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Enantioselective, Lewis Base-Catalyzed Carbosulfenylation of Alkenylboronates by 1,2-Boronate Migration

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Abstract

A catalytic, enantioselective method for the preparation of chiral, non-racemic, alkylboronic esters bearing two vicinal stereogenic centers is described. The reaction proceeds via a 1,2-migration of a zwitterionic thiiranium–boronate complex to give exclusively *anti* carbosulfenylation products. A broad scope of aryl groups migrate with good yield and excellent enantioselectivity (up to 99:1 e.r.). Similarly, a range of di- and trisubstituted alkenylboronic esters are competent reaction partners. This method provides access to both secondary and tertiary chiral alkylboronic esters.

Chiral, non-racemic, alkylboronic esters are valuable synthetic intermediates in modern organic chemistry.[1,2] These compounds undergo stereospecific functional group interconversions to afford alcohols, amines, and halides, and serve as useful partners for a myriad of transition metal-catalyzed cross-coupling reactions.[3] Consequently, numerous methods have been reported for the synthesis of enantiomerically enriched secondary and tertiary alkylboronic esters.[4] Many of these are reductive, oxidative, or isohypsic transformations of alkenylboronic esters, which are themselves readily prepared by hydroboration of abundant, inexpensive alkynes.[5] Of particular utility are the “conjunctive” coupling methods recently reported by Morken et al.[6] (Scheme 1A), in which a tetracoordinate alkenylboronate complex undergoes a 1,2-metalate rearrangement[7,8] in the presence of an aryl-palladium species. The net result is a secondary alkylboronic ester, and the entire process is rendered highly enantioselective by a chiral ligand. This process is attractive owing to its modular nature and broad scope. However, previous methods have not been widely used to access products with two vicinal stereogenic centers.[9]

In fact, diastereospecific 1,2-migrations of alkenylboronate complexes have been known for many decades. Zweifel et al. first reported the synthesis of olefins from *trans*-alkenylboranes in the presence of iodine and aqueous base (Scheme 1B).[10] This reaction proceeds through a zwitterionic iodonium–boronate complex. Because nucleophilic opening of haliranium ions is stereospecific, 1,2-migration of an alkyl group from the boronate complex results in an α-

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Supporting Information

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Experimental procedures and characterization data for all new compounds (PDF)

X-ray crystallographic data for (S,S)-**6ai** (CIF)

The authors declare no competing financial interest.

iodinated secondary borane as a single *anti* diastereomer. Aggarwal et al. have recently disclosed the synthesis of α-selenylated secondary boronic esters which proceeds through a very similar mechanism (Scheme 1C).[11] Treating an alkenylboronate complex with phenylselenyl chloride forms a zwitterionic seleniranium ion, which is opened by 1,2-migration to afford exclusively *anti* products. This transformation accommodates a broad scope of substrates which lead to bench-stable and synthetically useful products, but all in racemic form. An enantioselective variant has not yet been reported.

The activation of Lewis acids by chiral Lewis bases for enantioselective, electrophilic functionalization of olefins has been extensively developed in this laboratory[12] and is ideally suited to address this challenge (Scheme 1D). Combining chiral selenophosphoramide catalyst (*S*)-**5** with an appropriate Group 16 Lewis acid of type **4** ("sulfenylating agent") leads to a cationic donor–acceptor complex which is highly electrophilic at sulfur. This species effects the generation of enantiomerically enriched thiiranium ions with unactivated alkenes as well as more nucleophilic alkenes such as enoxysilanes.[13] The thiiranium ion is opened diastereospecifically by oxygen, nitrogen, and carbon nucleophiles, resulting in 1,2-*anti*-sulfeno-functionalized products. The specific challenge was whether alkenylboronate complexes could also serve as viable reactants in this process. Such highly reactive, anionic boronate complexes would likely be incompatible with the conditions used to generate the electrophilic sulfenium ions needed. Even if conditions could be found, the resulting thiiranium ions would need to trigger the subsequent 1,2-migration without configurational mutation to afford α-thiolated boranes in highly enantio- and diastereo-selective fashion.

Orienting experiments employed boronate complex **3aa**, generated from boronic ester **1a** and phenyllithium **2a**, in THF, and its reactivity was examined under a variety of conditions (Table 1).[14] Different sulfenylating agents (**4a**, **4b**, or **4c**) and solvents were evaluated in combination with catalyst (*S*)-**5**. The anticipated incompatibility of anionic complex **3aa** with the typical acidic promoters required to activate reagents **4** led to the initial investigation of saccharin-derived reagent **4a**, which can transfer its sulfenyl group to catalyst **5** without the aid of acid.[13] In dichloromethane, the desired product **6aa** was formed in good yield after 3 h at cryogenic temperature (entries 1 and 2). However, this observed reactivity simply resulted from background reaction between **3aa** and **4a**, leading to nearly racemic **6aa**. To mitigate this background reactivity, less reactive sulfenylating agents **4b** and **4c** were tested (entries 3–6). Although the background reaction was suppressed, no catalysis was observed.[15]

A recent report from this laboratory on Lewis base-catalyzed polyene sulfenocyclization revealed the salutary effect of hexafluoroisopropyl alcohol (HFIP) as a solvent for these reactions by obviating the need for acidic activators.[16] Inspired by these results, we explored the effects of polar protic solvents on the present system. Thus, employing **4a** in either methanol or ethanol led to the formation of **6aa** in synthetically useful yield and excellent enantioselectivity, with very little background reaction (entries 7–10). Although no reaction was observed with **4b** in ethanol ($pK_a = 16$),[17] a modest yield of **6aa** was obtained in tetrafluoroethanol (TFE) ($pK_a = 12$)[17] with moderate enantioselectivity (entries 11–14). Likewise, a modest yield was observed with **4c** in HFIP ($pK_a = 9$)[17] with similar enantioselectivity (entries 15 and 16), although significant decomposition of the boronate

complex was observed in this more acidic medium. These results suggest that, whereas protic solvents can attenuate the background reactivity of boronate complex **3aa**, only the most active sulfenylating agent **4a** is capable of sulfenyl group transfer to catalyst **5** in higher-pK_a alcohols, which are necessary to avoid decomposition of the boronate. Therefore, the conditions in entry 10 were selected to evaluate the scope of this transformation. The attenuation of boronate reactivity in protic solvents likely arises from hydrogen-bonding interactions that stabilize the anionic character of the pinacolate complex **3aa**.

The exploration of reaction scope began with an examination of the migrating groups (Table 2). Throughout this paper, compounds are identified by the nomenclature **Nxy** where **N** is the compound class (**3** = boronate complex, **6** = functionalized borane product, and **7** = alcohol resulting from borane oxidation), **x** is the alkenyl fragment being functionalized, and **y** is the migrating group. Tetracoordinate boronate complexes **3aa**–**3ai** were accessed by addition of organolithium reagents **2a**–**2i** to alkenylpinacolborane **1a** (Path A). Aryllithium reagents **2a**–**2d**, bearing electronically diverse 4-substituents, added and migrated efficiently to afford products **7aa**–**7ad** in high yields and excellent enantioselectivities after oxidation of the alkylboranes. To prevent self-condensation of 4-cyanophenyllithium **2e**, this reagent was generated in situ in the presence of **1a** to ensure immediate formation of “ate” complex **3ae**. Subsequent migration and oxidation afforded product **7ae** in good yield and high enantioselectivity. Complex **3af** led to the desired product **7af** in acceptable yield (60%), demonstrating that styrenyl olefins do not react at an appreciable rate under the reaction conditions. Using pyridinyl-substituted phenyllithium **2g** afforded product **7ag** in acceptable yield but diminished enantiomeric purity. Employing *n*-butyllithium as the nucleophile resulted in modest yield and enantioselectivity of **7ah**, demonstrating that alkyl groups migrate less efficiently.

Because the alkenylboronate complexes are sterically and electronically distinct from any previously investigated class of alkenes, it was deemed prudent to establish the absolute stereochemical course of this reaction. This circumspection was prescient, as an X-ray crystallographic structure determination[18] of intermediate **6ai** (derived from 2,6-dimethyl-phenyllithium **2i**, and en route to **7ai**) revealed that it possessed the (S,S)-configuration, *opposite* to that expected on the basis of our previous results and predictive models for facial selectivity.[12b] Evidently, the modes of interaction between the catalytic donor–acceptor complex and the boronate are much different than those which exist between this complex and simple alkenes.

Alternatively, boronate **3** can be generated from alkenyllithium reagent **8a** and arylboronic esters **9j**–**9n** (Path B). Products **7aj** and **7ak** were accessed in this manner from 2-tolylpinacolborane **9j** and 2-napththylpinacolborane **9k**, respectively. Path A could not be used to access boronate **3al** because halogen–lithium exchange of 5-bromo-*N*-tosylindole resulted in lithiation at multiple positions. Path B circumvented this problem, allowing the isolation of **7al** in 55% yield and 98:2 enantiomeric ratio (e.r.). Likewise, Path B was required to form boronate complex **3am** containing a 3-bromophenyl group, which afforded product **7am** in 85% yield after migration. Finally, even using Path B, product **7an** bearing a

methyl ester was isolated in only 32% yield, owing to the incompatibility of this functional group with organolithium reagents.[19]

The second stage of exploration of reaction scope focused on those alkenylboranes which could engage in carbosulfenylation (Table 3). It has been previously demonstrated that *trans*-1,2-disubstituted alkenes are optimal substrates for catalyst **5**, affording sulfeno-functionalized products in high yields and enantioselectivities. Accordingly, all *trans*-1,2-alkenylboronates **3ba**–**3ea** are excellent substrates for the present transformation. Pendant silyl ethers, primary alkyl chlorides, and primary alkyl bromides are compatible with the reaction conditions (products **7ba**–**7da**). A more congested *trans*-alkenylboronate **3ea** still affords product **7ea** in high yield and enantioselectivity. 1,2,2-Trisubstituted alkenylboronate **3fa** was not an effective substrate for this transformation, as product **7fa** was isolated in low yield and poor enantio-selectivity.[20a] In contrast, a 1,1,2-trisubstituted alkenylboronate **3ga** reacted quite efficiently to form product **7ga** in 76% yield and 96:4 e.r. Boronate **3ha** also reacted efficiently to form product **7ha** in 74% yield and 95:5 e.r. This outcome was unexpected, as geminal 1,1-disubstituted olefins are traditionally very poor substrates for catalyst **5**. Nevertheless, products **7ga** and **7ha** highlight the utility of this method for generating chiral, non-racemic, tertiary alcohols. Unsubstituted vinyl pinacolboronate **3ia** reacted to form product **7ia** in good yield but more modest enantioselectivity (84:16).[20b] As expected from previous work, a *cis*-alkenylboronate **3ja** was not well-recognized by catalyst **5**, and product **7ja** was isolated in acceptable yield but poor enantioselectivity (69:31).[21]

The stability of the sulfenyl pinacolborane products provides an ideal opportunity to examine their synthetic utility (Scheme 2). Reduction of enantiomerically enriched (99:1 e.r.) α-sulfenylated borane **6aa** led to different products depending on the exact conditions used. Addition of lithium metal to a solution of **6aa** and *tert*-butanol in ammonia afforded C–S cleavage product **11aa** in good yield, provided the reaction is quenched in a timely fashion. Alternatively, if **6aa** was treated with LDMAN (lithium *N,N*-dimethyl-1-aminonaphthalenide)[22] and the reaction aged for 1 h in the absence of any electrophile, an unusual rearrangement product **12aa** was observed, which displayed a modest erosion in e.r. (82:18).[23] This rearrangement likely proceeds through a boratirane ion intermediate.[24,25] Finally, treating **6aa** with LDMAN and an electrophilic reagent (isopropoxy pinacolborane) in the same pot afforded diborylated compound **13aa** in 68% yield, albeit with poor diastereoselectivity.[26] All attempts to oxidize α-sulfenylated borane **6aa** to a sulfoxide resulted only in elimination to form a *trans*-olefin.[27] Of course, **6aa** could first be oxidized to alcohol **7aa** using sodium perborate, and subsequent treatment with hydrogen peroxide afforded α-hydroxy sulfoxide **14aa** in 93% yield as a mixture of diastereomers. Treating this mixture with sodium carbonate in refluxing xylenes formed elimination product **15aa** in 89% yield with predominantly (*E*)-geometry. Finally, mesylation of **7aa** followed by treatment with 4-methoxyaniline afforded secondary amine **16aa** in 87% yield. The displacement is net retentive, indicating that the reaction proceeds through a thiiranium ion intermediate.[28]

In conclusion, an enantio- and diastereoselective, Lewis base-catalyzed carbosulfenylation of alkenylboronates has been described. The reaction proceeds by 1,2-boronate migration to

open a thiiranium ion, affording chiral, non-racemic alkyl boronic esters with two vicinal stereogenic centers.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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(14). The solid “ate” complex 3 obtained after solvent removal, while isolable, is not stable to air or moisture.

(15). Using THF as the reaction solvent resulted in diminished yield (4a) or no conversion (4b, 4c). Various additives (MgBr2, LiClO4, 12-crown-4, n-Bu4NBr, n-Bu4NOMs) had no significant influence on yield or enantioselectivity.

(16). Tao Z; Robb KA; Zhao K; Denmark SE Enantio-selective, Lewis Base-Catalyzed Sulfenocyclization of Polyenes. J. Am. Chem. Soc 2018, 140, 3569–3573. [PubMed: 29509003]

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(18). CCDC 1866767 contains the crystallographic data for compound 6ai. These data can be obtained free of charge from the Cambridge Crystallographic Data Center (www.ccdc.cam.ac.uk).

(19). The slight drop in enantioselectivity (87:13) observed for product 7an was perplexing and could not be explained solely on the basic of electronic effects, because similarly electron-deficient aryl groups migrated with high e.r. (see products 7ac–7ae). The only difference between the reaction mixtures in Path A and Path B is the presence of LiBr. Unlike lithium–halogen exchange of a bromoarene to form 2 (accomplished with n-BuLi), lithium–halogen exchange of an alkenyl bromide to form 8a requires tert-BuLi, which generates LiBr. Indeed, addition of exogenous LiBr to the reaction mixtures in Path A causes a drop in enantioselectivity, but only for electron-deficient migrating groups, whereas electron-rich migrating groups are unaffected by this additive.

(20). (a) The thiiranium ion opens to form the stabilized tertiary carbocation, which can eliminate boron to form an alkenyl sulfide, the major observed byproduct. See ref 11b.(b) We have also examined the reactivity of (E)-2-styryl(pinacolborane) and did not observe the desired product. Only the corresponding vinyl sulfide product was obtained. This substrate suffers from the same effect observed for the transformation of 3fa to 6fa described above.

(21). Denmark SE; Jaunet A Catalytic, Enantioselective, Intramolecular Carbosulfenylation of Olefins. J. Am. Chem. Soc 2013, 135, 6419–6422. [PubMed: 23597174]

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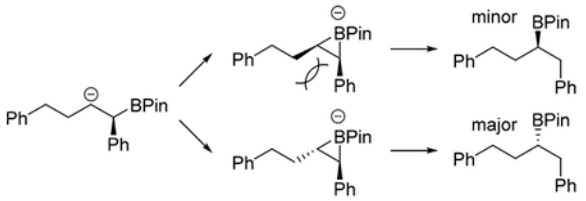
(23). The absolute configuration and e.r. of borane 12aa were determined by oxidation to 23 (44% yield over two steps from 6aa). Refer to the Supporting Information for details.

(24). For the intermediacy of similar species, see:Kropp MA; Baillargeon M; Park KM; Bhamidapaty K; Schuster GB Photochemistry of Alkynyl-, Alkenyl-, and Cyclopropyl-Substituted Borate Salts: The Di-π- and Cyclopropyl-π-Borate Rearrangements. J. Am. Chem. Soc 1991, 113, 2155–2163.Denmark SE; Nishide K; Faucher A-M On the Generation and Configurational Stability of (2S, 3S)-1,2,3-Triphenylborirane. J. Am. Chem. Soc 1991, 113, 6675–6676.

(25). A kinetic preference exists for formation of the anti-boratirane ion, which leads to (S)-12aa upon quenching.



(26). Both syn and anti diastereomers of 13aa display a modest erosion in enantioselectivity, similar in magnitude to that observed for 12aa. It can be inferred that the conversion of 6aa to 13aa also proceeds through a boratirane ion intermediate and that the benzylic boryl group originates from i-PrOBPin.

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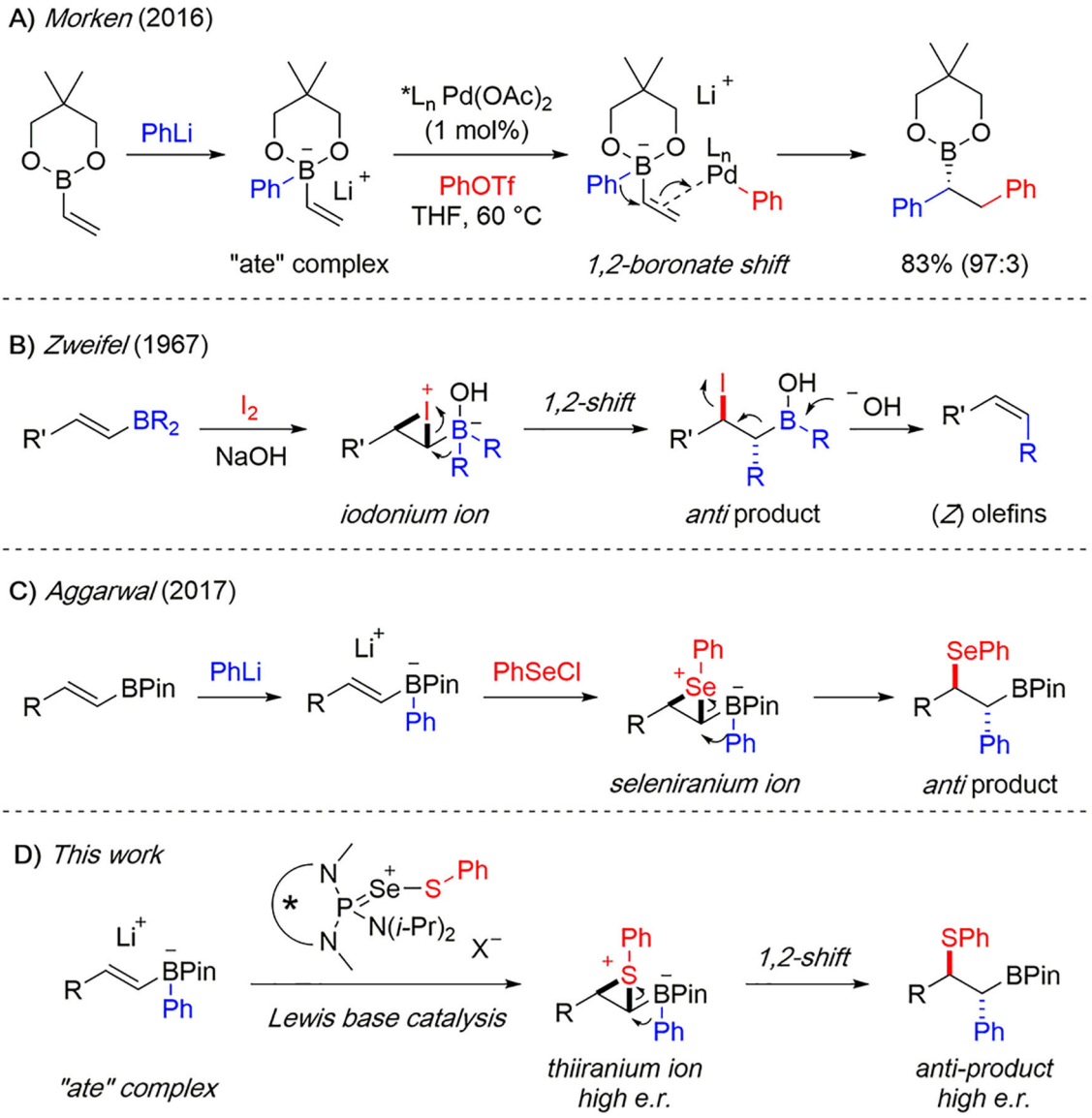
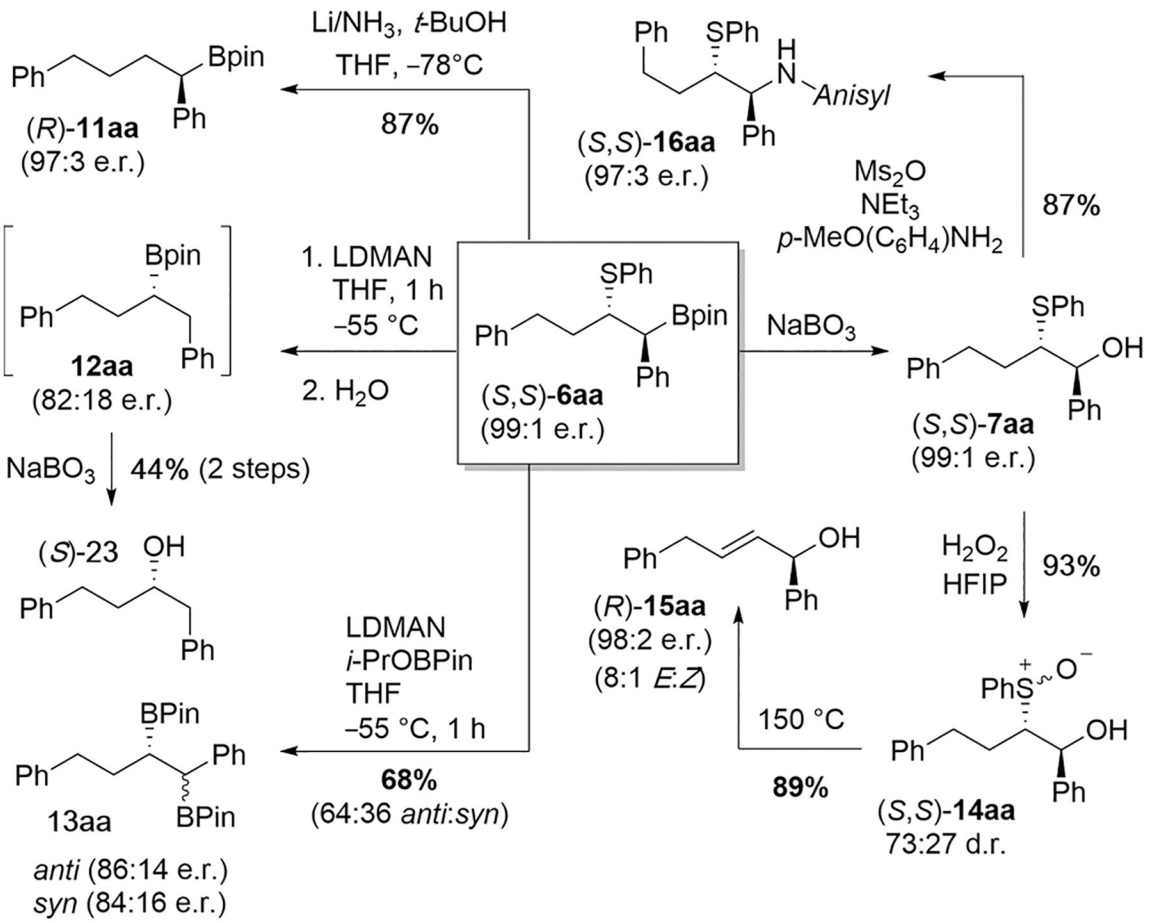
(28). We have attempted cross coupling reactions of 6aa to forge a C–C bond using two different conditions: (1) traditional Suzuki conditions (with iodobenzene) and (2) coupling with a lithiated furan: Bonet A; Odachowski M; Leonori D; Essafi S; Aggarwal VK Enantiospecific sp2–sp3 coupling of secondary and tertiary boronic esters. Nat. Chem 2014, 6, 584–589. [PubMed: 24950327] In both cases, only the elimination product (1,4-diphenyl-1-butene) was observed. The thioether must be removed before the pinacolboronic ester can engage in productive cross coupling.



Scheme 1.

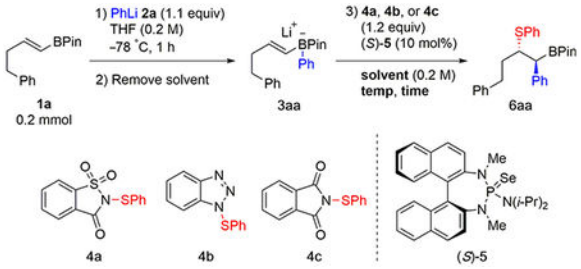
Stereoselective Construction of Chiral Alkylboranes by 1,2-Migration of Alkenylboronate Complexes



Scheme 2.
Product Manipulations

Table 1.

Reaction Optimization



Entry	3	Cat	Solvent	Temp (°C)	Time (h)	Yield (%)[a,b]	e.r.
1	**4a**	none	CH_2C1_2	−78	3	56[a]	--
2	**4a**	(*S*)-**5**	CH_2C1_2	−78	3	68[a]	55:45
3	**4b**	none	CH_2C1_2	−78	18	ll[b]	--
4	**4b**	(*S*)-**5**	CH_2C1_2	−78	18	16[b]	57:43
5	**4c**	none	CH_2C1_2	−20	36	31[b]	--
6	**4c**	(*S*)-**5**	CH_2C1_2	−20	36	37[b]	53:47
7	**4a**	none	MeOH	−60	24	10[b]	--
8	**4a**	(*S*)-**5**	MeOH	−60	24	47[a]	94:6
9	**4a**	none	EtOH	−60	24	14[b]	--
10	**4a**	(*S*)-**5**	EtOH	−60	24	80[a]	98:2
11	**4b**	none	EtOH	−20	24	7[b]	--
12	**4b**	(*S*)-**5**	EtOH	−20	24	10[b]	--
13	**4b**	none	TFE	−20	2	10[b]	--
14	**4b**	(*S*)-**5**	TFE	−20	2	32[b]	85:15
15	**4c**	none	HFIP	0	2	0[c]	--
16	**4c**	(*S*)-**5**	HFIP	0	2	27[a,c]	83:17

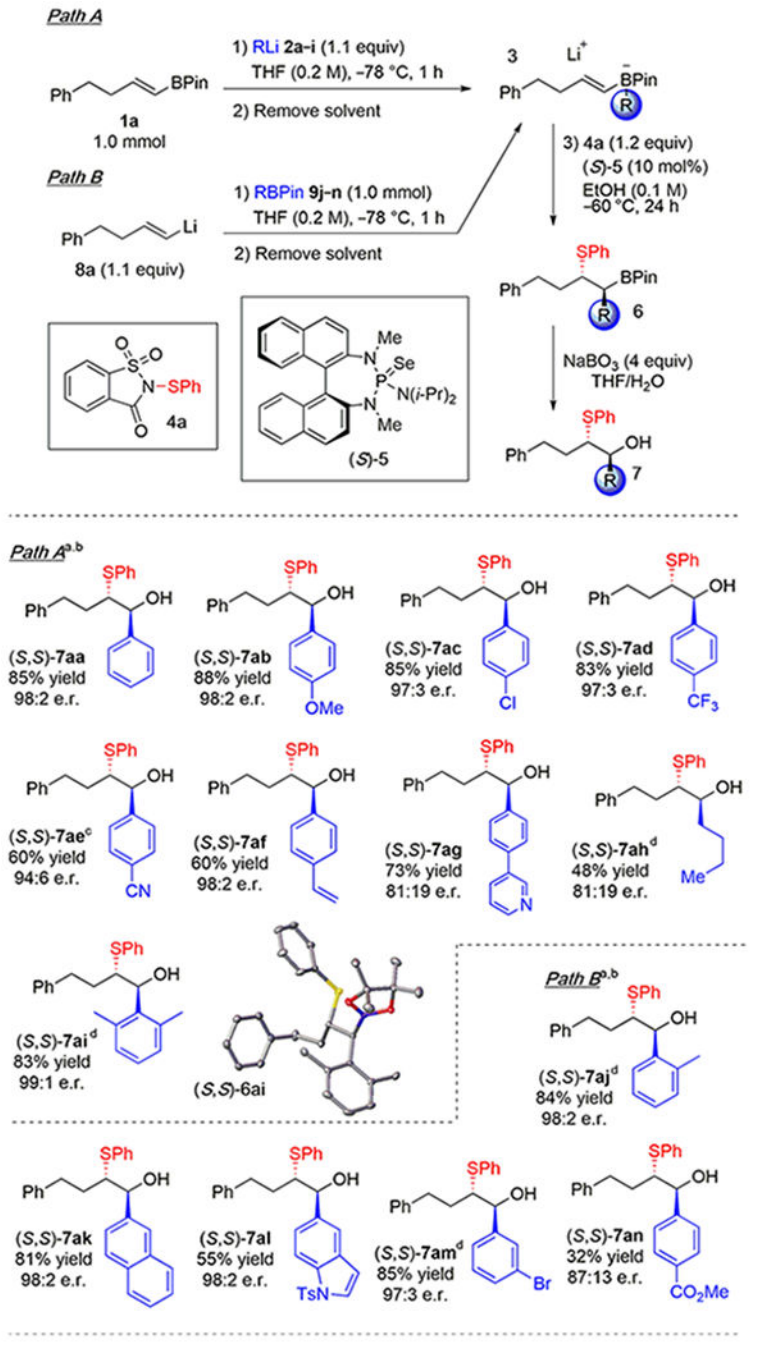
[a]Yield of isolated alcohol product **7aa** from oxidation. Conditions: $NaBO_3$ (4 equiv), THF/H_2O, 25 °C.

[b]Yield of pinacolborane **6aa** by ^1H NMR integration with an internal standard.

[c]Some decomposition of boronate complex observed.

Table 2.

Organolithium Scope



[a] Isolated yields of analytically pure material.

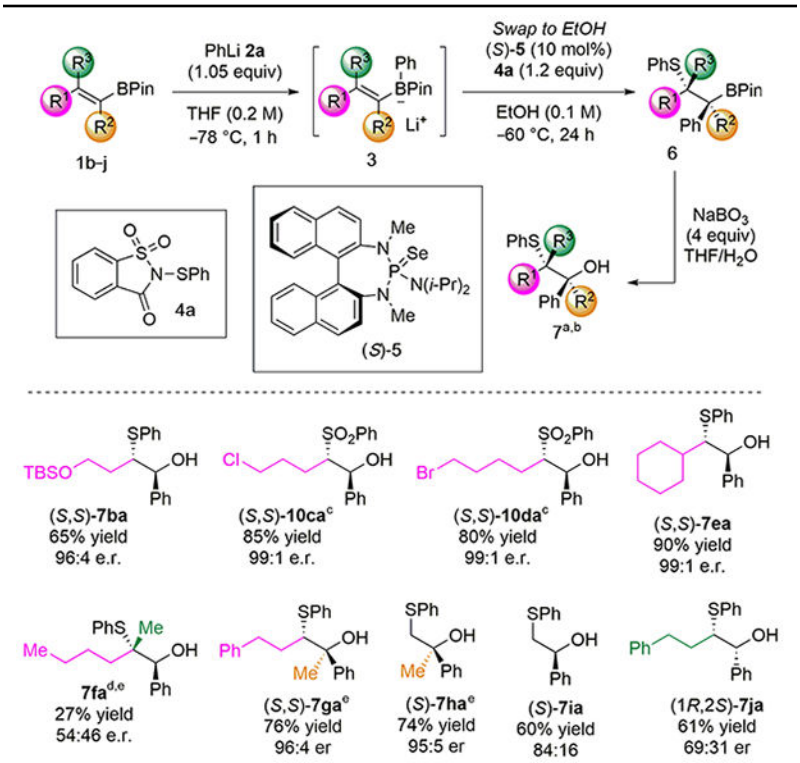
[b] Enantiomeric ratio determined by chiral stationary phase NP-HPLC or SFC.

[c] **2e** generated in the presence of **1a**.

[d] Conditions for oxidation of **6** to **7**: NaOH/H_2O_2/THF, 0 °C.

Table 3.

Alkenylboronate Scope



[a] Isolated yields of analytically pure material.

[b] Enantiomeric ratio determined by chiral stationary phase NP-HPLC or SFC.

[c] 7 oxidized to sulfone **10** with *m*-CPBA prior to isolation.

[d] Tentative absolute configuration shown.

[e] Conditions for oxidation of **6** to 7: NaOH/H_2O_2/THF, 0 °C.