C–Boron Enolates Enable Palladium Catalyzed Carboboration of Internal 1,3-Enynes

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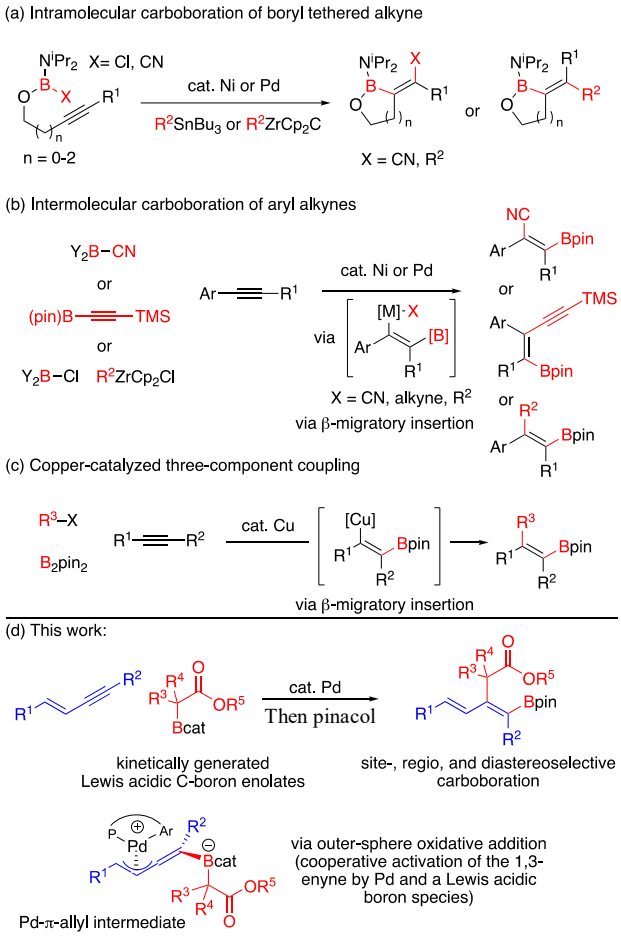
ABSTRACT: A new family of carbon-bound boron enolates, generated by a kinetically controlled halogen exchange between chlorocatecholborane and silylketene acetals, is described. These C-boron enolates are demonstrated to activativate 1,3-enyne substrates in the presence of a Pd(0)/Senphos ligand complex, resulting in the first examples of a carboboration reaction of an alkyne with enolate-equivalent nucleophiles. Highly substituted dienyl boron building blocks are produced in excellent site-, regio-, and diastereoselectivity by the described catalytic cis-carboboration reaction.

Alkenyl boronates are versatile building blocks in synthetic chemistry.[1] The ability of organoboron compounds to engage in Suzuki-Miyaura cross couplings[2] and to transform into various derivatives[3] have made alkenyl boronates highly appealing in organic synthesis. In this context, numerous approaches[4] have been developed to synthesize di-[5] and tri-[6] substituted alkenyl boronates. The synthesis of tetrasubstituted alkenyl[7] boronates on the other hand, particularly in regioselective and stereoselective fashion, has been more challenging.[8] Pioneering work by Suginome et al. (Scheme 1, a) established the nickel- or palladium catalyzed *intramolecular* boryl migration approach using alkyne substrates tethered with boryl moiety.[9] Similarly, nickel and palladium catalyzed *intermolecular* carboboration of alkynes with various carbon sources (Scheme 1b) was reported.[10] More recently, copper-catalyzed three-component coupling of an alkyne, B_2pin_2, and an electrophile (Scheme 1c) has received attention.[11] Despite these advances, carboboration reactions are still relatively limited in substrate scope and generality. In particular, stereoselective carborations to produce tetra-substituted alkenes often face regio- and dia-stereoselectivity issues for internal unsymmetrical alkynes.[11a-e] We recently reported the *trans*-hydroboration and *trans*-cyanoboration of 1,3-enynes catalyzed by a 1,4-azaborine biaryl phosphine (Senphos)-Pd complex.[12] The distinguishing feature of the Pd-Senphos catalyst system is the proposed unusual outer-sphere oxidative addition mechanism[13] (a cooperative activation of the 1,3-enyne by LPd(0) and a Lewis acidic boron species) that introduces the boron group into the alkyne substrate with concomitant formation of a Pd-π-allyl species (vs. a more conventional β-migratory insertion pathway by reactions illustrated in Scheme 1, a-c). Given the known versatility of Pd π-allyl intermediate to achieve diverse functionalizations,[14] we envisioned that new bond connections can be

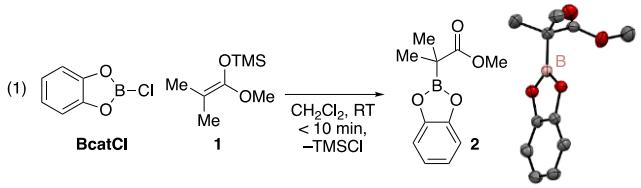
achieved with a variety of nucleophilic boron reagents. In this communication, we report the first carboboration reaction of an alkyne with a boron enolate, thus expanding the scope of carboboration reactions to include the ubiquitous family of enolate nucleophiles.[15] The highly substituted dienyl boronates (containing a tetra-substituted alkene unit) are produced with exquisite site-, regio-, and diastereo-selectivity (Scheme 1d). Senphos ligand type structures are demonstrated to be uniquely enabling in achieving high catalytic efficiency and selectivity in this transformation.

Scheme 1. Regio- and Stereoselective Synthesis of Tetrasubstituted Alkenyl boronates



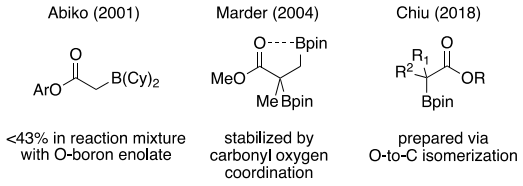
Key to successful development is the discovery of a new family of C-boron enolates as a suitably activating carboboration reagent. Treatment of a silylketene acetal **1** with catecholborane **BcatCl** cleanly furnishes C-catecholboron enolate **2**, which we have unambiguously structurally characterized by single crystal X-ray diffraction analysis (eq. 1). Compound **2** represents a rare example of a C-boron enolate without boron quaternization. The boron atom is completely planar (sum of bond angles = 360°), and the C=O bond is pointed in a direction relative to the C–B bond (∠B-C-C=O = –124.4(2)°) that is inconsistent with intramolecular coordination. The ^{1}H (*gem*-dimethyl signal at δ 1.5 ppm , ^{13}C (carbonyl carbon signal at δ 177.0 ppm), and ^{11}B NMR (signal at δ 34 ppm) of a $CDCl_3$ solution of **2** are also fully consistent with the C-boron enolate structure vs. O-boron enolate *in solution*.

Figure 1. Generation of C-boron enolates



To date, only few examples of unquaternized C-boron enolates have been reported.[16] Abiko et al. reported the first C-boron enolates derived from carboxylic esters in their double aldol reaction study, which exists as equilibrium with the corresponding O-boron enolates.[17] Marder's group observed C-boron enolates in a diborylation reaction, the stability of which was attributed to carbonyl oxygen coordination to β-boryl group.[18] Recently, Chiu group synthesized C-pinacolboron enolates through alkenyl ester 1,4-hydroboration followed by a thermodynamically driven O-to-C isomerization.[19]

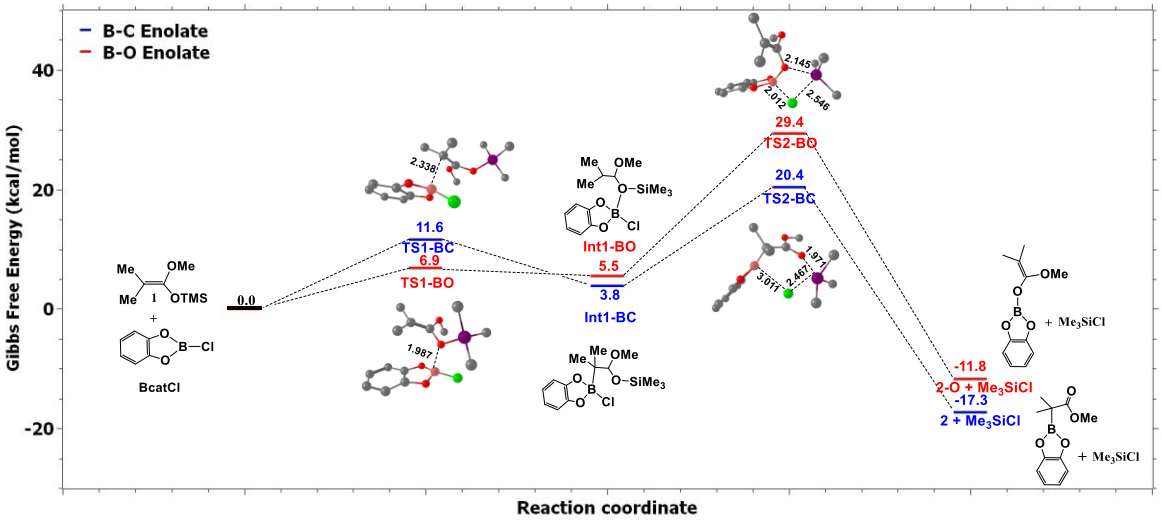
Scheme 2. C-Boron Enolates without Boron Quaternization accessed via thermodynamic control



The distinguishing feature of our method illustrated in eq 1 is that the C-boron enolate is formed under kinetically controlled conditions. The reaction between **BcatCl** and silylketene acetal **1** does not lead to an observable built up of O-boron enolate by NMR. Furthermore, DFT calculations (see ESI for computational details) for the reaction between **BcatCl** and silylketene acetal **1**, performed at the SMD(CH_2Cl_2)-W97XD/6-31G(d,p) level of theory (Scheme 3),[20,21] evidence a two-step mechanism (scheme 3) and predict that the rate-determining TMSCl elimination step is significantly more energetically unfavorable for the O-boron enolate pathway ($\Delta G^{\ddagger}$ = 29.4 kcal/mol, red color) than for the C-boron enolate pathway ($\Delta G^{\ddagger}$ = 20.4 kcal/mol,

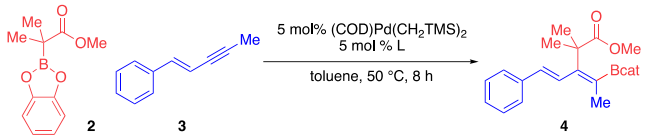
blue color). DFT calculations also predict that the kinetically favored C-boron enolate product is also more stable than the O-boron enolate by 5.7 kcal/mol.

Scheme 3. Energy profiles for the reaction between BcatCl and 1 computed at SMD(CH_2Cl_2)-W97XD/6-31G(d,p) level of theory (ΔG in kcal/mol).

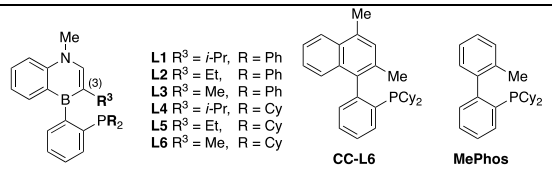


With a C-boron enolate in hand that is sufficiently Lewis acidic to possibly activate the 1,3-enyne substrate in an outer-sphere oxidative addition fashion, we surveyed a series of ligands to optimize the carboboration reaction. In the presence of 5 mol% (COD)Pd($CH_2TMS)_2$/ Senphos **L1**, reaction of 1,3-enyne **3** with C-boron enolate **2** (generated from 2 equiv. **BcatCl** and 3 equiv. silyl ketene acetal **1,** see Supporting Information for experimental details) in toluene at 50 °C affords the corresponding *cis*-carboboration product **4** in 10% yield with >98:2 *cis*-addition selectivity (Table 1, entry 1). In the absence of the catalyst under otherwise identical reaction conditions, no background reaction is observed. Switching the C(3) substituent R^3= *i*-Pr on the ligand to a sterically less demanding Et group improves the product yield (entry 2). A further decrease in the steric demand at the C(3) ligand position does not lead to further improvement in yield (entry 3, R^3 = Me). Interestingly, changing the R group on the phosphorous atom from R = Ph to Cy improves the product yield significantly when R^3 = Me (entry 6). However, the corresponding R^3= *i*-Pr ligand **L4** remains ineffective in supporting the Pd catalysis (entry 4). Moderate yield was achieved with ligand **L5** (R^3 = Et, R = Cy, entry 5). Having established the optimal ligand structure as **L6**, we determined that the corresponding carbonaceous ligand **CC-L6** (entry 7) and the commercially available, structurally related **MePhos**[22] (entry 8) are inferior ligands in terms of both efficiency and selectivity, highlighting the importance of the electronic structure provided by the BN heterocyclic Senphos ligands.[23] We also note that elevating the temperature from 50 °C to 60 °C results in a significant decrease in yield, presumably due to the competing decomposition of the reactive C-boron enolate **2** (entry 6 vs entry 9).[24]

Table 1. Ligand Survey of Internal 1,3-enyne *cis*-Carboboration[a]



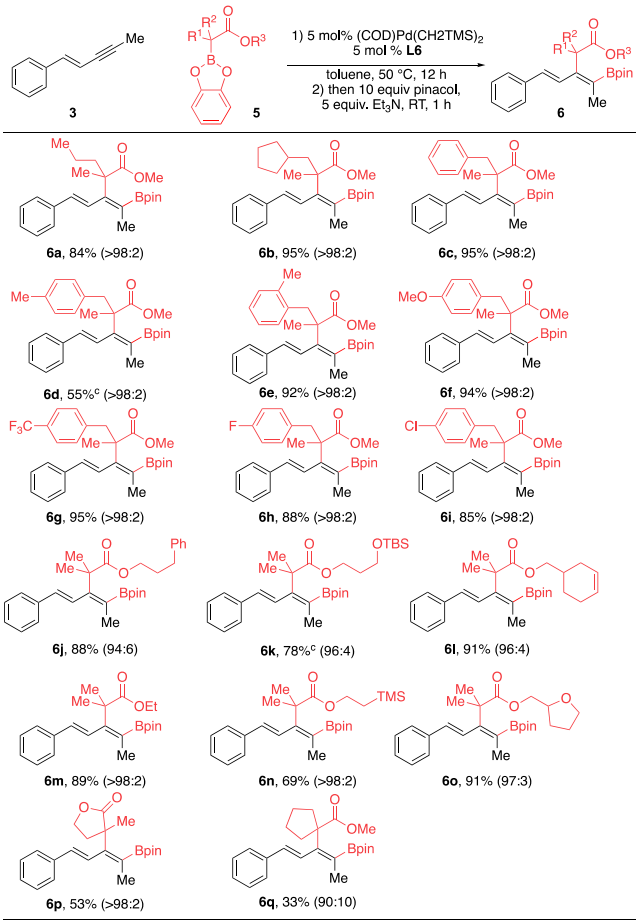
entry	L	Yield (%)[b]	Selectivity[b]
1	**L1**	10	> 98:2 *cis* addition
2	**L2**	45	> 98:2 *cis* addition
3	**L3**	43	> 98:2 *cis* addition
4	**L4**	5	N.D.
5	**L5**	72	> 98:2 *cis* addition
6	**L6**	**90(88)[c]**	**> 98:2 *cis* addition**
7	**CC-L6**	48	88:12 *cis* addition
8	**MePhos**	30	88:12 *cis* addition
9	**L6**	30[d]	> 98:12 *cis* addition



[a] See SI for detailed procedure. [b] Yield and selectivity were determined by ^{1}H NMR analysis of unpurified reaction mixtures with CH_2Br_2 as the internal standard. [c] Isolated yield (in parenthesis) of the Bpin adduct. [d] Reaction performed at 60 °C.

Having identified optimal conditions, we next explored the scope of this transformation with different C-boron enolates (**Table 2**). Aryl substituents such as methoxy (entry **6f**), trifluoromethyl (entry **6g**), and aryl halides (entries **6h** and **6i**) are well tolerated. For as of yet to be determined reasons, a lower yield was observed for the *para*-methyl substituted aryl C-boron enolate (**6d**) while the *ortho*-methyl substituted C-boron enolate (entry **6e**) performed with high efficiency. Silyl ether (entry **6k**) and cyclic alkene (entry **6l**) functional groups are also tolerated. Sterically demanding cyclic C-boron enolates (entries **6p** and **6q**) are also suitable substrates, albeit a lower yield was observed.

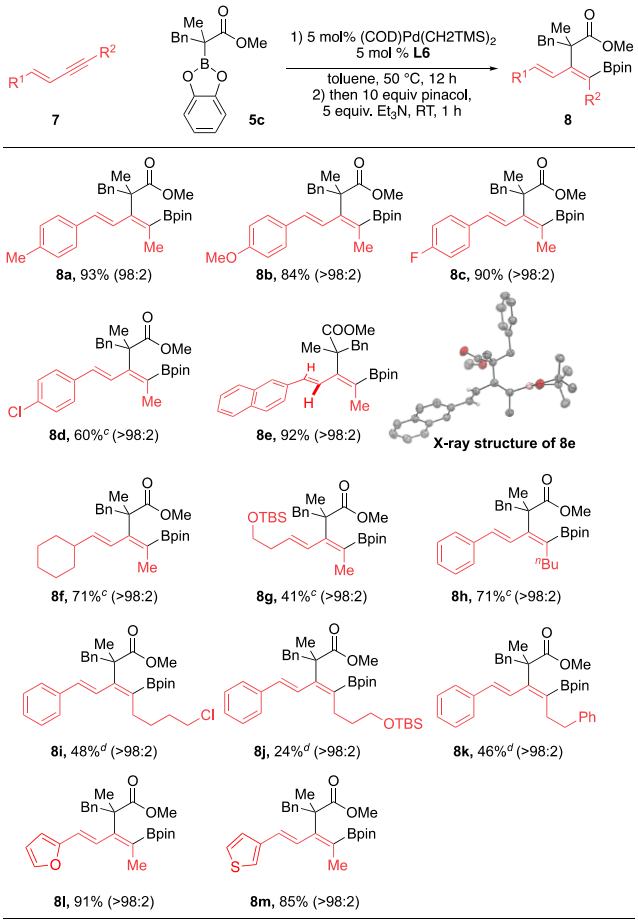
Table 2. Reaction Scope of C-Boron Enolates[a,b]



[a] See SI for detailed procedure. Selectivity was determined by ^{1}H NMR analysis of the purified product. [b] Isolated yields are reported as the average of two runs. [c] 18 h reaction time.

We then evaluated the generality of this method with respect to the internal 1,3-enyne (**Table 3**). 1,3-Enynes bearing an aryl group at the **R^1** position generally give higher yields than alkyl groups (entry **6c**, **8a-c** vs. **8f-g**). When the steric demand at the R^2 position increases (R^2 > Me), the reaction becomes more sluggish (entries **8h-k**), however, the high diastereoselectivity is maintained. We are pleased to determine that heteroaryl derived enynes (furan: entry **8l**, and thiophene: entry **8m**) are excellent substrates for the carboboration reaction. We have obtained the X-ray crystal structure of product **8e**,[25] thus unambiguously establishing the connectivity and the diastereoselectivity of the reaction. Notably, the solid structure of compound **8e** shows an almost perpendicular diene structure with a C=C–C=C dihedral angle of –69.4(2)°, which highlights the steric demand imposed by the highly substituted alkene.[26] Overall, Table 3 illustrates that across all surveyed 1,3-enynes high site-, regio- and diastereoselectivity can be achieved for the carboboration.

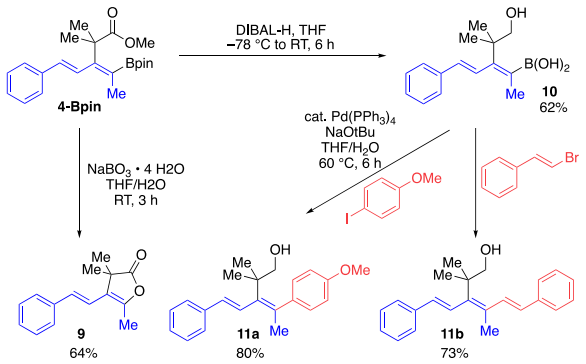
Table 3. Reaction Scope of Internal 1,3-Enynes[a,b]



[a] See SI for detailed procedure. Selectivity was determined by ^{1}H NMR analysis of the purified product. [b] Isolated yields are reported as the average of two runs. [c] 18 h reaction time. [d] 18 h reaction time with 10 mol% [Pd]/**L6**.

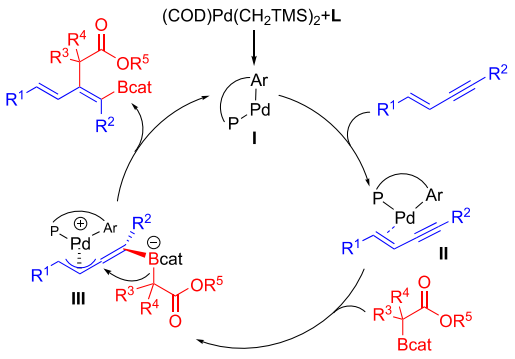
The highly substituted dienyl Bpin products can serve as useful intermediates in subsequent stereospecific transformations. For example, **4-Bpin** can be readily oxidized to afford the 2-furanone scaffold **9**, which comprises an important class of heterocyclic compounds in fragrances[27] and biologically active molecules.[28] Reduction of **4-Bpin** produces the dienyl boronic acid **10** which can further undergo Suzuki-Miyaura cross coupling with aryl or alkenyl halides to furnish the corresponding bis-aryl conjugated diene (**11a)** and triene (**11b**), respectively.

Scheme 4. Derivatization of Reaction Products



A plausible reaction mechanism is illustrated in Scheme 5. In the presence of Senphos ligand **L** the $(COD)Pd(CH_2TMS)_2$ precatalyst reductively eliminates 1,2-bis(trimethylsilyl)ethane to form the active LPd(0) species **I**,[29] which then subsequently binds to the 1,3-enyne. The LPd(0)-enyne complex **II** is then activated by the Lewis acidic C-boron enolate to furnish the outer-sphere oxidative adduct **III**. The Pd π-allyl is then attacked by an enolate equivalent to yield the product with concomitant regeneration of LPd(0) species **I**.[14] C-Boron enolates are uniquely effective for this coupling reaction due to its more Lewis acidic boron center (vs. O-boron enolate) that can help activate the enyne substrate via an outer-sphere oxidation mechanism.[30] The stronger Lewis acidic character of the C-boron enolate versus O-boron enolate is corroborated by the electronic structure calculations where an analysis of LUMOs with a strong boron contribution revelas a significant lower energy for C-boron enolate (see ESI).

Scheme 5. Proposed Catalytic Cycle



In summary, we discovered a new class of C-boron enolates via a kinetically controlled halogen exchange between chlorocatecholborane and silylketene acetals. These C-boron enolates are uniquely capable

in activating 1,3-enyne substrates in the presence of a Pd(0)/Senphos ligand complex via a proposed outer-sphere oxidative addition reaction mechanism, resulting in the first examples of a carboboration reaction of an alkyne with enolate-equivalent nucleophiles. The described catalytic *cis*-carboboration reaction produces highly substituted dienyl boron building blocks in high site-, regio-, and diastereoselectivity under mild conditions. Current efforts are directed toward developing new metal/Senphos-catalyzed processes as well as a better understanding of the underlying reaction mechanisms.

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