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Vinylidenation of Organoboronic Esters Enabled by a Pd-Catalyzed Metallate Shift.

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Abstract

Organoboron ‘ate’ complexes undergo a net vinyl insertion reaction to give 1,1-disubstituted alkenyl boronic esters when treated with stoichiometric allyl acetate and a palladium catalyst. Reactions that employ vinylolithium afforded good to excellent yields after one hour, while reactions that employ vinylmagnesium chloride furnished modest to good yields after 18 hours.

Graphical Abstract

α -Methylene Organoboronic Esters: These compounds are prepared in a catalytic fashion for precursor boronic esters by a Pd-catalyzed rearrangement of the derived ‘ate’ complexes.

Keywords

Boron; Allyl Complex; Palladium; Catalysis

Organoboronic esters are valuable reagents in contemporary synthetic chemistry owing to the variety of stereospecific transformations they undergo.¹ These processes include oxidation,² amination,³ cross-coupling,⁴ homologation,⁵ and alkynylation, among others.⁶ Because of this utility, the development of new methods for constructing organoboronic esters from new classes of starting materials holds significant value. A particularly powerful transformation that applies to organoboronic esters is the halogen-promoted Zweifel-Evans-Matteson⁷ reaction that results in olefination of organoboron reagents (Scheme 1, eq. 1). This process occurs by conversion of an organoboronic ester to the derived ‘ate’ complex, followed by halogen induced 1,2-metallate shift and, finally, elimination to establish the alkene. While this process has been applied broadly to accomplish vinylation reactions, recent advances from Aggarwal employing selenium activation allow for stereoselective *cis* or *trans* alkenylation as well.⁸ In this manuscript, we present a reaction design that allows Pd(allyl) electrophiles to activate alkenylboron ‘ate’ complexes for the metallate shift

reaction. While this activation mechanism has been employed in the context of conjunctive cross-coupling reactions, here we demonstrate the catalytic intermediate can be diverted towards β -hydride elimination⁹ that establishes an alkene while leaving the original boronic ester group intact (eq. 3). This process thereby affords strategically-useful 1,1-disubstituted alkenylboronic esters by a catalytic vinylidenation of organoboronic ester precursors (Scheme 1). While a number of methods allow construction of similarly-substituted boron reagents,^{10,11,12,13} the only direct conversion of an organoboron starting material to the vinylidenation product involves cross-coupling to (α -bromovinyl)-MIDA boronate (eq. 2) and this process is limited to C(sp²) boronic acids as starting materials.¹⁴

Recently, we developed Pd-catalyzed conjunctive cross-coupling reactions between an organoboronic ester, a vinyl lithium reagent, and a C(sp²) triflate to give chiral organoboronic esters with high levels of enantiopurity.¹⁵ This reaction has been expanded to include the use of Grignard reagents and C(sp²) halide electrophiles,¹⁶ alkenyl migrating groups,¹⁷ and has extended to nickel catalysts with both aryl¹⁸ and alkyl electrophiles.¹⁹ Perhaps unsurprisingly, direct extension to allyl electrophiles has proved a challenge, likely because η^3 coordination of the allyl group occupies a coordination site necessary for binding and activation of the 'ate' complex. Indeed, recent reports by Ready²⁰ suggest that enantioselective Pd-catalyzed reaction of indole-derived 'ate' complexes with allyl electrophiles, and similar racemic processes established by Ishikura²¹ and Murakami²², appear to occur by outer-sphere *anti* addition of electron-rich alkynyl- and indole-derived 'ate' complexes to the back side of the Pd(allyl). In this report, we show that catalyst features that allow Pd(allyl) complexes to bind an 'ate' complex and promote the metallate shift also allow β -hydrogen elimination of the intermediate and thus equation 3 to operate.

Initial efforts to promote metallate shift reactions with Pd(allyl) complexes showed that reactions with allyl electrophiles could deliver products of 1,2-rearrangement, but they were formed in low yield. As exemplified by the experiment in Scheme 2, when cinnamyl acetate was treated with (phenyl)vinylB(pin) 'ate' complex in the presence of Pd(OAc)₂ and wide-bite-angle bidentate diphosphine ligands, the conjunctive coupling product **1** was formed in very low yield and, in addition, small amounts of Suzuki-Miyaura coupling products (**2**) were formed, as well as acetophenone and allyl benzene. That the latter two compounds were formed in equal amounts signaled that a palladium-induced 1,2-metallate shift- β -hydrogen elimination process can operate (inset Scheme 2) and deliver the alkenylboronic ester, which is converted to **3** upon oxidative work-up.

With an initial experiment suggesting that catalytic cycles involving β -hydrogen elimination might provide a route to unique vinylidenation products, we considered alternate catalyst choices that might facilitate the metallate shift- β -elimination sequence. Of note, the coordinative saturation of bis(phosphine)-ligated palladium(allyl) complex **A** (Scheme 2) would render this species less able to bind and activate the 'ate' complex. To remedy this situation and to provide an open coordination site for β -hydrogen elimination from **B**, we considered replacing the bis(phosphine) ligand with monodentate structures. After a ligand survey using phenylB(pin), vinylmagnesium chloride, sodium triflate, and allyl acetate²³ (Table 1), it was found that monodentate phosphine ligands can provide higher yields compared to bidentate ligands, with PCy₃ being an optimal ligand (entry 9). Additionally, it

was found that increasing the amount of vinylmagnesium chloride and NaOTf leads to improved yields, and that the catalyst loadings could be reduced to 2.5 mol % with reaction times as short as one hour.

With optimized conditions, we embarked on a study of the generality of this reaction. As shown in Table 2, arylboronic esters (entries **6–9**) underwent the reaction in useful efficiency, and showed that the reaction tolerates both electron-donating and electron-withdrawing groups. Alkylboronic esters also proved to be competent substrates but benefitted from modified reaction conditions. In a previous study,⁹ the addition of DMSO as a co-solvent was found to stabilize the ‘ate’ complex formed from alkylboronic esters and Grignard reagents and this modification proved helpful to the reaction of these substrates here as well. However, the addition of DMSO retarded the reaction rate and 18 hours were required for these reactions to reach completion. Furthermore, changing the palladium source from Pd(OAc)₂ to Pd₂(dba)₃ gave slightly increased yields, but required catalyst loadings of 5% (see Supporting Information for details.). With these modifications, 3-phenylpropyl (**10**) and *n*-octyl (**11**) migrating groups were tolerated, as was a silyl ether (**12**). The reaction was also effective with cyclic substrates, including cyclopentyl (**13**), cyclohexyl (**14**), and *N*-Boc-protected piperidine (**15**) migrating groups. Migrating groups bearing potentially sensitive functional groups such as a monosubstituted olefin (**16**), amide (**17**), ester (**18**), or acetal (**19**) were also well-tolerated in this reaction. While examples in Table 2 suggest that the reaction is effective with Grignard-derived ‘ate’ complexes, it should be noted that alkyllithium derived ‘ate’ complexes often offer superior reactivity such that catalyst loading can be reduced to 1 mol% Pd, with many substrates still achieving complete conversion in one hour (**10–12**). Cyclic substrates (**13** and **14**), as well as tertiary substrate (**20**), required catalyst loadings of 5 mol% for productive reaction. Of note, it was also found that cycloalkenyl substrates (**21–23**), which proved unsuitable with vinylmagnesium chloride, were transformed to their corresponding 1,1-disubstituted boronic esters with Li-based reagents. Acyclic alkenylboronic esters, however, were not as effective in this reaction giving modest yields (**24–26**). Lastly, β -disubstituted vinylboronic esters (**27–28**) were ineffective substrates.

To examine features related to practical utility, the experiments in Scheme 3 were conducted. As the experiment in eq. 1 demonstrates, the vinylidenation occurs with complete stereospecificity: with enantiomerically-enriched boronic ester **29**, prepared by Pt-catalyzed asymmetric hydrosilylation reaction,²⁴ vinylidenation to **30** occurs in good yield and without erosion of enantiomeric purity. In addition, the experiment in equation 2 demonstrates that the vinylidenation could be conducted on preparative scale (> one gram) and occurs with similar efficiency as smaller scale reactions. Lastly, we examined cross-coupling of homologation products as a route to the natural product 7-deoxy-7,14-didehydroxydonol²⁵ (**33**, Scheme 3b). While experiments that directly employ the unpurified vinylidenation product **31** in cross-coupling with bromide **32** could deliver product, yields were low and not reproducible. However, **31** is stable to silica gel chromatography and, after purification, participated in efficient Suzuki-Miyaura reaction. After reduction of the aldehyde and TBAF deprotection natural product **33** was obtained in reasonable yield.

Conjunctive cross-coupling reactions involving diphosphine palladium complexes appear to occur by a low-barrier metal-induced metallate shift followed by reductive elimination.²⁶ Because the vinylidene insertion operates with an alternate Pd complex than previously described couplings, it was of interest to learn about this new reaction pathway. Analysis of the reaction was conducted by DFT (see Scheme 4 for description of method) and employed a complex between (η^3 -allyl)Pd(PCy₃) and the 'ate' complex as a starting point (**I-1**, the pathway involving a bis(phosphine)Pd(η^1 -allyl) is much higher in energy). As depicted in Scheme 4, metallate shift promoted by (PCy₃)Pd(η^3 -allyl) occurs via **TS-1** with an activation barrier of 11.5 kcal/mol and furnishes complex **I-2** as the product. It is notable that this barrier is higher than that involved in conjunctive cross-coupling reactions (ca. 5 kcal/mol); however, it is not so high that it provides an impediment to successful reaction. An important feature of the allyl ligand in complex **I-2** is that it can adopt the η^1 -bonding mode thereby providing an open coordination site for an agostic interaction²⁷ with the substrate β -hydrogen (to give **I-3**). This change in bonding mode is 12 kcal/mol uphill and is followed by an 8.8 kcal/mol β -hydrogen elimination via **TS-2**. While the β -hydrogen elimination is an endothermic process, it is followed by exothermic displacement of the alkenylboron as the allyl group reassumes the η^3 bonding mode (see Supporting Information for details).

In summary, we have described a catalytic vinylidenation of organoboronic esters that provides a new synthesis route to alkenylboronic esters.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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References

- (1). Hall DG, Ed. Boronic Acids: Preparation, Applications in Organic Synthesis and Medicine, 2nd ed; Wiley-VCH: Weinheim, 2011.
- (2). Brown HC, Synder C, Subba Rao BC, Zweifel G Tetrahedron 1986, 42, 5505.
- (3). Mlynarski SN, Karns AS, Morken JP J. Am. Chem. Soc 2012, 134, 16449. [PubMed: 23002712]
- (4). (a) Miyaura N, Suzuki A Chem. Rev 1995, 95, 2457. (b) Lennox AJ, Lloyd-Jones GC Chem. Soc. Rev 2014, 43, 412. [PubMed: 24091429] (c) Cherney AH, Kadunce NT, Reisman SE Chem. Rev 2015, 115, 9587. [PubMed: 26268813] (d) Rygus JPG, Crudden CM J. Am. Chem. Soc 2017, 139, 18124. [PubMed: 29149557]
- (5). Matteson DS, Sadhu KM J. Am. Chem. Soc. 1983, 105, 2077.
- (6). Wang Y, Noble A, Myers EL, Aggarwal VK Angew. Chem. Int. Ed 2016, 55, 4270.
- (7). Zweifel G, Polston NL, Whitney CC J. Am. Chem. Soc 1963, 90, 6243. Matteson DS Synthesis 1975, 147. Matteson DS, Jesthi PK J. Organomet. Chem 1976, 110, 25. Evans DA, Thomas RC, Walker JA Tetrahedron Lett. 1976, 17, 1427. Evans DA, Crawford TC, Thomas RC, Walker JA J. Org. Chem 1976, 41, 3947. [PubMed: 993895] For a recent advance in this area, see: Armstrong RJ, Niwetmarin W, Aggarwal VK Org. Lett 2017, 19, 2762. [PubMed: 28453280]
- (8). Armstrong RJ, García-Ruiz C, Myers EL, Aggarwal VK Angew. Chem., Int. Ed 2017, 56, 786.

- (9). For a recent relevant β -hydrogen elimination with Pd(allyl) complexes, see: Murray SA, Luc ECM, Meek SJ *Org. Lett* 2018, 20, 469. [PubMed: 29319323] Shvo Y, Arisha YAH J. *Org. Chem* 1998, 63, 5640. Chen Y, Romaire JP, Newhouse TR J. *Am. Chem. Soc* 2015, 137, 5875. [PubMed: 25918857] Chen Y, Turlik A, Newhouse TR J. *Am. Chem. Soc* 2016, 138, 1166. [PubMed: 26790471] Chen Y, Huang D, Zhao Y, Newhouse TR *Angew. Chem. Int. Ed* 2017, 56, 8258. Huang D, Zhao Y, Newhouse TR *Org. Lett* 2018, 20, 684. [PubMed: 29327930]
- (10). (a) Gao F, Hoveyda AH J. *Am. Chem. Soc* 2010, 132, 10961. [PubMed: 20698643] (b) Jang H, Zhugralin AR, Lee Y, Hoveyda AH J. *Am. Chem. Soc* 2011, 133, 7859. [PubMed: 21526827] (c) Moure AL, Arrayás RG, Cárdenas DJ, Alonso I, Carretero JC J. *Am. Chem. Soc* 2012, 134, 7219. [PubMed: 22500739] (d) Moure AL, Mauleón P, Arrayás RG, Carretero JC *Org. Lett* 2013, 15, 2054. [PubMed: 23570322] (e) García-Rubia AG, Romero-Revilla JA, Mauleón P, Arrayás RG, Carretero JC J. *Am. Chem. Soc* 2015, 137, 6857. [PubMed: 25955333] (f) Ojha DP, Prabhu KR *Org. Lett* 2016, 18, 432. [PubMed: 26760916] (g) Yoshida H *ACS Catal.* 2016, 6, 1799.
- (11). Takagi J, Takahashi K, Ishiyama T, Miyaura N J. *Am. Chem. Soc* 2002, 124, 8001. [PubMed: 12095344]
- (12). Guan W, Michael AK, McIntosh ML, Koren-Selfridge L, Scott JP, Clark TB J. *Org. Chem* 2014, 79, 7199. [PubMed: 24915498]
- (13). Coombs JR, Zhang L, Morken JP *Org. Lett* 2015, 17, 1708. [PubMed: 25799147]
- (14). Woerly EM, Miller JE, Burke MD *Tetrahedron* 2013, 69, 7732.
- (15). Zhang L, Lovinger GJ, Edelstein EK, Szymaniak AA, Chierchia MP, Morken JP *Science* 2016, 351, 6268.
- (16). Lovinger GJ, Aparece MD, Morken JP J. *Am. Chem. Soc* 2017, 139, 3153. [PubMed: 28161943]
- (17). Edelstein EK, Namirembe S, Morken JP J. *Am. Chem. Soc* 2017, 139, 5027. [PubMed: 28335597]
- (18). Chierchia MP, Law C, Morken JP *Angew. Chem. Int. Ed* 2017, 56, 11870.
- (19). Lovinger GJ, Morken JP J. *Am. Chem. Soc* 2017, 139, 17293. [PubMed: 29116784]
- (20). (a) Panda S, Ready JM J. *Am. Chem. Soc* 2017, 139, 6038. [PubMed: 28414430] (b) Panda S, Ready JM J. *Am. Chem. Soc* 2018, 140, 13242. [PubMed: 30240211]
- (21). (a) Ishikura M, Agata I *Heterocycles* 1996, 43, 1591. (b) Ishikura M, Kato H *Tetrahedron* 2002, 58, 9827.
- (22). Ishida N, Shinmoto T, Sawano S, Miura T, Murakami M *Bull. Chem. Soc. Jpn* 2010, 83, 1380.
- (23). For seminal reports on β -hydride elimination reactions promoted by allyl reagents as the oxidant, see: Shimizu I, Tsuji J J. *Am. Chem. Soc* 1982, 104, 5844. Shimizu I, Minami I, Tsuji J *Tetrahedron Lett.* 1983, 24, 1797. Minami I, Takahashi K, Shimizu I, Kimura T, Tsuji J *Tetrahedron* 1986, 42, 2971. Shvo Y, Arisha Y. *Org. Chem* 1998, 63, 5640.
- (24). Szymaniak AA, Zhang C, Coombs JR, Morken JP *ACS Catal.* 2018, 8, 2897.
- (25). Chung Y-M, Wei CK, Chuang D-W, El-Shazly M, Hsieh C-T, Asai T, Oshima Y, Hsieh T-J, Hwang T-L, Wu Y-C, Chang F-R *Bioorg. & Med. Chem* 2013, 21, 3866. [PubMed: 23647825]
- (26). Myhill JA, Zhang L, Lovinger GJ, Morken JP *Angew. Chem. Int. Ed* 2018, 57, 12799.
- (27). For a recent review of agostic interactions, see: Brookhart M, Green MLH, Parkin G *Proc. Nat. Acad. Sci* 2007, 104, 6908. [PubMed: 17442749]

- *Zweifel-Evans-Matteson Olefination* (ref. 7):

- *Burke vinylation* (ref. 14):

- *This work:*

Scheme 1.
Vinylidenation of Boronic Esters

Scheme 2.
Initial Observations of Boronic Ester Vinylidenation

Scheme 3.
Practical Features of Boronic Ester Vinylidene Homologation

Scheme 4.

Calculated reaction coordinate for metal-induced metallate shift/ β -hydrogen elimination involved in the vinylidenation reaction. Optimized geometries calculated using DFT (BP86/Def2-SVP; PCM solvent model with THF). G Values are in kcal/mol, calculated using DFT (PBE0-D3BJ/def2-TZVPP//BP86/def2-SVP; SMD solvent model with THF). Hydrogen atoms removed from structures for clarity.

Table 1.Ligand Survey for Vinylidenation of PhenylB(pin)^a

Entry	Ligand	Recovered 5 (%) ^b	Yield 6 (%) ^b
1	XantPhos	37	5
2	dppe	72	<2
3	PPh ₃	39	49
4	P(o-tolyl) ₃	46	35
5	PPh ₂ Me	61	24
6	PPh ₂ Cy	36	54
7	PPhCy ₂	18	61
8	CyJohnPhos	28	59
9	PCy ₃	28	65 (58)

^[a]Reactions conducted at initial [**5**] = 0.1 M.^[b]Yields determined by ¹H NMR using 1,1,2,2-tetrachloroethane as an internal standard. Yields in parentheses represent isolated yields.

Table 2.

Vinylation of Organoboronic Esters^[a]

^[a]Reactions conducted at [substrate] = 0.1 M. Yields are isolated yields and are an average of two experiments. Where necessary, yields are corrected to account for inseparable co-eluting unreacted starting material. For arylboronic esters, 2.5% Pd(OAc)₂/5% PCy₃ was employed; for alkylboronic esters with vinylmagnesium chloride, 2.5% Pd₂(dba)₃ and 20% PCy₃ were employed in 1:1 THF/DMSO solvent. For reactions employing vinylolithium, 1 mol% Pd(OAc)₂ and 2 mol% PCy₃ were employed. [b] Reaction time = 3 h. [c] Reaction employed 5 mol% Pd(OAc)₂ and 10 mol% PCy₃.