A Journal of the Gesellschaft Deutscher Chemiker

Angewandte International Edition GDCh Chemie

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Accepted Article

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To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.201804446
Angew. Chem. 10.1002/ange.201804446

Link to VoR: http://dx.doi.org/10.1002/anie.201804446
http://dx.doi.org/10.1002/ange.201804446

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Enantiodivergent Synthesis of Allenes by Point to Axial Chirality Transfer

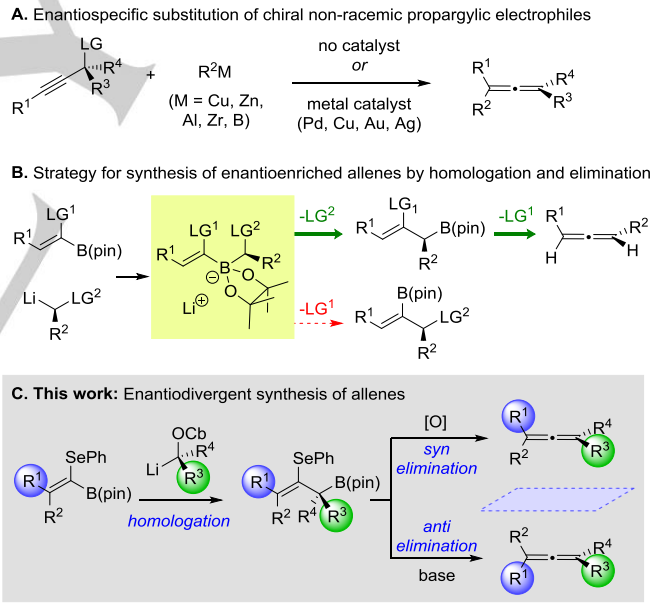
Roly J. Armstrong,[a] Meganathan Nandakumar,[a] Rafael M. P. Dias,[a] Adam Noble,[a] Eddie L. Myers[a] and Varinder K. Aggarwal*[a]

This paper is dedicated to George Zweifel

Abstract: An enantiodivergent method for the synthesis of multiply substituted allenes is described. Highly enantioenriched, point chiral boronic esters were synthesized by homologation of lithiated carbamates with α-seleno vinyl boronic esters and eliminated to form axially chiral allene products. By employing either oxidative or alkylative conditions, both *syn*- and *anti*-elimination could be achieved with complete stereospecificity. The process enables the synthesis of either (*M*) or (*P*) allenes from a single isomer of a point chiral precursor and can be employed for the enantioselective assembly of di-, tri- and tetrasubstituted allenes.

Allenes are versatile functional groups which can be employed in a wide range of chemical transformations.[1] The unique pattern of reactivity displayed by allenes stems from the consecutive arrangement of two orthogonal π-bonds – a feature which also results in axial chirality. Chiral non-racemic allenes are extremely valuable intermediates in synthesis and have additional applications in medicinal chemistry, materials science and catalysis.[2] Consequently, considerable effort has been placed on the development of asymmetric methods for allene synthesis.[3,4] Although various elegant strategies have been reported, the most general method involves nucleophilic substitution of enantioenriched propargylic electrophiles (Scheme 1A).[5] Whilst broad ranging, this method can result in lower enantiospecificity for tetrasubstituted allenes, for which only a handful of enantioselective preparative methods exist.[6] A further limitation of such strategies is that if the opposite enantiomer of allene is desired, then the synthesis must be repeated by first preparing the enantiomeric propargylic electrophile.[7]

We envisaged a complementary strategy in which a vinyl boronic ester bearing an α-leaving group (LG^1) is homologated with an enantioenriched lithium carbenoid (Scheme 1B).[8] A stereospecific elimination process would then convert the resulting point chiral intermediate into an axially chiral allene.[9] In such a process, there are two critical points at which selectivity must be controlled. Firstly, the boronate complex must undergo the desired 1,2-metallate rearrangement in which LG^2 is displaced, rather than a potentially competing rearrangement in which the vinylic leaving group (LG^1) is expelled.[10] Secondly, to obtain complete transfer of stereochemical information, the elimination process must proceed with very high stereospecificity.[11] The choice of vinylic leaving group (LG^1) is critical to controlling the selectivity in both of these key steps. We were attracted to selenium, since we hoped that its relatively poor leaving group ability would enable it to act as a spectator group during the lithiation-borylation process and then, upon activation undergo elimination (Scheme 1C). Moreover, we have recently shown that β-selenoboronic esters can undergo selective *anti*-elimination in the presence of base, or *syn*-elimination upon oxidation to the corresponding selenoxide.[12] Using this strategy, either enantiomer of a given chiral allene could be obtained from a single intermediate in a highly divergent manner. Herein, we describe the successful implementation of this strategy and its application to the enantiodivergent synthesis of di-, tri- and tetrasubstituted allenes.



Scheme 1. Previous work and strategy for enantiodivergent synthesis of allenes.

We commenced our study with vinyl boronic ester **1**, which was readily prepared as a single *Z*-isomer in three steps from benzaldehyde.[13] Boronate complex formation was carried out with lithiated carbamate **2**, followed by promotion of 1,2-metallate rearrangement by addition of magnesium bromide in methanol and warming to 40 °C (Equation 1).[14] Pleasingly, no competing reactions involving displacement of the vinylic selenide were observed and allylic boronic ester **3** was obtained in 91 % yield and 99:1 e.r.

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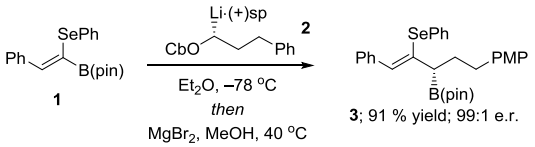
10.1002/anie.201804446

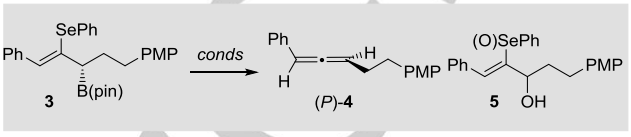
With highly enantioenriched material in hand, we turned our attention to the development of a protocol for *syn*-elimination. Upon treatment of a THF solution of boronic ester **3** with *m*CPBA at –45 °C, we obtained the desired allene product (*P*)-**4** in 41 % yield along with 41 % yield of alcohol **5** resulting from competing oxidation of the C–B bond (Table 1a, entry 1). We were delighted to find that (*P*)-**4** was formed with complete enantiospecificity, indicating that point to axial chirality transfer had occurred with high fidelity. Reducing the amount of *m*CPBA from 2 equiv. to 1.2 equiv. led to a small improvement in selectivity for elimination over oxidation and (*P*)-**4** was obtained in 53 % yield (Table 1a, entry 2). Lowering the temperature to -78 °C had very little impact, but carrying out elimination at 0 °C led to improved selectivity in favour of (*P*)-**4** (Table 1a, entries 3-4). Remarkably, when the elimination was performed at room temperature, the desired allene (*P*)-**4** was formed as the sole product in 88 % yield with complete enantiospecificity (Table 1a, entry 5).

(1) 

We next focused our attention on developing a procedure for enantiospecific *anti*-elimination. Employing sodium methoxide in THF, we were disappointed to obtain (*M*)-**4** in low yield and modest enantiospecificity (6 % yield, 44 % e.s.) along with a significant quantity of vinyl selenide **6** (Table 1b, entry 1). This result suggests that the selenide is too poor a leaving group to compete with facile base-mediated allylic protodeborylation. We rationalized that if we could convert the selenoether into a better leaving group the desired elimination process might become the dominant pathway. To test this hypothesis, **3** was transformed to the corresponding selenonium salt by alkylation with MeOTf followed by addition of sodium bicarbonate (Table 1b, entry 2). Pleasingly, these conditions resulted in clean elimination to form (*M*)-**4** in 59 % yield and significantly improved enantiospecificity (89 % e.s.). Employing aqueous bicarbonate provided (*M*)-**4** in an improved yield of 85 % with the same enantiospecificity (Table 1b, entry 3). We evaluated a range of different aqueous bases (See Supporting Information for full details) and found that in all cases (*M*)-**4** was produced with similar or reduced enantiospecificity (Table 1b, entries 4-6). When we carried out the elimination with sodium bicarbonate in methanol, we obtained the desired allene product (*M*)-**4** with almost complete enantiospecificity (98 % e.s.) in 79 % yield (Table 1b, entry 7). Finally, performing the reaction with a reduced quantity of MeOTf (2 equiv.) provided (*M*)-**4** in 83 % yield and 98 % e.s. (Table 1b, entry 8).

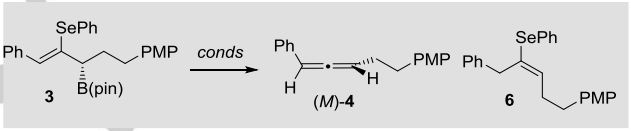
With optimized conditions for homologation and enantiodivergent elimination in hand, we set out to investigate the generality of the process, initially focusing our attention on variation of the vinyl partner (Table 2). Introduction of an electron-rich methoxy substituent was well tolerated – both enantiomers of the corresponding allene products (*P*)-**8** and (*M*)-**8** were obtained in 98:2 e.r. in excellent yields. Electron deficient and sterically encumbered vinyl partners also smoothly underwent the desired chemistry, providing allene products (*P*)-**10**, (*M*)-**10**, (*P*)-**12** and (*M*)-**12** all in excellent yields and with very high enantioselectivity. An aliphatic vinyl partner (synthesized in two steps from 1-pentyne) underwent efficient lithiation-borylation (71 % yield, 98:2 e.r.) and after enantiodivergent elimination, provided allene products (*P*)-**14** and (*M*)-**14** in 77 and 82 % yield respectively with complete enantiospecificity. We next investigated variation of the lithium carbenoid partner. We found that boronic ester **1** could be efficiently homologated with an enantioenriched carbenoid containing a silyl ether to form **15** which underwent enantiospecific elimination affording (*P*)-**16** (74 % yield, 98:2 e.r.) and (*M*)-**17** (76 % yield, 98:2 e.r.). [15,16]

Table 1a. Optimization of reaction conditions for *syn*-elimination.[a]



Entry	Conditions	T/°C	Yield **4**/%[b]	Yield **5**/%[b,c]	e.s. **4**[d]
1	*m*-CPBA (2 eq.)	-45	41	41	>99%
2	*m*-CPBA (1.2 eq.)	-45	53	18	>99%
3	*m*-CPBA (2 eq.)	-78	39	42	>99%
4	m-CPBA (2 eq.)	0	54	36	>99%
5	m-CPBA (2 eq.)	r.t.	88[e]	–	>99%

Table 1b. Optimization of reaction conditions for *anti*-elimination.[f]



Entry	Conditions	Yield **4**/%[b]	e.s. **4**[d]
1[g]	NaOMe, THF, r.t.	6 (+64% **6**)	44
2	MeOTf, CH_2Cl_2 then $NaHCO_{3(s)}$	59	89
3	MeOTf, CH_2Cl_2 then aq. $NaHCO_3$	85	89
4	MeOTf, CH_2Cl_2 then aq. Na_2CO_3	79	86
5	MeOTf, CH_2Cl_2 then aq. NaOH	55	84
6	MeOTf, CH_2Cl_2 then aq. K_3PO_4	74	83
7	MeOTf, CH_2Cl_2 then $NaHCO_3$, MeOH	79	98
8[h]	MeOTf, CH_2Cl_2 then $NaHCO_3$, MeOH	83[e]	98

[a] **3** (1.0 eq.), *m*-CPBA (1.2-2 eq.), THF. [b] Determined by ^{1}H-NMR analysis *vs* 1,1,2,2-tetrachloroethane. [c] Yields of **5** refer to combined yields of selenide and selenoxide (see SI for details). [d] determined by chiral HPLC. [e] Yield of isolated material. [f] **3** (1.0 eq.), MeOTf (5 eq.), CH_2Cl_2, r.t., then *base*, r.t. [g] **3** (1.0 eq.), NaOMe (5 eq.), THF, r.t. [h] Alkylation carried out with 2 eq. of MeOTf. PMP = 4-methoxyphenyl; pin = pinacolato.

Homologation of vinyl partner **1** with a lithiated carbamate derived from (–)-citronellol provided boronic ester **18** in 70 % yield as a single diastereoisomer. Elimination of this intermediate under either oxidative or alkylative conditions enabled access to either diastereoisomer of the resulting allene (*P*,*S*)-**19** or (*M*,*S*)-**20**. Similarly, employing a lithiated carbamate containing two additional stereogenic centres enabled the highly diastereoselective synthesis of allenes (*P*,*S*,*R*)-**22** and (*M*,*S*,*R*)-**23**. The modular nature of this synthesis is particularly noteworthy – each vinyl boronic ester could be paired with a series of different carbamates rapidly building up a large library of enantioenriched allenes.

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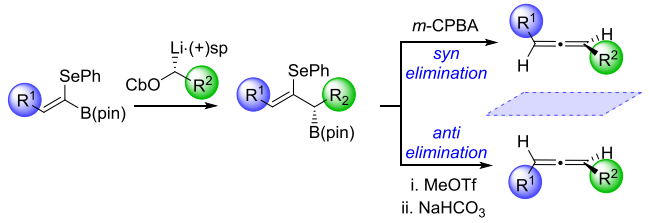
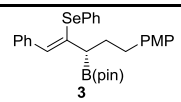
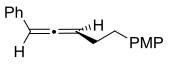
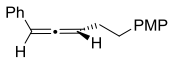
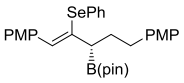
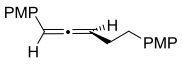
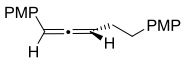
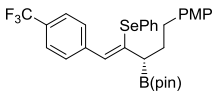
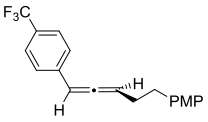
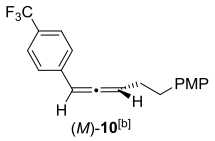
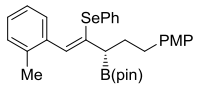
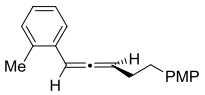
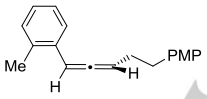
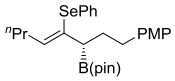
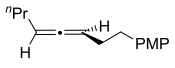
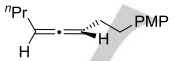
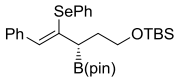
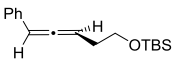
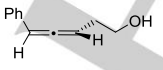
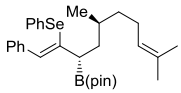
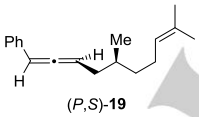
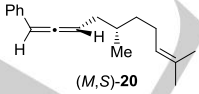
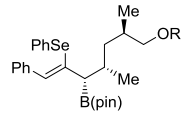
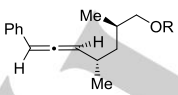
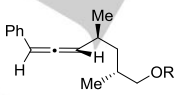
Table 2. Enantiodivergent synthesis of disubstituted allenes[a]



Homologation	*Syn*-elimination	*Anti*-elimination
 **3** 91 % yield; 99:1 e.r.	 (*P*)-**4** 88 % yield; 99:1 e.r.	 (*M*)-**4** 83 % yield; 98:2 e.r.
 **7** 70 % yield; 98:2 e.r.	 (*P*)-**8** 76 % yield; 98:2 e.r.	 (*M*)-**8** 83 % yield; 98:2 e.r.
 **9** 65 % yield; 98:2 e.r.	 (*P*)-**10** 87 % yield; 98:2 e.r.	 (*M*)-**10**[b] 56 % yield; 96:4 e.r.
 **11** 72 % yield; 98:2 e.r.	 (*P*)-**12** 88 % yield; 98:2 e.r.	 (*M*)-**12** 88 % yield; 98:2 e.r.
 **13** 71 % yield; 98:2 e.r.	 (*P*)-**14** 77 % yield; 98:2 e.r.	 (*M*)-**14** 82 % yield; 98:2 e.r.
 **15** 73 % yield; 99:1 e.r.	 (*P*)-**16** 74 % yield; 98:2 e.r.	 (*M*)-**17** 76 % yield; 98:2 e.r.
 **18** 70 % yield; >95:5 d.r.	 (*P*,*S*)-**19** 85% yield; >95:5 d.r.	 (*M*,*S*)-**20** 83% yield; >95:5 d.r.
 **21**[c] (R = TBDPS) 96 % yield; >95:5 d.r.	 (*P*,*S*,*R*)-**22** 89 % yield; >95:5 d.r.	 (*M*,*S*,*R*)-**23** 88 % yield; >95:5 d.r.

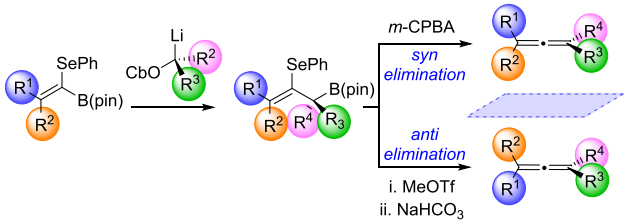
[a] Homologation: Carbamate (1.3 eq.), (+)-sparteine (1.3 eq.), ^{s}BuLi (1.2 eq.), Et_2O, -78 °C, 5 h then vinyl boronic ester (1 eq.), -78 °C, 1 h then $MgBr_2$ (2 eq.), -78 °C to reflux, 16 h. *Syn*-elimination: 1,2-selenoboronic ester (1 eq.), *m*-CPBA (2.0 eq.), THF, r.t., 30 min. *Anti*-elimination: 1,2-selenoboronic ester (1 eq.), MeOTf (2 eq.), CH_2Cl_2, r.t., 16 h then $NaHCO_3$ (20 eq.), CH_2Cl_2/MeOH, r.t., 3 h. [b] The a*nti*-elimination was performed by heating to 40 °C in the absence of $NaHCO_3$. See Supporting Information for exact conditions. [c] Lithium carbenoid prepared from the corresponding stannane by Sn–Li exchange. TBS = *tert*-butyldimethylsilyl; TBDPS = *tert*-butyldiphenylsilyl.

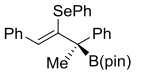
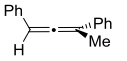
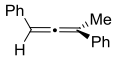
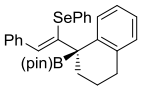
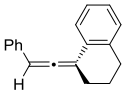
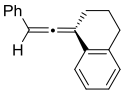
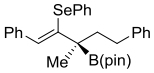
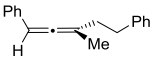
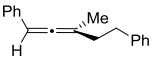
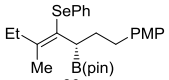
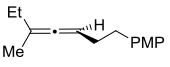
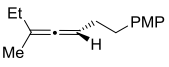
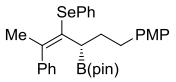
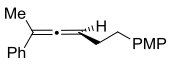
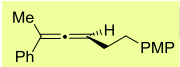
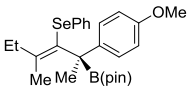
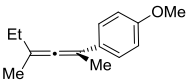
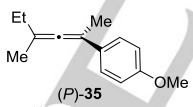
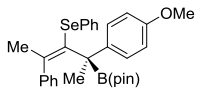
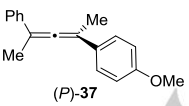
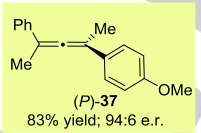
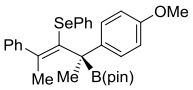
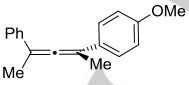
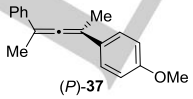
We next moved on to investigate the synthesis of trisubstituted allenes (Table 3). Accordingly, we carried out the one-carbon homologation of **1** with an enantiopure lithiated secondary benzylic carbamate.[8c] The resulting tertiary allylic boronic ester **24** was obtained in 88 % yield as a single enantiomer. Subjection of this intermediate to our optimized conditions for *syn*- and *anti*-elimination enabled access to either enantiomer of the corresponding trisubstituted allene (*M*)-**25** (87 % yield, 99:1 e.r.) and (*P*)-**25** (84 % yield, 99:1 e.r.). This approach was also successful with cyclic benzylic and aliphatic lithium carbenoids, providing allenes (*M*)-**27**, (*P*)-**27**, (*M*)-**29** and (*P*)-**29** all with very high yields and excellent enantioselectivity. We next explored introduction of an additional substituent to the vinyl partner. Allylic boronic ester **30** was synthesized in very high enantioselectivity by one carbon homologation of a tetrasubstituted vinyl boronic ester. Enantiodivergent elimination afforded allenes (*P*)-**31** and (*M*)-**31** in good yields with very high enantiospecificity. Homologation of a tetrasubstituted styrenyl boronic ester afforded enantioenriched tertiary boronic ester **32** in 69 % yield and 97:3 e.r. Both oxidative and alkylative elimination of **32** proceeded smoothly, however, we were surprised to find that both reactions generated the same enantiomer of allene product **33** with high enantiospecificity.

The asymmetric assembly of tetrasubstituted allenes is known to be particularly challenging, and only a small number of enantioselective methods are currently available for their synthesis.[6] We therefore set out to determine whether our methodology could target such materials. Accordingly, allylic boronic ester **34** was synthesized in high enantioselectivity by homologation of a tetrasubstituted vinyl boronic ester with a lithiated secondary benzylic carbamate. We were delighted to find that **34** could be eliminated to form either enantiomer of the corresponding tetrasubstituted allene (*M*)-**35** or (*P*)-**35** in good yields and excellent enantiospecificity (98:2 e.r. and 95:5 e.r. respectively). Interestingly, an allylic boronic ester **36** – bearing a phenyl substituent *cis* to the boronic ester – underwent oxidative and alkylative elimination to form the same enantiomer of the tetrasubstituted allene **37**. To determine whether this elimination proceeded by a *syn* or *anti* pathway it was necessary to determine the absolute stereochemistry of allene **37**. Since this compound was an oil, we were unable to establish its absolute configuration by X-ray crystallographic analysis. We therefore simulated the electronic circular dichroism spectra (ECD) for (*P*)-**37** at the CAM-B3LYP/6-311(d,p) level of theory.[17] The simulated data for (*P*)-**37** was a good match for the experimental ECD spectrum, enabling us to determine that both oxidative and alkylative elimination pathways proceed *via* a *syn*-mechanism (Scheme 2a). This inversion of selectivity in the alkylative elimination of **36** and **32** likely arises because the conformation necessary for *anti*-elimination results in significant A-1,3 strain between the tetravalent boron and a bulky phenyl substituent (Scheme 2b).[18] In this case, an alternative *syn*-elimination pathway with fewer unfavourable steric interactions becomes preferred. We rationalized that the isomeric allylic boronic ester **38** ought to develop significantly less A-1,3 strain and might therefore undergo enantiodivergent elimination. Pleasingly, this proved to be the case, and using this approach both (*M*)-**37** and (*P*)-**37** were efficiently synthesized with high enantiospecificity.

10.1002/anie.201804446

Table 3. Enantiodivergent synthesis of tri- and tetrasubstituted allenes.

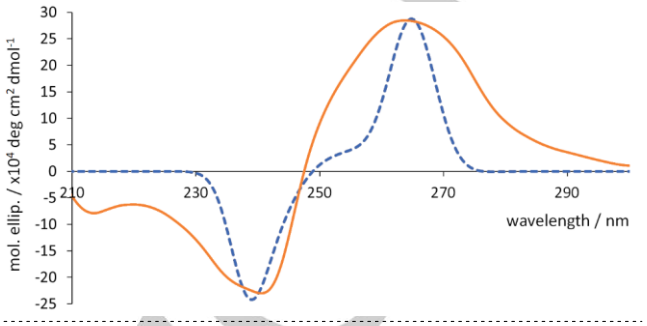


Homologation[a]	*Syn*-elimination[b]	*Anti*-elimination[c]
 **24** 88 % yield; >99:1 e.r.	 (*M*)-**25** 87 % yield; 99:1 e.r.	 (*P*)-**25** 84 % yield; 99:1 e.r.
 **26** 70 % yield; 98:2 e.r.	 (*M*)-**27** 76 % yield; 97:3 e.r.	 (*P*)-**27** 92 % yield; 98:2 e.r.
 **28** 78 % yield; >99:1 e.r.	 (*M*)-**29** 84 % yield; 99:1 e.r.	 (*P*)-**29** 85 % yield; 99:1 e.r.
 **30** 65 % yield; 99:1 e.r.	 (*P*)-**31** 75 % yield; 97:3 e.r.	 (*M*)-**31** 70 % yield; 97:3 e.r.
 **32** 69 % yield; 97:3 e.r.	 (*M*)-**33** 81 % yield; 95:5 e.r.	 (*M*)-**33** 84 % yield; 94:6 e.r.
 **34** 83 % yield; 99:1 e.r.	 (*M*)-**35** 80 % yield; 98:2 e.r.	 (*P*)-**35** 78 % yield; 95:5 e.r.
 **36** 65 % yield; 99:1 e.r.	 (*P*)-**37** 71 % yield; 90:10 e.r.	 (*P*)-**37** 83% yield; 94:6 e.r.
 **38** 61 % yield; 99:1 e.r.	 (*M*)-**37** 75 % yield; 94:6 e.r.	 (*P*)-**37** 82 % yield; 89:11 e.r.

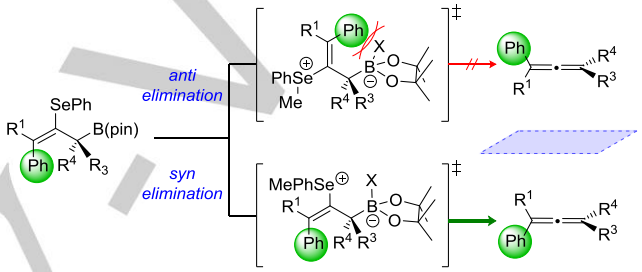
[a] See supporting Information for the preparation of allylic boronic esters. [b] *Syn*-elimination: 1,2-selenoboronic ester (1 eq.), *m*-CPBA (2.0 eq.), THF, r.t., 30 min. [c] *Anti*-elimination: 1,2-selenoboronic ester (1 eq.), MeOTf (2–5 eq.), CH_2Cl_2, r.t., 16 h then $NaHCO_3$ (20 eq.), CH_2Cl_2/MeOH, r.t., 3 h.

In conclusion, we have developed a new method for the enantiodivergent synthesis of allenes by point to axial chirality transfer. Homologation of vinyl boronic esters with enantioenriched lithium carbenoids followed by *syn*- or *anti*-elimination enabled efficient access to either enantiomer of the resulting allene products. The method is extremely general, enabling the highly convergent synthesis of di-, tri- and even tetrasubstituted allenes bearing a range of different aromatic and aliphatic groups. This method serves as a useful alternative to nucleophilic addition to propargylic electrophiles and will find widespread use for the synthesis of chiral, non-racemic allenes.

A. Experimental *vs* Simulated ECD Spectra of (*P*)-**37**



B. *Syn*-alkylative elimination caused by A-1,3 strain



Scheme 2. Determination of absolute configuration for allene (*P*)-**37** and rationalization for observed selectivity. (a) Experimental ECD spectra (solid line) 0.23 mM in MeOH, r.t. Simulated ECD spectra (dashed line) calculated at the CAM-B3LYP/6-311(d,p) level of theory. (b) Rationalization for *syn*-elimination driven by A-1,3-strain.

Acknowledgements

We thank EPSRC (EP/I038071/1) and Bristol University for financial support. R.M.P.D. is greatful to the CAPES (Coordenação de Aperfeiçoamento de Pessoal de Nível Superior) Foundation for a fellowship (grant no. 88881.120469/2016-01). M.N. thanks the EU for a H2020 Marie Skłodowska-Curie Fellowship (grant no. 749862).

Keywords: allenes • boronic esters • enantiodivergent • elimination • enantiospecific

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10.1002/anie.201804446

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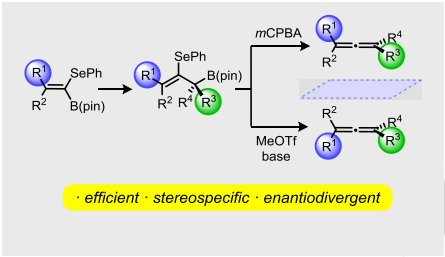
Entry for the Table of Contents

COMMUNICATION

An enantiodivergent method for the synthesis of axially chiral allenes is described. By employing either oxidative or alkylative conditions, both *syn*- and *anti*-elimination could be achieved with essentially complete stereospecificity. This process enables the synthesis of either (*M*) or (*P*) allenes from a single isomer of point chiral precursor and can be employed for the enantioselective assembly of di-, tri- and tetrasubstituted allenes.



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Page No. – Page No.

Enantiodivergent Synthesis of Allenes by Point to Axial Chirality Transfer