Enantioselective Synthesis

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Enantioselective Synthesis and Cross-Coupling of Tertiary Propargylic Boronic Esters Using Lithiation–Borylation of Propargylic Carbamates**

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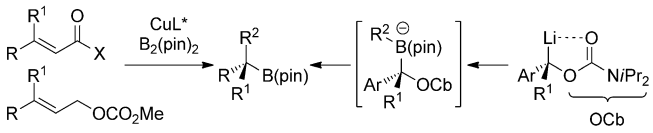
Chiral tertiary boronic esters have been shown to be useful intermediates in organic synthesis, as they can undergo a variety of functional group transformations, for example, conversion to alcohols, amines, quaternary centers, or aryldialkylmethines with high stereospecificity.[1] Recently, such intermediates have become available in high *ee* through two distinct methods: 1) borylation of Michael acceptors[2] or allylic electrophiles,[3] and 2) lithiation–borylation of secondary benzylic carbamates (Scheme 1),[4] which can deliver exceptionally high enantioselectivities over a broad range of substrates (> 99.1 e.r.).

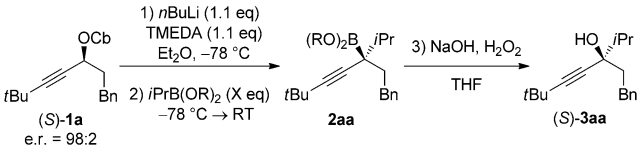


Scheme 1. Existing methods for the synthesis of enantiomerically enriched tertiary boronic esters. B(pin) = pinacolatoboron.

Although the lithiation–borylation method can be used in the synthesis of tertiary boronic esters with high enantioselectivities, it is limited to benzylic[4] and, more recently, allylic substrates,[5] as unsaturation is required to enable the deprotonation of the substituted carbamate to occur. We were keen to broaden the scope of this useful method, particularly towards propargylic substrates such as chiral tertiary propargylic boronic esters, which could potentially participate in an even broader array of functional group transformations. Herein, we describe our success in achieving this goal.

We began our study with propargylic carbamates bearing a terminal *t*Bu group, as Hoppe had shown that hindered alkyl groups were necessary for configurational stability of the lithiated carbamate at −78 °C.[6] We were pleased to find that lithiation–borylation of carbamate **1a** with the hindered isopropyl boronic acid pinacol ester (*i*Pr-Bpin) did indeed give the tertiary boronic ester **2aa** (Table 1, entry 1). In

Table 1: Effect of the boronic ester diol on the lithiation–borylation reaction.



Entry	Diol [(OR)$_2$]	X [equiv]	Product	Yield [%]	e.r.[a]	e.s. [%][b]
1	pinacol	2	**2aa**	55[c]	51:49	2
2	pinacol	3	**2aa**	55[d]	52:48	4
3	neopentyl	2	**3aa**	51[d]	68:32	38
4	neopentyl	3	**2aa**	80[c]	89:11	81
5	ethylene glycol	2	**3aa**	48[d]	98:2	100

[a] Enantiomeric ratio determined after oxidation to alcohol **3**. [b] See ref. [8]. [c] Yield as determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. [d] Yield of isolated product. TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine.

contrast to other electrophiles, which had been reported to give mixtures of α- and γ-attack, or exclusively γ-attack, the regioselectivity of the homologation was exclusively α to the carbamate.[6,7] In related reactions, high α regioselectivity (with retention of stereochemistry) was also observed in the case of allylic substrates.[5] In both cases, the origin of selectivity may be a result of the coordination of the oxygen of the boronic ester to lithium, thereby delivering the boronic ester to the same site (and the same face as lithium).

However, in distinct contrast to the lithiation–borylation with secondary benzylic and allylic carbamates, the alcohol was found to be racemic, even when an excess of the boronic ester was used (entries 1 and 2). We believed that this was due to reversibility in formation of the boron "ate" complex.[4b,9] Upon warming the ate complex, it was possible that reversibility back to the lithiated carbamate could compete with 1,2-metallate rearrangement, especially as the propargylic lithiated carbamate was expected to have similar stability to the corresponding lithiated benzylic and allylic carbamates, which

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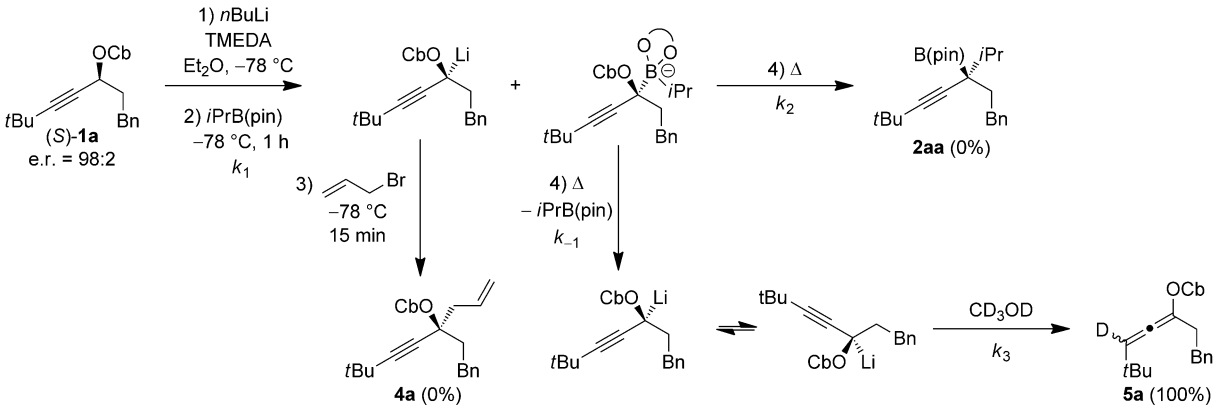


Scheme 2. The "two electrophile test" to determine the extent of the reversibility of the ate complex formation. Reaction conditions: 1) Carbamate (1 equiv), *n*BuLi (1.1 equiv), TMEDA (1.1 equiv), −78 °C, 20 min, 2) *i*Pr-B(pin) (3 equiv), −78 °C, 1 h, 3) allyl bromide, −78 °C, 10 min, 4) CD_3OD, −78 °C to RT, 16 h; yield determined by ^{1}H NMR spectroscopy. Bn = benzyl, B(pin) = pinacolatoboron, TMEDA = tetramethylethylenediamine.

were known to react reversibly in some cases.[10] However, above about −70 °C the lithiated propargylic carbamate is configurationally unstable and so could racemize.[6] Recombination of this racemic lithiated carbamate with the boronic ester would result in an erosion of e.r. This hypothesis was tested using the "two electrophile test".[4b] Carbamate **1a** was deprotonated at −78 °C and reacted with *i*PrBpin (Scheme 2). Before warming the reaction mixture to room temperature, allyl bromide was added followed 10 min later by CD_3OD. The product of allylation (**4a**) would indicate that the boron ate complex formation was incomplete whereas any allene **5a** formed by deuteration would show that the boron ate complex formation was reversible. Analysis of the crude reaction mixture by ^{1}H NMR indicated the presence of a single product: allene **5a**, with no boronic ester **2aa** or allylated product **4a** observed.

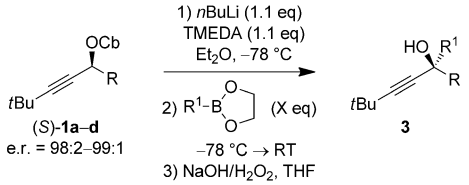
Several conclusions can be drawn from this experiment:

1) Deprotonation was complete after 20 min at −78 °C, as no starting material was recovered.
2) Formation of the boron ate complex was complete after 1 hour at −78 °C, as no allylation was observed.
3) Upon warming, all of the boron ate complex formed reverted back to lithiated carbamate and was trapped by CD_3OD to give **5** as the sole product. This means that the rate of reversibility is greater than the rate of 1,2-metallate rearrangement ($k_{-1} \gg k_2$), which accounts for the significantly lower enantioselectivity observed. Furthermore, the rate of reversibility for propargylic carbamates is considerably greater than for benzylic and allylic carbamates.[11]

We reasoned that less hindered boronic esters would be less prone to reversibility and so should lead to higher enantioselectivity. Indeed, upon changing from pinacol to neopentyl glycol to ethylene glycol, we saw a steady increase in e.r. from ca. 50:50 to 89:11 to 98:2 (Table 1, entries 1–5). Thus, we were able to obtain full retention of stereochemical information from the carbamate using the ethylene glycol boronic ester. The stereochemistry of the borylation reaction was determined by X-ray analysis of an alcohol derivative (see the Supporting Information).[12]

We tested a range of alkyl boronic esters and propargylic carbamates with in situ oxidation and found that tertiary propargylic alcohols could be obtained in consistently excellent e.r. (Table 2). An excess of the boronic ester was found to give slightly higher enantioselectivities (compare entries 1 and 2, and entries 3 and 4) as previously reported for the corresponding reactions of aryl-stabilized lithiated carbamates.[4a] In the case of phenylboronic acid glycol ester (entry 8), whereas homologation proceeded effectively, rapid protodeboronation of the resulting tertiary boronic ester occured upon workup. The method was also extended to the less hindered α-methyl carbamate **1b** and the more hindered

Table 2: Substrate scope of lithiation–borylation of carbamate **1**.



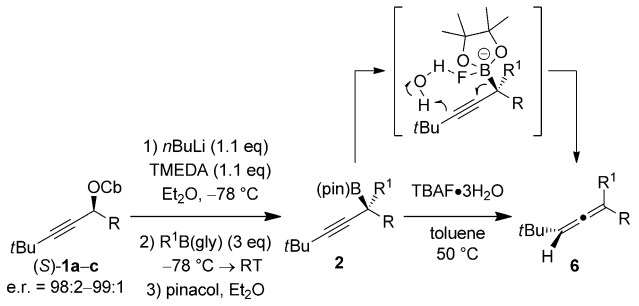
Entry	R[a]	R^1	X [equiv]	Product (% yield)[a]	e.r.	e.s. [%]
1	CH_2Bn **a**	*i*Pr **a**	1.5	**3aa** (42)	96:4	96
2	CH_2Bn **a**	*i*Pr **a**	3	**3aa** (48)	98:2	100
3	CH_2Bn **a**	Et **b**	1.5	**3ab** (57)	96:4	96
4	CH_2Bn **a**	Et **b**	3	**3ab** (58)	98:2	100
5	CH_2Bn **a**	Cyp **c**	3	**3ac** (54)	98:2	100
6	CH_2Bn **a**	allyl **d**	3	**3ad** (44)	96:4	96
7	CH_2Bn **a**	benzyl **e**	3	**3ae** (52)	95:5	94
8	CH_2Bn **a**	Ph **f**	3	**3af** (0)	–	–
9	Me **b**	*i*Pr **a**	3	**3ba** (48)	96:4	94
10[b]	*i*Bu **c**	Et **b**	3	**3cb** (44)	95:5	92

[a] Yield of isolated product. [b] The reaction mixture was heated at 40 °C for 48 h. Bn = benzyl, Cyp = cyclopropyl, TMEDA = tetramethylethylenediamine.

α-*iso*-butyl carbamate **1c**, both of which afforded the corresponding alcohols in high e.s. (entries 9 and 10).

This method provides a new approach to the synthesis of tertiary propargylic alcohols in high e.r.,[13] compounds which are of considerable value in synthesis; furthermore, this motif is a key component in the HIV drug, Efavirenz.[14] However, we also wanted to isolate the tertiary propargylic boronic esters to further explore their potential in synthesis. Ethylene glycol boronic esters are extremely moisture sensitive and so transesterification of the homologated boronic ester with pinacol was carried out, which enabled the isolation of a range of tertiary propargylic pinacol boronic esters in excellent e.r. (Table 3).

Table 3: Transesterification and protodeboronation of tertiary propargylic boronic esters.



Entry	R	R^1	Product (% yield)[a]	e.s. [%]	Product (% yield)[a]	e.s. [%]
1	CH_2Bn **a**	*i*Pr **a**	**2aa** (47)	100	**6aa** (95)	100
2	CH_2Bn **a**	*i*Pr **a**	–	–	**6aa** (42)[b]	100
3	CH_2Bn **a**	Et **b**	**2ab** (67)	100	**6ab** (57)[b]	ND[c]
4[e]	Me **b**	*i*Pr **a**	**2ba** (81)	96	**6ba** (43)[b,d]	ND[c]
5[e]	*i*Bu **c**	Et **b**	**2cb** (50)	92	**6cb** (84)[d]	100
6	$(CH_2)_2$Ar[f] **d**	Et **b**	**2db** (66)	100	**6db** (99)	100

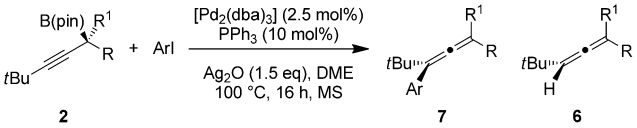
[a] Yield of isolated product. [b] One pot reaction from carbamate **1a**. [c] We were unable to separate the enantiomers by HPLC, SFC, or GC (see the Supporting Information). [d] Pentane was used as the reaction solvent. [e] The reaction mixture was heated at 40 °C for 48 h. [f] Ar = *p*MeOC$_6$H$_4$. Bn = benzyl, gly = glycol, ND = not determined, TBAF = tetrabutylammonium fluoride.

The fluoride-mediated protodeboronation of tertiary benzylic boronic esters has been reported to give tertiary alkanes in high e.r. and with retention of configuration.[15] In the case of propargylic boronic esters, the reaction with tetrabutylammonium fluoride (TBAF) proceeded through a *syn*-S_E' mechanism[16] to give trisubstituted allenes[17] **6** in excellent yield and enantioselectivity (Table 3). The stereochemistry of the protodeboronation reaction was determined by X-ray analysis[12] (see the Supporting Information), which indicated that protonation had once again occurred with retention of configuration. A one-pot procedure from carbamate **1a** gave allene **6aa** directly, without detriment to the yield or e.r. (entry 2). The reaction was successfully applied to a range of tertiary propargylic boronic esters (entries 3–6).

We next turned our attention to the significantly more challenging enantioselective Suzuki–Miyaura cross-coupling. The use of sp^3 hybridized organoboron species has been traditionally problematic owing to slow transmetallation and competing β-hydride elimination, although there are now several reports on the enantioselective cross-coupling of secondary boronic esters.[18,19] However, we are not aware of any reports on the enantioselective cross-coupling of a tertiary boron intermediate.[20,21] The cross-coupling of tertiary propargylic pinacol boronic ester brings with it further complications, as the coupling, if successful, could occur at the α or γ positions, thus leading to propargylic or allenic products, respectively. Related examples of the cross-coupling of allylic boronic acids/esters have been described, where the γ cross-coupled product was the major isomer observed, although mixtures were often obtained.[22]

We began our investigations using the conditions of Crudden,[18] and were delighted to find that cross-coupling of **2ab** with phenyl iodide gave allene **7aba** in high yield and very high enantiospecificity (98% e.s.; Table 4). The reaction was extended to a range of electron rich and electron poor

Table 4: Scope of cross-coupling of boronic ester **2** with aryl iodide.

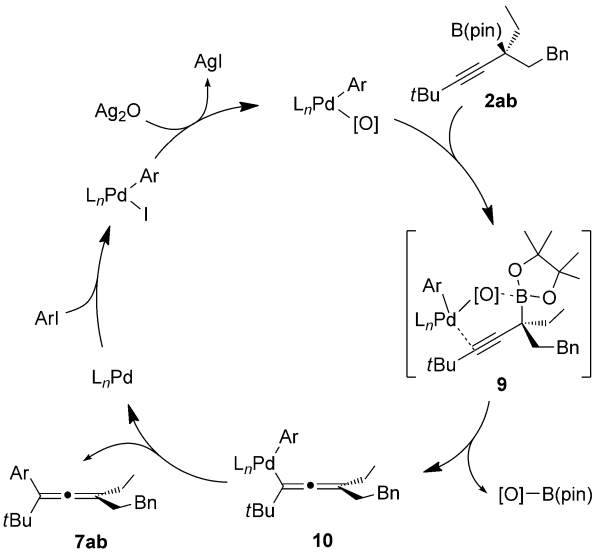


Entry	R	R^1	Ar	Ratio **7**:**6**[a]	Product (% yield)[b]	e.s. [%]
1	CH_2Bn **a**	Et **b**	Ph **a**	100:0	**7aba** (83)	98
2	CH_2Bn **a**	Et **b**	*p*BrC$_6$H$_4$ **b**	90:10	**7abb** (65)	98
3	CH_2Bn **a**	Et **b**	*p*AcC$_6$H$_4$ **c**	95:5	**7abc** (80)	98
4	CH_2Bn **a**	Et **b**	*p*MeOC$_6$H$_4$[c] **d**	80:20	**7abd** (72)	98
5	Me **b**	*i*Pr **a**	*p*AcC$_6$H$_4$ **c**	100:0	**7bac** (70)	98
6	*i*Bu **c**	Et **b**	*p*AcC$_6$H$_4$ **c**	100:0	**7cbc** (71)	100
7	$(CH_2)_2$Ar[d] **d**	Et **b**	Ph **a**	100:0	**7dba** (75)	98

[a] Determined by ^{1}H NMR analysis of crude material. [b] Yield of isolated product. [c] [Pd(PPh$_3$)$_4$] (5 mol%) was used as the Pd/ligand source. [d] Ar = *p*MeOC$_6$H$_4$. dba = dibenzylideneacetone, DME = 1,2-dimethoxyethane, MS = molecular sieves.

aryl iodides, as well as a range of tertiary propargylic boronic esters, which lead to fully substituted allenes in good yield and essentially perfect e.s.[23] Competing protodeboronation of the boronic ester was observed in some cases. This method enables the preparation of all-carbon tetrasubstituted allenes in highly enantiomerically enriched form, compounds which have only rarely been previously described.[24]

Our proposed mechanism of the cross coupling reaction, which accommodates the regio- and stereoselectivity observed, is shown in Scheme 3. We propose that activation of the boronic ester through a palladium–hydroxy species[25] would facilitate transmetallation through a six-membered transition state structure **9**.[26] This would lead to an allenyl palladium intermediate[22c] **10**, which after reductive elimination would give the all-carbon tetrasubstituted allene **7ab**. Although the tetrasubstituted allenes prepared in Table 4 were either oils or solids which did not lead to crystals suitable for X-ray crystallography, we were able to prepare a crystalline derivative that was suitable for analysis, which clearly



Scheme 3. Proposed mechanism to account for the stereochemistry of the cross-coupling. Bn = benzyl, B(pin) = pinacolatoboron, TMEDA = tetramethylethylenediamine.

shows the orientation of the four substituents around the allene moiety (Figure 1).[12] This enabled us to determine the absolute configuration of the tetrasubstituted allene, which showed that cross-coupling had occurred with retention of configuration.

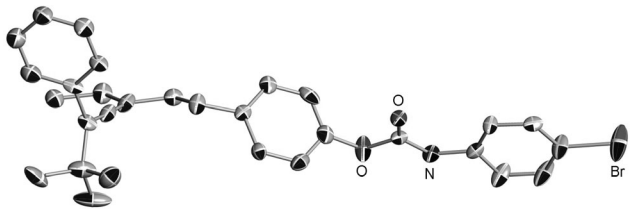


Figure 1. X-ray structure of a tetrasubstituted allene derived from **7 dba**. Thermal ellipsoids set at 30% probability.

In conclusion, we have found that the lithiation–borylation reaction of propargylic carbamates can be used to give tertiary propargylic boronic esters in very high e.r. provided that the less hindered ethylene glycol boronic esters are employed. These versatile intermediates undergo a range of highly stereoselective transformations, including protodeboronation to give tertiary allenes, and Suzuki–Miyaura cross-couplings of tertiary boron species leading to tetrasubstituted allenes with essentially perfect enantiospecificity.

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Keywords: allenes · boronic esters · cross-coupling · lithiation · propargylic alcohols

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