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Conjunctive functionalization of vinyl boronate complexes with electrophiles: a diastereoselective three-component coupling†

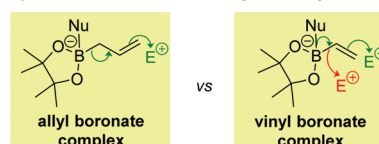
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A method for the conjunctive functionalization of vinyl boronate complexes with electrophiles is described. The overall process represents a three-component coupling between a vinyl boronic ester, carbon nucleophile and an electrophile, thus affording complex multi-functionalized products from simple starting materials. The diastereoselectivity (*syn* or *anti*) of this process is strongly dependent upon the nature of the electrophile.

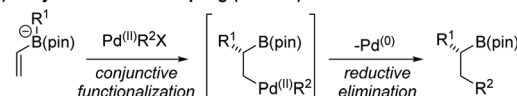
Boronic esters are versatile reagents which have been employed in a wide array of synthetic transformations.¹ They are easy to handle, bench stable materials that can be readily activated by the addition of a suitable nucleophile to form a boronate complex.² It is well known that the trivalent boron atom of allylic boronic esters can undergo activation with a Lewis base, leading to strongly nucleophilic character at the γ -position. Consequently, allylic boronic esters can be combined with a range of electrophiles, most notably in allylboration of aldehydes and imines (Scheme 1a).³ In contrast, the reactivity of boronate complexes derived from vinyl boronic esters has been less extensively explored. Upon treatment of a vinyl boronate complex with an electrophile two possible reaction pathways could be envisaged: (1) direct functionalization of an electron rich carbon–boron bond;⁴ (2) a conjunctive functionalization process, in which the π -system of the vinyl group reacts with the electrophile, triggering a 1,2-metallate rearrangement (Scheme 1a). The latter class of reaction is of particular interest since it represents a three-component coupling between a nucleophile, a vinyl boronic ester and an electrophile. Moreover, the boronic ester is retained in the product, serving as a versatile handle for further functionalization.^{1,5}

Although the electrophilic functionalization of vinyl boronate complexes has not received a great deal of attention, several interesting examples have been reported.^{6–8} Recently, Morken

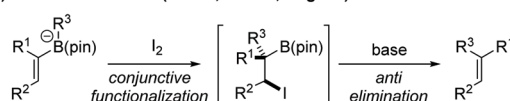
(a) Nucleophilic functionalization of allyl and vinyl boronate complexes



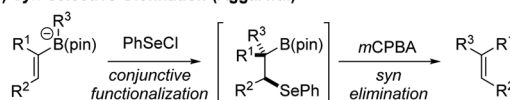
(b) Conjunctive cross-coupling (Morken)



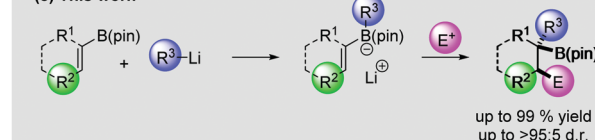
(c) Zweifel Olefination (Evans, Brown, Negishi)



(d) Syn-selective Olefination (Aggarwal)



(e) This work



Scheme 1 Previous work and strategy for three-component conjunctive coupling.

and co-workers disclosed an elegant enantioselective conjunctive variant of the Suzuki–Miyaura reaction (Scheme 1b).⁹ Mechanistically, this process involves β -functionalization of a vinyl boronate complex by a palladium(II) aryl species, followed by reductive elimination. Another notable example of conjunctive functionalization is the Zweifel olefination (Scheme 1c).¹⁰ In this process, a vinyl boronate complex undergoes stereospecific reaction with iodine, resulting in the formation of a β -iodoboronic ester (likely *via* a transient iodonium ion). This intermediate is unstable, undergoing *anti* elimination in the presence of a weak base to afford olefin products. Recently we reported a conjunctive functionalization of

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vinyl boronate complexes with PhSeCl (Scheme 1d).¹¹ The β -seleno-boronic ester intermediates were not isolated, but were treated with mCPBA, resulting in *syn* elimination to form the corresponding alkenes. In this work, we aimed to develop a conjunctive three-component coupling process to obtain boron containing products, which would not undergo β -elimination. The scope with respect to each of the three coupling partners has been evaluated and the factors that influence the efficiency and diastereoselectivity of these reactions are discussed.

We commenced our study by evaluating the functionalization of *E*-disubstituted boronic ester **1**. Addition of PhLi to a solution of **1** in THF at $-78\text{ }^\circ\text{C}$ resulted in clean boronate complex formation and upon addition of PhSeCl, we were pleased to find that the product of three-component coupling **2** could be isolated in 82% yield as a single diastereoisomer (Table 1). The *anti* diastereoselectivity of the reaction was confirmed by X-ray crystallographic analysis of the product. We then carried out an identical sequence beginning with *Z*-vinyl boronic ester **3**. This provided the *syn* diastereoisomer **4** (>95:5 d.r.) in 70% yield, indicating that the process is completely stereospecific. Primary and secondary organolithiums could also be employed in the process, affording alkyl-substituted products **5** and **6** in excellent yields and very high diastereoselectivity. MeLi also served as a successful nucleophile, affording **7** in 79% yield, which is particularly noteworthy given the known poor migratory aptitude of a methyl group.^{10c} A vinyl boronic ester containing an α -substituent was also well tolerated and **9** was formed in 78% yield. When trisubstituted vinyl boronic ester **10** was used as the starting material, **11** was obtained in 93% yield (>95:5 d.r.). The other diastereoisomer could be obtained in 93% yield by employing the corresponding *Z*-vinyl boronate **12** as the starting material. Homobenzyl substituted boronic esters **14** and **16** also reacted successfully, affording products **15** and **17** in excellent yields and diastereoselectivity. A silyl-ether-containing substrate also reacted cleanly, affording **19** in 73% yield. We were pleased to find that cyclic boronic esters **20** and **22** also efficiently underwent the desired reaction. The latter example demonstrates that high chemoselectivity can be obtained in the presence of a Boc-protected amine.

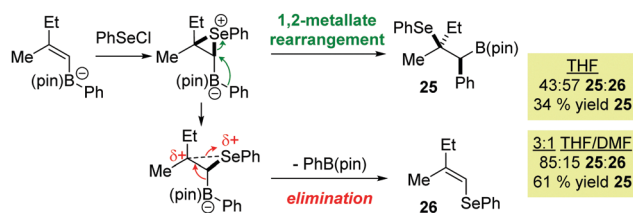
We next attempted the coupling of β,β -disubstituted vinyl boronic ester **24**. Disappointingly, we found that the desired product **25** was formed in a modest yield of 34% yield, along with 45% yield of vinyl selenide **26**. A plausible mechanism accounting for the formation of **26** is outlined in Scheme 2. Initially, the vinyl boronate complex derived from **24** undergoes reaction with PhSeCl to form a zwitterionic seleniranium intermediate. This species can either undergo the desired 1,2-migration, or eliminate to form vinyl selenide **26** along with PhB(pin).¹² For the majority of examples, the former pathway predominates, but in the case of boronate complexes derived from β,β -disubstituted boronic esters, the ability to build up partial positive charge at the tertiary β -carbon allows the $\text{C}_\beta\text{-Se}$ bond to lengthen and facilitates the elimination process. We found that the reaction solvent has a significant influence on which pathway is preferred (see ESI† for full details of optimization). Ultimately, we found that in a 3 : 1 THF/DMF mixture, formation of **26** was suppressed and **25** could be obtained as a single diastereomer in 61% yield.

Table 1 Conjunctive three-component coupling: boronic ester and RLi scope^a

Boronic ester	RLi	Product	Result ^{b,c}
	PhLi		2: 82 % yield >95:5 d.r.
	PhLi		4: 70 % yield >95:5 d.r.
	^t BuLi		5: 91 % yield >95:5 d.r.
	ⁱ PrLi		6: 84 % yield >95:5 d.r.
	MeLi		7: 79 % yield >95:5 d.r.
	PhLi		9: 78 % yield
	PhLi		11: 93 % yield >95:5 d.r.
	PhLi		13: 93 % yield >95:5 d.r.
	PhLi		15: 89 % yield >95:5 d.r.
	PhLi		17: 71 % yield >95:5 d.r.
	PhLi		19: 73 % yield >95:5 d.r.
	PhLi		21: 92 % yield >95:5 d.r.
	PhLi		23: 86 % yield >95:5 d.r.
	PhLi		25: 61 % yield ^d >95:5 d.r.
	PhLi		26: 35 % yield ^d >95:5 d.r.
	ⁱ PrLi		29: 85 % yield ^e >95:5 d.r.
	ⁱ PrLi		30: 75 % yield ^e 95:5 d.r.

^a Reaction conditions: vinyl boronic ester (1.0 eq.), RLi (1.05 eq.), THF; then PhSeCl (1.2 eq.), THF. ^b Yields of isolated products. ^c d.r. was determined by integration of crude ¹H NMR spectra. ^d Reaction with PhSeCl carried out in 3 : 1 THF/DMF. ^e Reaction with PhSeCl carried out in 1 : 1 THF/CF₃CH₂OH.



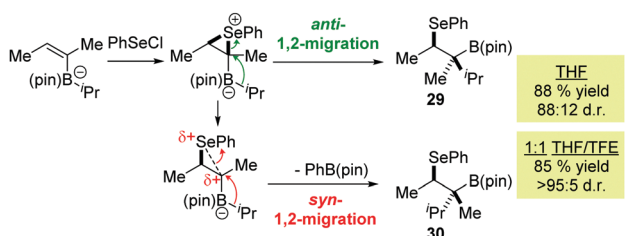


Scheme 2 Competing pathways in the formation of **25** and the effect of solvent.

These conditions were also applied to the three-component coupling of isomeric vinyl boronic ester **27** affording the product **28** in 35% yield as a single diastereomer (Table 1).

We next carried out a three-component coupling between **10**, ⁱPrLi and PhSeCl. Given that this vinyl boronic ester had been reacted with an aryl lithium to afford **11** in very high diastereoselectivity (*vide supra*) we did not anticipate that this process would be problematic. We were therefore surprised to find that **29** was isolated as an 88:12 mixture of diastereoisomers (Scheme 3). We attribute this reduced diastereoselectivity to the pathway shown in Scheme 3, whereby partial opening of the seleniranium intermediate enables a partial positive charge to develop at the tertiary α -carbon. This allows a *syn* 1,2-migration process to compete with the usual *anti* migration, resulting in the formation of both **29** and **30**. After solvent optimization (see ESI† for full details) we found that carrying out the reaction in a 1:1 mixture of THF/trifluoroethanol suppressed the undesired pathway, providing **29** in very high diastereoselectivity. We suspect that trifluoroethanol is able to modulate the reactivity of the intermediate seleniranium cation by functioning as a hydrogen bond donor to the basic pinacol oxygen atoms.¹³ An analogous reaction with isomeric vinyl boronic ester **12** afforded the product **30** in 75% yield and 95:5 d.r.

Taking boronate complexes derived from isomeric vinyl boronic esters **10** and **12** as representative examples, coupling with a series of electrophiles was investigated (Table 2; results with PhSeCl are also shown for clarity). With PhSeCl the reaction was extremely efficient, producing **31** and **32** in excellent yield. Both products were obtained as a single diastereoisomer indicating that the process is stereospecific. To confirm the relative configuration of **31** and **32**, we subjected them to methoxide promoted *anti* elimination. As expected, this resulted in the formation of isomeric alkenes **39** and **40**, respectively (Table 3, entries 3 and 4). We next investigated fluorination of vinyl boronate complexes.^{2d} Employing Selectfluor, β -fluoroboronic



Scheme 3 Eroded diastereoselectivity in the formation of **29**. TFE = CF₃CH₂OH.

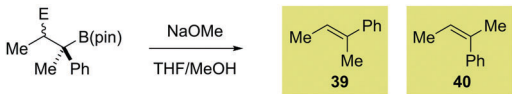
Table 2 Conjunctive three-component coupling: electrophile scope^a

Boronic ester	Electrophile	Product	Result ^{b,c}
10	PhSeCl	11	93 % yield >95:5 d.r.
12	PhSeCl	13	93 % yield >95:5 d.r.
10	PhSeCl	31	99 % yield >95:5 d.r.
12	PhSeCl	32	91 % yield >95:5 d.r.
10	Selectfluor	33	72 % yield ^d 89:11 d.r.
12	Selectfluor	34	66 % yield ^d 91:9 d.r.
10	PhSeCl	35	90 % yield 52:48 d.r.
12	PhSeCl	36	86 % yield 67:33 d.r.
10	PhSeCl	37	50 % yield 53:47 d.r.
12	PhSeCl	37	28 % yield 60:40 d.r.
10	PhSeCl	38	40 % yield ^d 53:47 d.r.
12	PhSeCl	38	43 % yield ^d 55:45 d.r.

^a Reaction conditions: vinyl boronic ester (1.0 eq.), PhLi (1.05 eq.); then electrophile (1.2 eq.). For details of solvent and reaction conditions see ESI. ^b Yields of isolated products. ^c d.r. was determined by integration of crude ¹H and ¹⁹F NMR spectra. ^d ¹⁹F NMR yield using α,α,α -trifluorotoluene as an internal standard.

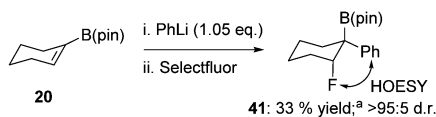
esters **33** and **34** were obtained in good yield and high diastereoselectivity (Table 2). Upon exposure of these compounds to sodium methoxide, we were surprised to isolate the unexpected isomers of alkenes **40** and **39** (Table 3, entries 5 and 6). There are two possible explanations for this observation: (1) β -fluoroboronic esters **33** and **34** are formed by a selective *syn* migration process; (2) elimination proceeds *via* a *syn* pathway. To differentiate between these two scenarios, we carried out fluorination of a cyclic boronate complex, obtaining **41** as a single diastereoisomer (Scheme 4). HOESY experiments revealed that an unusual *syn* migration process had occurred. By analogy, we propose that a similar *syn* pathway is involved in the formation of **33** and **34**. This surprising result suggests that *anti* diastereoselectivity is only observed in cases where vinyl boronate complexes are activated



Table 3 Determination of relative configuration by *anti* elimination^a


Entry	Substrate	d.r.	Major product	<i>E/Z</i> selectivity ^b
1	11 (E = SePh)	> 95 : 5	39	> 95 : 5
2	13 (E = SePh)	> 95 : 5	40	< 5 : 95
3	31 (E = SPh)	> 95 : 5	39	96 : 4
4	32 (E = SPh)	> 95 : 5	40	29 : 71
5	33 (E = F)	89 : 11	40	17 : 83
6	34 (E = F)	91 : 9	39	92 : 8

^a Reaction conditions: β -substituted boronic ester (1.0 eq.), NaOMe (10 eq.), THF/MeOH (8:1). ^b Determined by integration of the crude ¹H NMR spectrum.



Scheme 4 Probing the diastereoselectivity of fluorination. Reaction conditions: vinyl boronic ester (1.0 eq.), PhLi (1.05 eq.), THF; then Selectfluor I (1.2 eq.), MeCN/THF (5:1). ^a ¹⁹F NMR yield using α,α,α -trifluorotoluene as an internal standard.

by electrophiles that form closed three-membered ring intermediates. In line with this hypothesis, electrophilic carbon reagents, such as tropylium tetrafluoroborate and 1,3-benzodithiolium tetrafluoroborate led to competing *syn* and *anti* functionalization, resulting in low levels of diastereoselectivity (Table 2). Finally, we investigated the reaction of vinyl boronate complexes with Umemoto's reagent, a process that is expected to occur by addition of a trifluoromethyl radical followed by single-electron oxidation to form a carbocation intermediate.¹⁴ As expected, near identical diastereomeric mixtures of trifluoromethylated products were obtained regardless of which isomer of vinyl boronic ester was employed.

In summary, a conjunctive three-component coupling between vinyl boronic esters, carbon nucleophiles and electrophiles has been developed. The diastereoselectivity of the process is strongly dependent upon the nature of the electrophile. Reactions that proceed *via* closed three-membered cyclic intermediates exhibit very high *anti* diastereoselectivity. In the case of more reactive, charged electrophiles, the increasingly asynchronous nature of the bond formation enables *syn* migration to compete, in some cases becoming the preferred pathway. This work will be of use for the synthesis of boron-containing materials and will inform the development of other conjunctive functionalization processes.

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Notes and references

- Synthesis and application of organoboron compounds*, ed. E. Fernández and A. Whiting, Springer, Heidelberg, 2015.
- (a) H. C. Brown, N. R. De Lue, G. W. Kabalka and H. C. Hedgecock, *J. Am. Chem. Soc.*, 1976, **98**, 1290–1291; (b) H. C. Brown and B. Singaram, *Acc. Chem. Res.*, 1988, **21**, 287–293; (c) R. Larouche-Gauthier, T. G. Elford and V. K. Aggarwal, *J. Am. Chem. Soc.*, 2011, **133**, 16794–16797; (d) C. Sandford, R. Rasappan and V. K. Aggarwal, *J. Am. Chem. Soc.*, 2015, **137**, 10100–10103.
- (a) *Organic Reactions: Allylboration of Carbonyl Compounds*, ed. H. Lachance and D. G. Hall, Wiley, Weinheim, 2009, vol. 73; (b) J. W. J. Kennedy and D. G. Hall, *Angew. Chem., Int. Ed.*, 2003, **42**, 4732–4739; (c) S. E. Denmark and J. Fu, *Chem. Rev.*, 2003, **103**, 2763–2794.
- (a) N. R. Candeias, F. Montalbano, P. M. S. D. Cal and P. M. P. Gois, *Chem. Rev.*, 2010, **110**, 6169–6193; (b) A. J. J. Lennox and G. C. Lloyd-Jones, *Chem. Soc. Rev.*, 2014, **43**, 412–443; (c) H. C. Brown, T. Hamaoka and N. Ravindran, *J. Am. Chem. Soc.*, 1973, **95**, 5786–5788; (d) S. Lee and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2007, **129**, 15438–15439; (e) A. Mitchell and J. W. Bode, *J. Am. Chem. Soc.*, 2009, **131**, 18057–18059.
- (a) H. K. Scott and V. K. Aggarwal, *Chem. – Eur. J.*, 2011, **17**, 13124–13132; (b) R. Jana, T. P. Pathak and M. S. Sigman, *Chem. Rev.*, 2011, **111**, 1417–1492; (c) C.-Y. Wang, J. Derosa and M. R. Biscoe, *Chem. Sci.*, 2015, **6**, 5105–5113; (d) C. Sandford and V. K. Aggarwal, *Chem. Commun.*, 2017, **53**, DOI: 10.1039/C7CC01254C.
- For selected examples with alkynyl boronate complexes, see: (a) M. Naruse, K. Utimoto and H. Nozaki, *Tetrahedron Lett.*, 1973, **14**, 2741–2744; (b) N. Miyaura, T. Yoshinari, M. Itoh and A. Suzuki, *Tetrahedron Lett.*, 1974, **15**, 2961–2964; (c) K. K. Wang and S. Dhumrongvaraporn, *Tetrahedron Lett.*, 1987, **28**, 1007–1010; (d) N. Ishida, W. Ikemoto, M. Narumi and M. Murakami, *Org. Lett.*, 2011, **13**, 3008–3011.
- For selected examples with aromatic boronate complexes, see: (a) G. M. Davies, P. S. Davies, W. E. Paget and J. M. Wardleworth, *Tetrahedron Lett.*, 1976, **17**, 795–798; (b) I. Akimoto and A. Suzuki, *Synthesis*, 1979, 146–147; (c) M. Ishikura and H. Kato, *Tetrahedron*, 2002, **58**, 9827–9838; (d) A. Bonet, M. Odachowski, D. Leonori, S. Essafi and V. K. Aggarwal, *Nat. Chem.*, 2014, **6**, 584–589; (e) M. Odachowski, A. Bonet, S. Essafi, P. Conti-Ramsden, J. N. Harvey, D. Leonori and V. K. Aggarwal, *J. Am. Chem. Soc.*, 2016, **138**, 9521–9532.
- For conjunctive intramolecular alkylation, see: Y. Kobayashi, M. Asano and Y. Kiyotsuka, *Heterocycles*, 2009, **77**, 787–791.
- (a) L. Zhang, G. J. Lovinger, E. K. Edelstein, A. A. Szymaniak, M. P. Chierchia and J. P. Morken, *Science*, 2016, **351**, 70–74; (b) G. J. Lovinger, M. D. Aparece and J. P. Morken, *J. Am. Chem. Soc.*, 2017, **139**, 3153–3160.
- (a) G. Zweifel, H. Arzoumanian and C. C. Whitney, *J. Am. Chem. Soc.*, 1967, **89**, 3652–3653; (b) D. A. Evans, T. C. Crawford, R. C. Thomas and J. A. Walker, *J. Org. Chem.*, 1976, **41**, 3947–3953; (c) H. C. Brown and N. G. Bhat, *J. Org. Chem.*, 1988, **53**, 6009–6013; (d) S. Xu, C.-T. Lee, H. Rao and E. Negishi, *Adv. Synth. Catal.*, 2011, **353**, 2981–2987.
- R. J. Armstrong, C. García-Ruiz, E. L. Myers and V. K. Aggarwal, *Angew. Chem., Int. Ed.*, 2017, **56**, 786–790.
- In analogy with related reactions of vinyl silanes, this process proceeds with stereochemical retention: T. A. Blumenkopf and L. E. Overman, *Chem. Rev.*, 1986, **86**, 857–873.
- I. Shuklov, N. Dubrovina and A. Börner, *Synthesis*, 2007, 2925–2943.
- (a) Y. Wang, A. Noble, C. Sandford and V. K. Aggarwal, *Angew. Chem., Int. Ed.*, 2017, **56**, 1810–1814; (b) M. Kischkewitz, K. Okamoto, C. Mück-Lichtenfeld and A. Studer, *Science*, 2017, **355**, 936–938.

