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Enantiospecific Alkynylation of Alkylboronic Esters

Yahui Wang, Adam Noble, Eddie L. Myers, and Varinder K. Aggarwal*

Abstract: Enantioenriched secondary and tertiary alkyl pinacolboronic esters undergo enantiospecific deborylative alkynylation through a Zweifel-type alkenylation followed by a 1,2-elimination reaction. The process involves use of α-lithio vinyl bromide or vinyl carbamate species, for which application to Zweifel-type reactions has not previously been explored. The resulting functionalized 1,1-disubstituted alkenes undergo facile base-mediated elimination to generate terminal alkyne products in high yield and excellent levels of enantiospecificity over a wide range of pinacolboronic ester substrates. Furthermore, along with terminal alkenes, internal and silyl-protected alkenes can be formed by simply introducing a suitable carbon- or silicon-based electrophile after the base-mediated 1,2-elimination reaction.

Stereoselective methods for the synthesis of alkynes have received renewed interest as a result of their considerable synthetic utility across an array of modern reactions, including click reactions with azides, gold-catalyzed cycloisomerization, and enyne/diyne metathesis. Alkyne-substituted stereocenters can be installed with high enantioselectivity by a number of methods, including the asymmetric addition of acetylides to carbonyls, transformation of chiral aldehydes or ketones into the corresponding alkenes and copper-catalyzed allylic substitution reactions. As an alternative, we considered stereospecific conversion of chiral alkylboronic esters into alkenes because alkylboronic esters themselves are versatile intermediates that can be readily prepared with high enantioselectivity using a variety of methods, including by a lithiation–borylation method developed within our laboratory.

The Suzuki–Miyaura reaction could potentially be used to transform boronic esters into alkenes in conjunction with an alkynyl halide. However, the use of chiral boronic acids/esters in such cross-coupling reactions is not known; the only reported examples are those that utilize primary sp³-, sp²-, and sp-type boron species, which are compounds that undergo facile transmetalation. Another attractive method involves electrophile-induced 1,2-migration of an alkynyl boronate followed by deboration (Scheme 1 A). However, this approach is only applicable to symmetric trialkylboranes (BR)³¹,¹⁴ and borinic esters (BR,OR)³⁵ which suffer from a number of drawbacks, including difficulty in preparing an enantioenriched form, poor stability, and the poor atom economy of subsequent transformations (two R groups are wasted in borane transformations). As such, the majority of examples involve simple, non-chiral boron reagents and the only enantiospecific examples utilize secondary borinic esters that require lengthy syntheses. Furthermore, these methods are not applicable to direct synthesis of terminal alkynes and cannot be used to access alkenes with t-quaternary stereocenters.

Compared to boranes and borinic esters, boronic esters [BR(OR)₂] are atom-economic substrates, which are easier to prepare and handle; however, they do not undergo alkynylation reactions owing to the reversibility of alkynyl boronate complex formation. Here, the addition of electrophiles leads to trapping of the acetylide and recovery of the boronic ester starting material (Scheme 1B, pathway (i)). In contrast, vinyl boronate complexes of alkylboronic esters are much more stable with respect to fragmentation and undergo facile electrophile-induced 1,2-migration and deboration.

Scheme 1. Alkynylation of alkyl boron species.
by the so-called Zweifel olefination.\textsuperscript{[17]} We questioned whether alkynes could be generated using a variant of this transformation by implementing suitably functionalized vinyl anions that would allow the resulting substituted alkene (Zweifel product) to undergo elimination and thereby unmask the alkyne (Scheme 1B, pathway (ii)).\textsuperscript{[18]} Such a method would enable the use of readily available alkylboronic esters to prepare chiral alkynes that are not easily accessed using established methods. Herein, we report the development of an alkynylation method that enables enantiospecific transformation of structurally diverse secondary and tertiary pinacolboronic esters into terminal and internal alkynes.

To test our strategy, we started with commercially available vinyl bromide 2a, which can be lithiated at the opposition with LDA at low temperature.\textsuperscript{[19]} Initially, we focused on optimizing conditions for the preparation of bromoalkene intermediate 3a (Table 1). Treatment of a THF solution of vinyl bromide (2a, 1.3 equiv) and secondary boronic ester 1a at −78°C with LDA (1.3 equiv) presumably generated vinylboronate 5, which, after addition of a methanolic solution of L2 (1.5 equiv) and subsequent warming to room-temperature, gave the required alkene 3a together with starting material 1a in a circa 1:1 ratio (entry 1, Table 1). Switching the solvent to less coordinating TBME ( tert-butyl methyl ether) or EtO\textsubscript{2}O (albeit with some THF present owing to 2a being added as a 1.0 M solution in THF) led to increased conversion to 3a. However, small amounts of insertion product 4a, a compound formed by 1,2-migration of vinylboronate 5, were also detected (entries 2 and 3, Table 1).\textsuperscript{[20]} The significant amounts of 1a recovered (likely because of the instability of 1,1-lithiobromoethene)\textsuperscript{[20d,e]} and competing rearrangement of 5 into 4a, prompted us to conduct the transformation at a lower temperature (−95°C) and increase the relative amounts of vinyl bromide and LDA used (2.0 equiv). Under these conditions, conversion into 3a was improved and 4a was not detected (entry 4, Table 1). Finally, conducting the reaction in Et\textsubscript{2}O, whilst adding both vinyl bromide and LDA as solutions in THF\textsuperscript{[21]} (Et\textsubscript{2}O/THF 3:2) gave a 96% conversion to 3a (entry 6, Table 1). Use of this mixture of solvents was superior to exclusive use of either THF or Et\textsubscript{2}O, the latter leading to complete recovery of starting material (entries 5 and 7, Table 1).

Once an efficient process was established for generating the 1,1-bromoalkynylalkyne 3a, we investigated a variety of conditions for effecting dehydrobromination. Our attempts to unmask the alkyne in situ, by addition of basic reagents after treatment with I\textsubscript{2}/MeOH, only led to isolation of 3a. However, subsequent work-up and treatment of a solution of crude 3a with either TBAF (5.0 equiv, DMF, 60°C, 1 h)\textsuperscript{[22]} or LDA (2.6 equiv, THF, −78°C to RT)\textsuperscript{[23]} led to isolation of alkyne 6a in good yield and with complete enantiospecificity (Scheme 2). Using the optimized conditions, we converted a variety of enantioenriched secondary boronic esters 1 into their corresponding alkynyl derivatives 6 (Scheme 2). The transformation occurred cleanly in the presence of cyclopropyl, alkyne, azide, electron-rich aryl, silyl ether, and tert-butyl ester functional groups, and showed essentially com-
plete enantiospecificity. The alkylation method was also successfully applied to hindered boronic ester 1h, derived from menthol, leading to alkynes 6h/6h'.

Alkylation of tertiary boronic esters was more challenging. Using conditions optimized for the alkylation of secondary boronic esters, only 42% of substrate 1j was converted into vinyl bromide 3j, and significant amounts of insertion product 4j and starting material were also detected (10% and 48%, respectively; Scheme 3). Presumably, increased steric hindrance close to the boron atom slows both vinyl boronate formation and subsequent electrophilic activation, thus allowing decomposition of the vinyllithium reagent and 1,2-migration of the vinyl boronate to become competing reaction pathways. In an effort to diminish side-reactions, we investigated the use of vinyl carbamate 2b (readily prepared from THF, 'BuLi, and ClCH (Cb = N,N,N-Pr3NCO)) in place of vinyl bromide 2a. We anticipated that the corresponding vinyllicyclic stability would be more stable with respect to decomposition, and that the poorer leaving-group ability of the carbamate would engender slower 1,2-migration and faster electrophilic activation of the corresponding vinyl boronate. Indeed, treating a THF solution of vinyl carbamate 2b and tertiary boronic ester 1j with LDA (~78°C, 1 h) followed by I2/MeOH gave the 1,1-O-carbamoylalkylalkene 3j' with excellent conversion (Scheme 3).

Dehydro-O-carbamoylation was effected using either 'BuLi/Et3O or LDA/THF to give the corresponding alkyne derivative 6j in good yield (89% and 88% yield, respectively, from 1j in 100% es; Scheme 4). Other enantioenriched tertiary boronic esters, including alkene-bearing, diaryl, and non-benzylic substrates, were converted into their alkyne derivatives in good yield and with complete enantiospecificity (6k–m, Scheme 4). Sterically hindered secondary boronic esters, such as cyclopropyl substrate 1b and cholesterol derivative 1o, were transformed into the corresponding alkyne derivatives 6b and 6o in good yield and enantio-/diastereospecificity using the vinyl carbamate technique. By comparison, boronic esters 1b and 1o produced low to moderate yields when vinyl bromide was used as the reagent. Pleasingly, double alkylation of 1,2-bis(boronic ester) 1n was also achieved to give 1,2-diyne 6n in high yield and enantiospecificity. However, application of the alkylation procedure to allylic boronic ester 1p failed because the intermediate vinyl boronate complex reacted with iodine as an allylic metal reagent, leading to fragmentation.

The alkylation of secondary benzylic boronic esters presented additional challenges owing to the enhanced acidity of the sp3 benzylic center. Under the optimized conditions enantioenriched substrate 1q was converted into vinyl carbamate intermediate 3q' in excellent yield. However, subsequent elimination with 'BuLi resulted in significant racemization, with the alkyne product 6q' being formed in 78% yield but with only 22% es (entry 1, Table 2). We hypothesized that the excess 'BuLi present after elimination resulted in post-reaction racemization and that this process could be prevented by reducing the amount of base used. Indeed, reducing the stoichiometry of 'BuLi from 2.5 to 1.1 equivalents led to much improved enantiospecificity (essentially complete), albeit with a concomitant reduction in yield (entries 1–4, Table 2). Interestingly, use of LDA resulted in considerably higher levels of racemization (entries 5 and 6, Table 2).

Finally, we wished to demonstrate the versatility of the alkylation method by extending it to the synthesis of internal and protected alkynes. This was achieved by taking advantage of the acetylide intermediate, which formed upon elimination of bromide or carbamate en route to the alkyne and could be trapped with a variety of electrophiles. For example, carbon electrophiles produced internal alkynes 7 and 8, whereas silyl chlorides generated alkyne 9; all in very high yield (Scheme 5).

In summary, enantioenriched secondary and tertiary boronic esters can be alkynylated in good yield and with
Table 2: Alkynylation of secondary benzylic boronic esters. 

| Entry | Base (x equiv) | corr. [%] | yield [%] | e.r.[1] | es [%] |
|-------|----------------|----------|-----------|---------|-------|
| 1     | BuLi (2.5)     | > 99     | 78        | 61:39   | 22    |
| 2     | BuLi (2.0)     | > 99     | 70        | 76:24   | 53    |
| 3     | BuLi (1.5)     | 75       | 60        | 95:5    | 92    |
| 4     | BuLi (1.1)     | 60       | 43 (37)   | 98:2    | 98    |
| 5     | LDA (2.5)      | > 99     | 87        | 50:50   | 0     |
| 6     | LDA (1.1)      | 49       | 39        | 63:37   | 27    |

[a] The elimination reactions were conducted using 3q' (0.25 mmol) in EtOAc (2.5 mL) at −78°C, then allowed to warm to 0°C for 0.5 h.
[b] Determined by 1H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. Number in parentheses shows the yield of isolated product after column chromatography. [c] Determined by chiral-phase GC.

Scheme 5. Trapping of intermediate acetylides with electrophiles.

high levels of enantiospecificity using a method involving a Zweifel-type olefination followed by a 1,2-elimination reaction. Either vinyl carbamates or vinyl bromides can be employed; the former demonstrates a broader substrate scope (applicable to secondary and tertiary boronic esters), whereas the latter can be eliminated using mild base (TBAF). Owing to the variety of functional groups into which alkynes can be transformed, we believe that these methods significantly contribute to the realization of a future where most organic molecules could be prepared from boronic ester building blocks.

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Keywords: alkynes · alkynylation · boronic esters · synthetic methods

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The pathway was predominant in our initial investigations of the reaction of alkylnyl boronates of pinacol boronic esters with I₂.