). Yields and enantiomeric ratios of the isolated products **11–18** are indicated below each entry (average of two runs per substrate). [a] Conversion to **17** and **18**; values determined by analysis of 400 or 600 MHz ^{1}H NMR spectra of crude mixtures with DMF as internal standard. [b] Product isolated and characterized as the 1,4-diketone upon oxidation.



Scheme 4. Gram-Scale Enantioselective Synthesis of 1,4-Dicarbonyl **20** with 1.0 mol % Rh catalyst loading.

The synthetic applicability of this method towards the gram scale synthesis of enantioenriched 1,4-diketones with lower catalyst loading, is highlighted in the efficient preparation of diketone **20** through a telescoped process. Treatment of cycloheptenone **19** with 1.0 g of indole-derived diboron **7f** in the presence of 1.0 mol % Rh catalyst, followed by oxidation of the crude product with $NaBO_3$•$4H_2O$ affords 1,4-diketone **20** in 87% yield and 97:3 er.



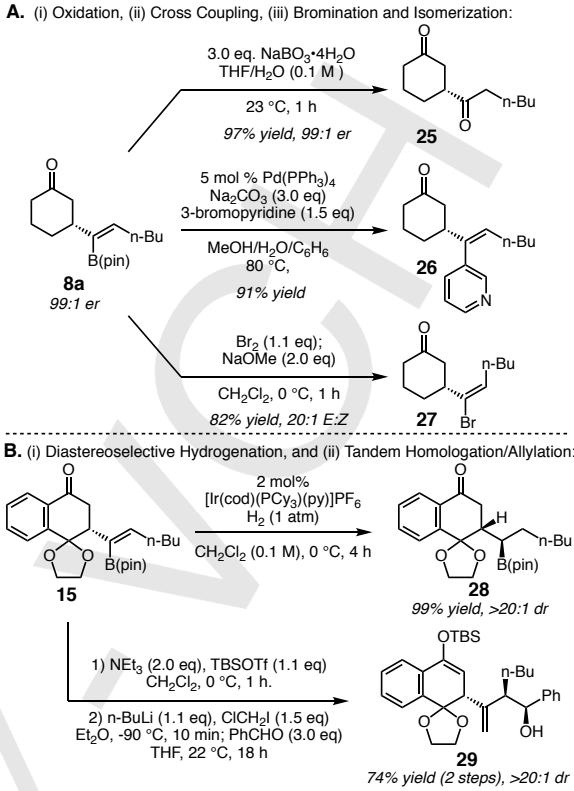
Scheme 5. Mechanistic Insights of 1,1-Diborylalkene Transmetalation. See SI for details.

Next, we sought to garner information regarding the mechanism of 1,1-diborylalkene transmetalation.[23],[14a] While the reaction with **L5** seemed straightforward the observation of *E/Z* mixture of products with other **L1–L3** suggested otherwise. In this regard, isotopically enriched **Z-^{10}B-7a** was regioselectively synthesized (see SI for details) and subjected to a variety of reaction conditions (Scheme 5). Accordingly, if transmetalation is site-selective for the sterically less hindered *E*-B(pin) group, product **8a** will show mass ions related to the increased abundance of ^{10}B proportional to the transmetalation selectivity. Mass spectral analysis of **8a**, formed under standard reaction conditions with **Z-^{10}B-7a** (Scheme 5A), shows an isotopic composition consistent with that expected for a reaction where *either boronate is transmetalated non-selectively (55:45 E-B(pin):Z-B(pin))*. This surprising outcome indicates that transmetalation proceeds equally effectively from either B(pin) group, and the resulting Z-α-boryl–C(sp^2)-Rh(I) species

10.1002/anie.201907757

isomerizes to the *E*-isomer, which undergoes faster 1,4-addition. The observed isomerization is consistent with stereomutation observed in other hetero-gem-bismetallic alkenyl species.[24] As a control reaction to check for alkoxide promoted boron exchange in **Z-^{10}B-7a**,[25] stoichiometric reaction between **Z-^{10}B-7a** and one equivalent of **21** in MTBE in the absence of K_2CO_3 or H_2O/MeOH, followed by quench with **6** (2 equiv) was performed (Scheme 5B). The reaction furnished cyclohexanone **8a** in 82% NMR yield (1.0:2.6 *E/Z*), and the isotopic composition of the separate ***E*-8a** and ***Z*-8a** isomers shows that they arise primarily from a slightly *Z*-selective transmetalation (34:66 *E:Z*), which is followed by 1,4-addition with minimal *E*↔*Z* alkenyl–Rh isomerization. The corresponding catalytic reaction with 2.5 mol % $[Rh(cod)Cl]_2$ in MeOH and K_2CO_3 also affords a similar result (Scheme 5C): 95% NMR yield, 1.0:3:3 *E/Z*, and with isotopic distributions indicating ***E*-8a** and ***Z*-8a** are formed by 33:67 *E:Z* TM, with slow interconversion of both alkenyl–Rh intermediates prior to 1,4-addition. The preference for TM of the *Z*-B(pin) likely occurs due to the sterically smaller (cod)Rh–OR being able to react more readily with the more hindered but strained *Z*-B(pin). Overall, these data provide a working mechanism, where (**L5**)-Rh reactions proceed via a non-selective transmetalation of **22** → **23** and **24**, followed by alkenyl-Rh isomerization and enantioselective 1,4-addition through *E*-alkenyl-Rh **23**. In comparison, (cod)-Rh and (**L1**)-Rh undergo *Z*-selective TM, followed by 1,4-addition from both **23** and **24** with equal facility and minimal alkenyl-Rh stereomutation. Notably, in all cases, **L1**–**L5**, only high enantioselectivity is observed in the 1,4-addition of the *E*-alkenyl-Rh **24**.[26] Such non-observable subtleties related to site-selective TM and isomerization could be relevant to other stereospecific reactions of 1,1-alkenyldiborons.[20]

The 1,4-ketoalkenylboronate esters accessed through the conjugate addition method can be further elaborated through a wide variety of synthetically valuable transformations. For example, compound **8a** can be easily oxidized to the corresponding 1,4-diketone **25** with no loss of er, providing a general access to otherwise inaccessible chiral, non-racemic cyclic 1,4-diketones. In addition, **8a** can engage in subsequent Pd-catalyzed cross coupling to generate stereodefined trisubstituted alkenes; the synthesis of heterocycle **26** in 91% yield from 3-bromopyridine is representative. Generation of the opposite alkene isomer inaccessible through the 1,4-addition method can be achieved through a stereospecific boron–bromine exchange.[27] Treatment of boronate ester **8a** with Br_2 and NaOMe results in alkene stereoinversion to generate alkenylbromide **27** in 82% yield (>20:1 *E:Z*). The 1,4-keto-alkenylboronate esters also participate in a variety of diastereoselective transformations (Scheme 6B). For example, compound **15** undergoes hydrogenation in the presence of 2 mol % Crabtree's catalyst in CH_2Cl_2 to afford the corresponding C(sp^3)-boronate ester **28** in 99% yield and >20:1 dr, which can be further elaborated. Remarkably, conversion of ketone **15** to the corresponding enoxysilane, followed by a telescoped homologation and allylation sequence with chloroiodomethane and benzaldehyde, respectively, furnishes silylenolether **29** in 74% yield (2 steps) bearing two additional stereocenters formed in >20:1 dr, and a 1,1-disubstituted olefin.



Scheme 6. Synthetic Versatility of 1,4-Ketoalkenylboronate Esters. See SI for details.

In summary, we have introduced a catalytic enantioselective conjugate addition of α-boryl–C(sp^2) nucleophiles for the synthesis of 1,4-ketoalkenylboronate esters. Reactions employ easily accessible 1,1-diborylalkenes and proceed in excellent yields, dr, and er. Mechanistic data shows that the reactions with (**L5**)-Rh arise from a non-selective transmetalation followed by isomerization, and 1,4-addition through the *E*-alkenyl-Rh. The resulting 1,4-ketoalkenylboronate esters are readily transformed into the corresponding 1,4-dicarbonyls, as well as to a range of useful molecular scaffolds. Further studies on the reactivity of 1,1-diborylalkenes are in progress.

Acknowledgements

Financial support was provided by the United States National Institutes of Health, Institute of General Medical Sciences (R01GM116987) and the University of North Carolina at Chapel Hill. We thank Dr. Chun-Hsing Chen of UNC for X-ray structure elucidation of **15**. AllyChem is acknowledged for donations of $B_2(pin)_2$.

Keywords: 1,1-Diborylalkenes • Conjugate addition • Rhodium • Enantioselective • Umpolung

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[21] CCDC 1935756 contains the supplementary crystallographic data for compound **15**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

[22] For example, reactions with either benzylideneacetone or *E*-3-nonen-2-one resulted in <5% conv.

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[25] The possibility that 1,1-diboron species undergo thermal isomerization was explored, but ruled out through a hydroboration/protodeboration experiment (see Supporting Information).

[26] Unfortunately, further examination of the transmetalation step between **7a** and **21** by ^{1}H NMR analysis (>98% consumption of **7a** in 6 h at 22 °C) proved inconclusive.

[27] C. Morrill, R. H. Grubbs, *J. Org. Chem.* **2003**, *68*, 6031–6034.

10.1002/anie.201907757

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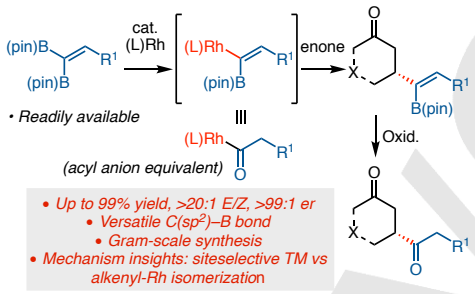
Layout 1:

COMMUNICATION

An enantioselective method for the synthesis of 1,4-keto-alkenylboronate esters via a Rh-catalyzed 1,4-addition is disclosed. A variety of alkenyl gem-diboronate esters react smoothly with a range of cyclic enones to afford products bearing an *E*-alkenylboron, which are isolated in up to 99% yield, >20:1 *E/Z*, and >99:1 er. Mechanistic studies show the site-selectivity of transmetalation and reactivity is ligand dependent.



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Page No. – Page No.

Catalytic Enantioselective Synthesis of 1,4-Keto-Alkenylboronate Esters and 1,4-Dicarbonyls.